NICOTINE UPTAKE AND ABUSE LIABILITY ASSESSMENTS OF 5 BLU DISPOSABLE ELECTRONIC CIGARETTES IN COMPARISON TO A COMBUSTIBLE CIGARETTE

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Study Protocol - FINAL (v0 Original): 13 Jul 2021

NICOTINE UPTAKE AND ABUSE LIABILITY ASSESSMENTS OF 5 BLU DISPOSABLE ELECTRONIC CIGARETTES IN COMPARISON TO A COMBUSTIBLE CIGARETTE

Study No.: Fontem-PK-01

Protocol Version 0 (Original): 13 July 2021

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

SPONSOR SIGNATURE PAGE

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

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

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SYNOPSIS

Title	Nicotine uptake and abuse liability assessments of 5 blu disposable electronic cigarettes in comparison to a combustible cigarette
Objectives	**Primary objectives:** • To determine the pharmacokinetics (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. **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.
Phase of study	**Phase I**
Endpoints	**Primary endpoints:** • Baseline-adjusted plasma nicotine $Cmax_{0\text{-}120}$, $Cavg_{0\text{-}120}$, $Tmax_{0\text{-}120}$, $AUC_{0\text{-}120}$, $Cmax_{120\text{-}180}$, $Tmax_{120\text{-}180}$, $AUC_{120\text{-}180}$, $Cavg_{120\text{-}180}$, $AUC_{0\text{-}180}$ • Ratio of $Cmax_{120\text{-}180}/Cmax_{0\text{-}120}$ • Ratio of $Cavg_{120\text{-}180}/Cavg_{0\text{-}120}$ • Subjective effects measures: o Product liking assessment o Intent to Use Product Again assessment o Urge to Smoke Questionnaire o Product Evaluation Scale (PES) • Mass change of blu disposable e-cigarettes during puffing **Secondary endpoints:** • Puff topography (e.g., count, duration, volume, flow rate, and inter-puff interval) **Safety Endpoints:** • Heart rate and blood pressure during product use sessions • Adverse events (AE)/Serious adverse events (SAE)
Study design	This will be a part-randomized, open-label abuse liability assessment (ALA) and puffing topography study of nicotine-containing products carried out in 20 healthy adult volunteers who smoke combustible cigarettes. Subjects will attend the study site for a Screening Visit (Visit 1) within 14 days of entry into the study. At this visit, following informed consent, subjects will complete a nicotine use history questionnaire and also undergo a brief, observed trial use session with one of the blu disposable e-cigarettes they will use during the study. A nasal swab will be used to collect a sample of mucus that will be used to test for a COVID-19

	antigen. Blood and urine samples for laboratory assessments will be collected, and an alcohol breath test will be conducted. Medical history will be reviewed, exhaled carbon monoxide (eCO) will be measured, an ECG will be conducted, and vital signs will be assessed. Those who satisfy the inclusion/exclusion criteria will be entered into the study. Subjects will attend the study site 6 times (Visits 2-7) during the main study for ALA and puff topography assessments. 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 be provided with a supply of their assigned product to use at home for the day before their next visit (familiarization). 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, and subjects will be provided with a supply of their assigned product for familiarization before their next visit through Visit 6.
Study site	This study will be carried out as a single-center study in the United States.

<table>
<tr><td>Study products</td><td>
<table>
<tr><th>Product</th><th>Flavor</th><th>Nicotine Strength</th></tr>
<tr><td>A</td><td>[redacted]</td><td>2.4%</td></tr>
<tr><td>B</td><td>[redacted]</td><td>2.4%</td></tr>
<tr><td>C</td><td>[redacted]</td><td>2.4%</td></tr>
<tr><td>D</td><td>[redacted]</td><td>2.4%</td></tr>
<tr><td>E</td><td>[redacted]</td><td>2.4%</td></tr>
<tr><td>F</td><td colspan="2">Subject’s Usual Brand Combustible Cigarette</td></tr>
</table>
</td></tr>
<tr><td>Use regimen</td><td>

During individual visits, there will be 2 use sessions.
During the defined use session (first session), subjects will be asked to smoke a single cigarette or use the assigned blu disposable e-cigarette by taking 10 puffs over a period of 4.5 minutes. Total time for this session is 120 minutes.
The second use session is an hour-long ad libitum puffing session with no restrictions.

</td></tr>
<tr><td>Subjects</td><td>

20 male or female current cigarette smokers who may also be occasional users of e-cigarettes.
Aged between 21 and 65 years of age and deemed healthy during pre-study screening.

</td></tr>
<tr><td>Inclusion/ Exclusion Criteria</td><td>
The key inclusion criteria are:

Subjects must be current smokers (≥10 per day) of factory-made combustible cigarettes (eCO >10 ppm at screening) for at least 6 continuous months before Visit 1 and may be occasional users of e-cigarettes.
Subjects have urine cotinine >200 ng/mL at Screening

The key exclusion criteria are:

Subjects who, in the judgment of the study physician, have recent or active COVID 19 infection, based on results from COVID-19 screening, body temperature ≥100.4°F, and/or laboratory test results suggestive of recent exposure to SARS-CoV-2.
Subjects who have an acute illness (e.g., upper respiratory tract infection, viral infection) requiring treatment in the 4 weeks prior to Visit 1.
Subjects with significant abnormalities in their clinical laboratory evaluations or electrocardiogram.
Subjects who have used any nicotine or tobacco product other than e-cigarettes or factory-made combustible cigarettes in the 14 days prior to Visit 1.
Subjects who are self-reported or observed (during the trial session at Visit 1) non-inhalers during ENDS/cigarette use.
Subjects who have used any prescription or over-the-counter smoking cessation treatments, including, but not limited to any form of nicotine replacement therapy (NRT), varenicline, or bupropion within 30 days prior to Visit 1.

</td></tr>
</table>

	• Subject has a history or diagnosis of adult asthma, COPD (including emphysema and chronic bronchitis), or use of an inhaler within the past 3 months. • Subject has an active respiratory infection at time of the Screening Visit.
Duration of Study	Screening duration: approximately 14 days. Study duration: approximately 3 weeks.
Blood Sampling	Total blood draw volume is expected to be 510 mL for each subject during the study.
Post-Study Tests	A post-study follow-up will be performed with all subjects 5 to 7 days after their last study site visit, which will be conducted via a telephone call with the subjects. A full physical examination and safety assessments will be conducted only if indicated after review by the study physician.
Safety Data	On-study safety evaluations will include measurement of heart rate and blood pressure at the start, during, and at the end of each study site visit, temperature checks before each study site visit, and pregnancy tests in female subjects at the start of each product use visit. AEs reported by the subjects or observed by study personnel will be monitored from the time a subject uses the first investigational product/own brand cigarette (Visit 2) until the end of the study and will be reported by subjects at the follow-up. Any concomitant medications taken in the 30 days prior to Visit 1 through follow-up will also be recorded.
Bioanalysis	Nicotine analysis will be performed at an appropriate analytical laboratory using validated methods.
Statistics	Since this study is the first to examine the nicotine PK in subjects using these blu disposable e-cigarettes, no formal power calculations will be performed. A summary of statistical analysis plans follows. **Analysis of Nicotine Pharmacokinetics:** Pharmacokinetic parameters of plasma nicotine levels will be calculated using non-compartmental methods. Plasma concentrations and the computed plasma PK parameters will be listed for each study product and subject. Plasma nicotine levels will be plotted as mean concentration in relation to time, with 95% confidence intervals of the mean for each product at each time point. The following PK parameters will be calculated; all parameters will be baseline adjusted using the value at time -5 minutes: • $Cmax_{0\text{-}120}$ = Maximum plasma concentration during defined use session • $Tmax_{0\text{-}120}$ = Time of maximum plasma concentration during defined use session • $AUC_{0\text{-}120}$ = Area under the plasma concentration-time curve from time 0 to 120 minutes during defined use session • $Cavg_{0\text{-}120}$ = Average concentration from 0 to 120 minutes defined as AUC0-120/120 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 AUC120-180/60 minutes. • AUC_{0-180} = Area under the plasma concentration-time curve from time 0 minutes to 180 minutes during both puffing sessions • Ratio of $Cmax_{120-180}/Cmax_{0-120}$ = ratio of these two parameters • Ratio of $Cavg_{120-180}/Cavg_{0-120}$ = ratio of these two parameters A one-way or repeated measures analysis of variance will be conducted on $Cmax_{0-120}$ 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. **Analysis of Subjective Effects Measures:** Where applicable, responses to the questionnaires recorded as Visual Analog Scale (VAS) scores or Likert scales will be treated as continuous variables and summarized descriptively by study product and time point for each questionnaire item using means, standard deviations (SD), medians, and ranges. The maximum response (E_{max}) and time to maximum response (T_{max}) will be determined for the Urge to Smoke questionnaire. **Analysis of Puff Topography Data:** Summary statistics of the puff topography parameters will be presented including means, SD, medians, and ranges. **Analysis of Safety Data:** Safety data will be descriptively summarized by study product. Individual data will be provided in listings. AEs and incidence of device events and malfunction/misuse will be tabulated, and summary statistics for vital signs may be computed and provided, as deemed appropriate.

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.

ABBREVIATIONS

AE	Adverse event
AUC	Area under the nicotine concentration-time curve
BMI	Body mass index
bpm	Beats per minute
°C	Degree Celsius
CFR	Code of Federal Regulations
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
Cmax	Maximum measured plasma concentration
CO	Carbon monoxide
CPD	Cigarette(s) per day
CRF	Case report form
CRU	Clinical research unit
CTP	Center for Tobacco Products
CYP	Cytochrome P450
e-cigarette	Electronic cigarette
e-liquid	Electronic cigarette liquid
ECG	Electrocardiogram
Emax	Maximum reduction from baseline VAS score
ENDS	Electronic nicotine delivery systems
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
g	Gram
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization
IRB	Institutional Review Board
K_2-EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
m^2	Meters squared
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram

mL	Milliliter
mmHg	Millimeters of mercury
PES	Product Evaluation Scale
PK	Pharmacokinetic(s)
PMTA	Premarket Tobacco Product Application
ppm	Parts per million
QA	Quality Assurance
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SOP	Standard operating procedure
Tmax	Time to reach the maximum measured plasma concentration
US	United States
VAS	Visual analog scale

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1. INTRODUCTION AND BACKGROUND

1.1 Background

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" [1].

Over the past several years, a number of pharmacokinetic (PK)/pharmacodynamic studies of ENDS have been published. Very early devices showed very little, if any, nicotine absorption, compared with the typical 15 ng/mL Cmax achieved almost immediately after smoking a combustible cigarette after 12 hours of abstinence [2, 3]. Through innovation, nicotine delivery has improved, with Cmax after acute use (typically 10 puffs or 5 minutes) following 12 hours of overnight abstinence from smoking or vaping ranging from 25% to near 100% of combustible cigarettes from some devices and e-liquid nicotine concentrations [4-10]. Puff topography parameters, including puff duration, puff volume, and flow rate have also been investigated [11-18].

1.2 Study Purpose

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 (CTP) 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.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

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.

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.

2.2 Study Endpoints

Primary endpoints:

- Baseline-adjusted plasma nicotine $Cmax_{0\text{-}120}$, $Cavg_{0\text{-}120}$, $Tmax_{0\text{-}120}$, $AUC_{0\text{-}120}$, $Cmax_{120\text{-}180}$, $Tmax_{120\text{-}180}$, $AUC_{120\text{-}180}$, $Cavg_{120\text{-}180}$, $AUC_{0\text{-}180}$
- Ratio of $Cmax_{120\text{-}180}/Cmax_{0\text{-}120}$
- Ratio of $Cavg_{120\text{-}180}/Cavg_{0\text{-}120}$
- 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-cigarettes during puffing

Secondary endpoints:

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

Safety endpoints:

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

3. SUMMARY OF STUDY DESIGN

3.1 Design and Procedures

This will be a part-randomized, open-label abuse liability assessment (ALA) and puffing topography study of nicotine-containing products carried out in 20 healthy adult volunteers who smoke combustible cigarettes.

Subjects will be queried for symptoms of COVID-19 at each encounter (both in person and during telephone reminder calls for visits) (Section 13.1). In addition, at each study site visit, body temperature will be assessed before allowing the subject to enter the clinic.

Subjects will attend the study site for a Screening Visit (Visit 1) within 14 days of entry into the study. At this visit, following informed consent, subjects will complete a nicotine use history questionnaire and also undergo a brief, observed trial use session with one of the blu disposable e-cigarettes they will use during the study. A nasal swab will be used to collect a sample of mucus that will be used to test for a COVID-19 antigen. Blood and urine samples for laboratory assessments will be collected, and an alcohol breath test will be conducted. Medical history will be reviewed, exhaled carbon monoxide (eCO) will be measured, an ECG will be conducted, and vital signs will be assessed. Those who satisfy the inclusion/exclusion criteria will be entered into the study.

Subjects will attend the study site 6 times (Visits 2-7) during the main study for ALA and puff topography assessments. 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); see Section 7.1 for information about study products. Subjects will be provided with a supply of their assigned product to use at home for the day before their next visit (familiarization).

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, and subjects will be provided with a supply of their assigned product for familiarization before their next visit through Visit 6.

3.2 Follow-Up

Between 5 and 7 days after the last study site visit (Visit 7), a post-study follow-up will be performed, which will be conducted via a telephone call with the subjects. A full physical examination and safety assessments will be conducted only if indicated, after review by the study physician.

3.3 End of Study Definition

The end of study is defined as the date of the follow-up call or the physical examination and safety assessments, if indicated.

4. STUDY POPULATION

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

4.1 Inclusion Criteria

4.1.1 Screening Visit

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

1. Healthy males or females within the ages of 21 to 65 years, inclusive.
2. Subjects will have a body mass index (BMI) of 18.5 to 35.0 kg/m^2, inclusive, and a body weight exceeding 52 kg (males) or 45 kg (females).
3. Subjects must be current smokers (≥10 per day) of factory-made combustible cigarettes (eCO >10 ppm at screening) for at least 6 continuous months before Visit 1, and may be occasional users of e-cigarettes.
4. Urine cotinine >200 ng/mL.
5. Subject demonstrates understanding of the study and willingness/consent to participate as evidenced by voluntary written informed consent and has received a signed and dated copy of the consent form.
6. Subject understands and is willing, able, and likely to comply with all the study procedures and restrictions.
7. Subject is in good general health in the opinion of the investigator, with no clinically significant and relevant abnormalities of medical history.
8. Subject has a seated systolic blood pressure ≤160 mmHg, diastolic blood pressure ≤95 mmHg, and heart rate ≤100 bpm.
9. Females of childbearing potential are, in the opinion of the investigator, practicing a reliable method of contraception.

4.1.2 Visits 2 to 7

10. Abstinence from all forms of nicotine for 12 hours before the start of each product use visit, confirmed by an exhaled breath CO reading ≤15 ppm.

4.2 Exclusion Criteria

4.2.1 Screening Visit

Subjects will be excluded from the study if there is evidence of any of the following criteria at Screening or during the study, in the opinion of the investigator:

1. Subjects who, in the judgment of the study physician, have recent or active COVID-19 infection, as evidenced by the following:
    a. Endorsement of symptoms that could indicate COVID-19 during screening (Section 13.1) and/or
    b. Body temperature ≥100.4°F and/or
    c. Laboratory test results suggestive of active or recent exposure to SARS-CoV-2 (Section 9.4).
2. Subjects who have participated in another clinical study within 30 days of Visit 1 or who have previously participated in this study.
3. Subjects who have an acute illness (e.g., upper respiratory tract infection, viral infection) requiring treatment in the 4 weeks prior to Visit 1.
4. Subjects with significant abnormalities in their clinical laboratory evaluations or ECG.
5. Subjects who have used any nicotine or tobacco product other than e-cigarettes or

factory-made combustible cigarettes in the 14 days prior to the Visit 1.
6. Subjects who are self-reported or observed (during the trial session at Visit 1) non-inhalers during ENDS/cigarette use.
7. Subjects who have used any prescription or over-the-counter (OTC) smoking cessation treatments, including, but not limited to any form of nicotine replacement therapy (NRT), varenicline, or bupropion within 30 days prior to Visit 1.
8. Is planning to quit smoking during the study or postponing a quit attempt in order to participate in the study.
9. Subjects who have used prescription or OTC bronchodilator medication (e.g., inhaled or oral β-adrenergic agonists) to treat a chronic condition within the 12 months prior to Visit 1 or have a history of lung disease.
10. Subjects who have received any medications or substances that interfere with the cyclooxygenase pathway within 14 days prior to Visit 1 or are known to be strong inducers or inhibitors of cytochrome P450 (CYP) enzymes within 14 days or 5 half-lives of the drug (whichever is longer) prior to Visit 1.
11. Women who are pregnant or who have a positive urine pregnancy test.
12. Women who are breast-feeding an infant.
13. Subject has a history or diagnosis of adult asthma, COPD (including emphysema and chronic bronchitis), or use of an inhaler within the past 3 months.
14. Subject has an active respiratory infection at time of Screening.
15. Subject has been hospitalized in the 28 days prior to Visit 1.
16. Subject has a history of schizophrenia, psychosis, or bipolar disorder.
17. Subject provides a positive drugs of abuse urine test at Visit 1. Tested drugs will include cocaine, amphetamines, methamphetamines, opiates (morphine, heroin), barbiturates, and benzodiazepine.
18. Subject has a self-reported use of more than 21 drinks per week. A drink is defined as 1.5 oz of spirits (e.g., whiskey, vodka), 12 oz of beer, or 5 oz of wine.
19. Subjects who have lost or donated more than 450 mL of blood within the 2 months preceding the first product use.
20. Subject is an employee of the sponsor or the study site, or members of their immediate family.
21. In the opinion of the investigator, the subject should not participate in this study.

4.2.2 Visits 2 to 7

22. Subject continues to meet all Screening exclusion criteria. Pregnancy test to be performed on all female subjects at each visit before product use.
23. Any emergent medical condition (including, but not limited to COVID-19) or concomitant medication that may have an impact on the safety and objectives of the study (at the investigator's discretion).

4.3 Study Restrictions

4.3.1 Food and Beverages

Before Visits 2 to 7, food and beverage restrictions include:

- No alcohol should be consumed for 24 hours before the appointment time.
- No caffeinated beverages for 1 hour before the appointment time or during each

product use session. Water will be permitted during the hour before the appointment but not during each product use episode. An exception to the water restriction can be made if a subject starts coughing uncontrollably while smoking/vaping the study products.

- No food for 1 hour before the appointment time or during each product use session.

4.3.2 Nicotine

Subjects must abstain from the use of any nicotine-containing products (e.g., cigarettes, e-cigarettes, oral tobacco products) for a period of 12 hours prior to Visits 2 to 7.

4.3.3 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 Screening through the end of study will be recorded. Except for those medications noted in the exclusion criteria, prescription or OTC 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 OTC products such as analgesics (e.g., ibuprofen, acetaminophen), antihistamines, nasal decongestants, and dietary supplements are permitted.

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 joint decision will be made by the investigator and sponsor to continue or discontinue the subject. Any exceptions will be documented and required medications that might impact study endpoints should be considered during interpretation of the study results.

4.3.4 Tobacco Use/Considerations

For a period of 1 day before Visits 3 to 7, subjects will undergo an at-home familiarization period with their assigned product (blu disposable e-cigarette) they are to use at the next study visit. During each familiarization period, subjects will be allowed to smoke their usual brand of cigarettes but will be instructed to predominantly use the blu disposable e-cigarette as their primary source of nicotine.

Subjects must abstain from use of any tobacco- or nicotine-containing products for a period of at least 12 hours prior to each product use visit.

5. CRITERIA FOR PREMATURE DISCONTINUATION OF STUDY PRODUCT USE OR SUBJECT WITHDRAWAL FROM STUDY

Subjects should be encouraged to complete all study assessments. However, subjects may refuse additional study product use or withdraw consent to participate in this study at any time without penalty or loss of benefits to which they are otherwise entitled.

5.1 Premature Discontinuation (Drop Out) from Study Product Use

All subjects who were randomized, used at least one of the study products, and are prematurely discontinued from the study should have End of Study assessments performed on the day of discontinuation.

Reasons for premature discontinuation from study product use will be recorded on the appropriate page(s) of the case report form (CRF) and may include, but are not limited to:

- Withdrawal of consent
- Significant subject noncompliance, defined as refusal or inability to adhere to the protocol requirements (e.g., subject restrictions and Schedule of Assessments and Procedures)
- The occurrence of an AE or serious adverse event (SAE) that, in the opinion of the investigator, warrants the subject's permanent discontinuation from study product use
- The investigator determines that it is in the best interest of the subject to withdraw from study participation due to a reason other than an AE or SAE.

In the event of study product discontinuation due to an AE, study site personnel should notify the medical monitor as soon as possible.

5.2 Replacement of Subjects

The study aims to have 20 subjects complete all 6 study visits (Visits 2-7). Twenty of the subjects who have qualified at Screening will be scheduled to attend Visit 2. An additional 2 qualified subjects will be designated as alternates. They will also attend Visit 2 but will only be randomized if any of the original 20 subjects do not complete Visit 2. After Visit 2, subjects who drop out or are withdrawn may be replaced at the discretion of sponsor.

6. SUBJECT IDENTIFICATION AND BLINDING

It is not possible to blind the study products.

Each subject who signs the informed consent at Screening will be assigned a Screening Number beginning with 1001.

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.

7. STUDY PRODUCTS/MATERIALS

7.1 Description of Study Products

All blu disposable e-cigarettes (Table 1) will be provided by the sponsor.

Table 1: Study Products

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

blu disposable e-cigarettes are intended for one-time use only and cannot be disassembled. Disposables contain an internal tank pre-filled with-e-liquid and include an internal battery that is not rechargeable. Upon taking a draw on the disposable, a sensor activates the battery to generate heat. Once heated, e-liquid is converted to vapor. Instructions provided to subjects will include: 1. Remove the rubber cap from the mouthpiece at the end of the disposable. 2. As you inhale, the blue LED tip on the end of the disposable will illuminate.

At Visit 2, subjects will smoke their own brand of combustible cigarette.

7.2 Study Product Accountability

Records will be maintained showing the receipt and disposition of the study supplies. The sponsor will be permitted, at intervals, and upon request during the study, to check the supplies storage and dispensing procedures and records.

Subjects will be instructed to attend the clinic at Visit 2 with a sufficient supply of their usual brand of combustible cigarette to smoke during the 2 use sessions.

All study products will be stored in a locked, limited-access area at the study site. The site staff will document and reconcile the total number of products shipped to the site, the total number of products dispensed during the study, and the total number of products remaining at the end of clinical conduct.

Following completion of the clinical phase of the study and sponsor review of accountability, all used and unused supplies (other than those required for retention purposes) will either be returned to the sponsor together with accountability records or will be destroyed and Certificates of Destruction provided to the sponsor.

7.3 Study Product Use and Mass Change

During the PK testing at Visits 3 to 7, an unused blu disposable e-cigarette will be used for each subject. A backup blu disposable e-cigarette will be available in the unlikely event that there is a malfunction. Before both the standardized and *ad lib* puffing sessions, the staff will weigh the product and record the weight in the source document. Immediately after each puffing session, the staff will again weigh the product and record the weight in the source document.

The number of cigarettes smoked and e-cigarettes used in each respective *ad lib* session will also be recorded.

Study products for dispensing 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 site staff for each subject.

The study staff will document the start time and stop time of each product use episode.

Subjects will smoke their usual brand combustible cigarette and use the study products only in designated areas of the clinical site.

8. VISIT DURATION AND WINDOWS

8.1 Visit 1 (Screening)

Following a telephone screening interview conducted by the study staff, qualified subjects will be scheduled for Visit 1. Visit 1 will last approximately 1.5 hours.

8.2 Visits 2 to 7 (Combustible Cigarette Smoking and ENDS Use)

Visit 2 will occur between 2 and 14 days after Visit 1.

Visits 2 to 7 will be scheduled before 1 pm, and each of these visits will last approximately 3.5 hours. Visits 2 to 7 will occur at least 2 days following the previous visit.

8.3 Post-study Assessments

Between 5 and 7 days after the last study site visit (Visit 7), a post-study follow-up will be performed, which will be conducted via a telephone call with the subjects. A full physical examination and safety assessments will be conducted only if indicated after review by the study physician.

9. STUDY PROCEDURES

Study procedures will be performed as delineated in the Study Events Flow Chart.

9.1 Informed Consent

The investigator or designee will obtain written informed consent from each subject participating in the study after thoroughly explaining the aims, objectives, procedures, payment schedule, and potential hazards of the study. Subjects will be made aware that they are free not to participate in the study and that they can withdraw at any time. Subjects will receive a copy of the informed consent that they and the site staff and investigator signed. Subjects will be re-consented with an updated consent form if any new information becomes available that could affect the participant's willingness to continue.

9.2 Demographic Data

The site staff will record each subject's date of birth, sex, and race/ethnicity.

9.3 Clinical Laboratory Assessments

Two 10 mL and two 5 mL blood samples and a urine sample will be collected for biochemistry, hematology, and urinalysis testing. All clinical laboratory tests will be conducted by a laboratory accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]). 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:

Clinical Chemistry [1]
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Blood urea nitrogen

Urinalysis [2]
- Bilirubin
- Blood, occult
- Glucose
- Ketones
- Nitrite

- Carbon dioxide (bicarbonate)
- Creatinine
- Estimated glomerular filtration rate
- Glucose
- Potassium
- Sodium
- Total protein
- Uric acid
- pH
- Protein
- Specific gravity
- Urobilinogen
- WBC esterase

Hematology

- Eosinophils
- Basophils
- Hematocrit
- Hemoglobin
- Lymphocytes
- Monocytes
- Neutrophils
- Platelet count
- Red blood cell count
- White blood cell count with differential

[1]Clinical 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 clinical chemistry sample being taken.
[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.

9.4 SARS-CoV-2 (Coronavirus)

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.

At Visit 1, a nasal swab will be used to collect a sample of mucus that will be used to test for a COVID-19 antigen (*CareStart*^{TM}, Access Bio, Inc). It is a rapid test (results in 10 minutes). Subjects will not be allowed in the clinic for their visit unless the result is negative. If the test is positive, subjects will be excluded from the study.

The rapid test may be administered during the study if the subject reports or shows symptoms suggestive of COVID-19.

9.5 Urine Screen for Drugs of Abuse and Alcohol Breath Test

The site staff will administer a commercially available urine dipstick screen for the following drugs of abuse: cocaine, amphetamines, methamphetamines, cannabis, opiates (morphine, heroin), phencyclidine, barbiturates, and benzodiazepines. Subjects with a positive test will be excluded from the study.

In addition, an alcohol breath test will be conducted. Subjects with a reading >0.01% will be excluded from the study.

9.6 Inclusion/Exclusion Criteria

The site staff will assess each potential subject's eligibility to participate in the study based on the inclusion/exclusion criteria (Sections 4.1 and 4.2).

9.7 Urine Pregnancy Test

The site staff will administer a commercially available urine dipstick pregnancy test to all females.

9.8 COVID-19 Screening

In addition to the lab test for COVID-19 (Section 9.4), subjects will be queried for symptoms of COVID-19 at each encounter (both in person and during telephone reminder calls for visits) during the study (Section 13.1). In addition, at each study site visit, body temperature (SmartGlow EXERGEN Temporal Scanner) will be assessed before allowing the subject to enter the clinic. Subjects with results ≥100.4°F will not be allowed to enter the clinic.

The study physician will take into account the answers on the COVID-19 screen, temperature results, and laboratory test (Section 9.4) to determine if subjects should be excluded from the study (results at Screening), rescheduled, or discontinued.

9.9 Electrocardiogram

A single 12-lead ECG will be taken following resting in the supine position for at least 5 minutes. ECGs will be interpreted, signed, and dated by appropriate site personnel.

9.10 Medical History and Record of Concomitant Medication

The site staff will obtain and record a medical history from each subject. Any relevant medical history within the previous year, including surgeries, allergies, and drug sensitivities will be included. Any concomitant medications taken within the previous 30 days will also be recorded. Any changes to concomitant medications will be documented throughout the study.

A physical examination may be conducted during Screening if deemed necessary by the study physician to assess the subject's eligibility for the study. A symptom-driven physical examination may be conducted at other times as deemed appropriate by the investigator or designee.

9.11 Tobacco/Nicotine Product Use

9.11.1 Nicotine Use History Questionnaire

Subjects will be required to report previous tobacco and nicotine product use histories to satisfy the study inclusion and exclusion criteria. The study staff will administer a questionnaire that collects data on previous and current use of combustible and non-combustible tobacco products, ENDS products, and NRTs (Section 13.2.1).

9.11.2 Fagerström Test for Nicotine Dependence Questionnaire

The FTND is a self-administered questionnaire widely used to measure nicotine dependence among cigarette smokers [19]. Subjects respond to a series of 6 questions, and responses will be summed to produce a total score (Section 13.2.2).

9.11.3 Exhaled Carbon Monoxide

The site staff will obtain an eCO level from each subject using a Bedfont Micro + carbon monoxide monitor. The manufacturer's instructions for obtaining the samples will be

followed, with subjects taking a deep breath and holding it for 15 seconds before exhaling into the mouthpiece of the device.

9.11.4 Urinary Cotinine

Urinary cotinine will be analyzed and must be >200 ng/mL for the subject to be eligible for the study.

9.12 Vital Signs, Height, and Weight

The subject's height and weight will be recorded. The BMI will be calculated using a standard formula of weight (kg)/[height (m)]^2.

Site personnel will measure blood pressure and heart rate (Omron Model Number: HEM-907XL) after the subject has spent at least 5 minutes in the seated position. At product use visits, blood pressure and heart rate will be recorded at -10 (baseline), 8, 60, 120, and 180 minutes.

9.13 Trial of Study Products

At Screening, potential subjects will participate in a brief, observed trial use of a blu disposable e-cigarette to demonstrate that they can successfully comply with the instructions for use of study products using the following protocol:

- Study staff will instruct the subject on the proper use of the ENDS device.
- Subject will take up to 5 *ad lib* puffs from Study Product C (Table 1) to become familiar with the product and demonstrate that they can inhale the aerosol without excessive coughing or discomfort.
- Based on the testing, subject expresses confidence in his/her ability to use each of the study products during the at-home familiarization period as well as the puffing sessions during Visits 3 to 7.

9.14 Product Use Sessions (Visits 2 to 7)

9.14.1 Defined Product Use Session

During Visits 2 to 7, subjects will undergo a product use session in which they take 10 puffs from their usual brand of combustible cigarette (Visit 2 only) or 10 puffs from their randomly allocated blu disposable e-cigarette. The beginning of each puff will be separated by a period of 30 seconds. For each puff, subjects will be instructed to achieve a puff duration of at least 1 second. Blood samples will be taken for nicotine PK analysis (Section 9.14.3).

9.14.2 *Ad libitum* Product Use Session

During Visits 2 to 7, subjects will undergo an additional product use session during which they use the cigarette (Visit 2 only) or blu disposable e-cigarettes *ad libitum*, i.e., by taking as many and as frequent puffs as they desire. Subjects may use as many cigarettes and e-cigarettes as they would like. During this session, puffing topography measurements will be made using the CReSS Pocket device (Section 9.14.4), and blood samples will be taken for PK analysis (Section 9.14.3).

9.14.3 Nicotine Pharmacokinetics

At Visits 2 to 7, a 4 mL blood sample for plasma nicotine analysis will be drawn into a plastic K_2-EDTA (lavender top) vacutainer tube at -5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 135, 150, 165, and 180 minutes relative to the first puff of the combustible cigarette/blu disposable e-cigarette at that visit; i.e., at the start of the defined use session.

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

Procedures for processing and storing samples will be performed according to the laboratory manual.

Plasma samples will be shipped in batches on dry ice for analysis to a commercial bioanalytical laboratory. The level of nicotine will be measured in samples at each time point and following analysis, all samples will be stored for up to one year and then destroyed. Nicotine bioanalysis will be conducted in accordance with appropriate standards including Good Laboratory Practice.

9.14.4 Puff Topography

Puff topography will be evaluated in the second product use session at Visits 2 to 7. Subjects will engage in a 1 hour *ad libitum* product use session with either their usual brand cigarette or the assigned blu disposable e-cigarette, both of which will be used with the CReSS Pocket topography device.

9.14.5 Mass Change

For both the defined and *ad libitum* use sessions, the e-cigarette will be weighed before and after use, and these weights will be recorded.

9.14.6 Subjective Effects Questionnaires

The Urge to Smoke, PES (7-point scale), Product Liking (VAS), and Intent to Use Product Again (VAS) questionnaires will be completed on paper. The Urge to Smoke questionnaire will be completed up to 30 seconds prior to the scheduled blood draw; however, if necessary, the blood draw will take precedence over completing the questionnaire. For any other questionnaires scheduled at the same time as a PK blood draw, they will be completed within approximately 2 minutes after the scheduled blood draw.

9.14.6.1 Urge to Smoke Questionnaire

The Urge to Smoke questionnaire (Appendix 13.2.4) will be administered at the same time points when there is a blood draw for nicotine PK; i.e., at -5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 135 (or 15 minutes into *ad lib* session), 150 (or 30 minutes into *ad lib* session), 165 (or 45 minutes into *ad lib* session), and 180 (or 60 minutes into *ad lib* session) minutes relative to the first puff of the cigarette/ENDS at that visit during Visits 2 to 7.

9.14.6.2 Product Evaluation Scale (PES)

The PES (Appendix 13.2.6) will be administered at 180 minutes (i.e., 60 minutes into *ad lib* session) relative to the first puff of the cigarette/ENDS at that visit at Visits 2 to 7.

9.14.6.3 Product Liking Questionnaire

The Product Liking questionnaire (Appendix 13.2.3) will be completed at approximately 180 minutes (i.e., 60 minutes into *ad lib* session) relative to the first puff of the cigarette/ENDS at that visit at Visits 2 to 7.

9.14.6.4 Intent to Use Product Again Questionnaire

The Intent to Use Product Again questionnaire (Appendix 13.2.5) will be completed at approximately 180 minutes (i.e., 60 minutes into *ad lib* session) relative to the first puff of the cigarette/ENDS at that visit at Visits 2 to 7.

9.15 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.

9.15.1 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.

9.15.1.1 Adverse Event Monitoring

The subjects will be instructed to inform the investigator or staff of any AEs and intercurrent illnesses experienced during the study. 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. When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

9.15.1.2 Reporting

All AEs occurring during this clinical trial after the subject has used the first study product will 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 use, and severity for each event.

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 use 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.

9.15.1.3 Serious Adverse Events

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 hospitalization or prolongation of existing hospitalization, 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 hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Life threatening is defined as an AE that in the view of the investigator (or designee) or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE that is not consistent with the known risk information associated with the study product.

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 site'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 IRB, in compliance with GCP reporting guidelines, and the site monitor of any SAE.

9.15.2 Pregnancy

A pregnancy occurring in a female study subject during the study will be documented in the clinical conduct study report to the IRB. 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 site staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site staff will follow up with the subject until the end of pregnancy, if in compliance with the site'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.

9.15.3 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.

9.16 Blood Sample Collection

Blood sampling will include 2x10 mL and 2x5 mL blood draws during Visit 1 for clinical laboratory assessments and 16x5 mL PK blood draws (4 mL to fill the vacutainer, 1 mL wasted to assure proper blood flow and to clear residual blood and saline from the extension tube connected between the catheter the vacutainer tube) at Visits 2 to 7. Therefore, total blood draw volume is expected to be 510 mL for each subject during the study.

10. DATA ANALYSIS

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 LA Clinical Trials, LLC 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 SAP.

10.1 Sample Size Estimation

Since this study is the first to examine the nicotine PK in subjects using all of these blu disposable e-cigarettes, no formal power calculations will be 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.

10.2 Analysis Populations

10.2.1 Safety Population

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

10.2.2 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. This population will be used in the summary and analysis of PK, subjective effects, topography, and product use.

10.2.3 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. 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 have this evidence of not meeting the abstinence criteria in ≥50% of their visits will be excluded from the PK Subpopulation.

10.3 Data Analysis, Summarization, and Statistical Methods

SAS software (version 9.3 or higher, Cary, NC) will be used for all data presentation and summarization including summary tables, graphs, and data listings, except as noted in 10.3.1. In general, all data will be listed by subject and time point and summarized by study product and time point 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 summarized based on reduced denominators.

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

Pharmacokinetic parameters of plasma nicotine levels will be calculated using noncompartmental methods with the Phoenix WinNonlin version 8 software platform (Certara, Princeton, NJ). Plasma concentrations and the computed plasma PK parameters will be listed for each study product and subject.

Plasma nicotine levels will be plotted as mean concentration in relation to time, with 95% confidence intervals of the mean for each product at each time point.

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

- $Cmax_{0\text{-}120}$ = Maximum plasma concentration during defined use session
- $Tmax_{0\text{-}120}$ = Time of maximum plasma concentration during defined use session
- $AUC_{0\text{-}120}$ = Area under the plasma concentration-time curve from time 0 to 120 minutes during defined use session
- $Cavg_{0\text{-}120}$ = Average concentration from 0 to 120 minutes defined as AUC0-120/120 minutes.
- $Cmax_{120\text{-}180}$ = Maximum plasma concentration during the *ad libitum* puffing session
- $Tmax_{120\text{-}180}$ = Time of maximum plasma concentration during the *ad libitum* puffing session
- $AUC_{120\text{-}180}$ = Area under the plasma concentration-time curve from time 120 minutes to 180 minutes during the *ad libitum* puffing session
- $Cavg_{120\text{-}180}$ = Average concentration from 120 to 180 minutes defined as AUC120-180/60 minutes.
- $AUC_{0\text{-}180}$ = Area under the plasma concentration-time curve from time 0 minutes to 180 minutes during both puffing sessions
- Ratio of $Cmax_{120\text{-}180}/Cmax_{0\text{-}120}$ = ratio of these two parameters
- Ratio of $Cavg_{120\text{-}180}/Cavg_{0\text{-}120}$ = ratio of these two parameters

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 summarized by study product using descriptive statistics.

A one-way or repeated measures analysis of variance will be conducted on the Outcomes Population $Cmax_{0\text{-}120}$ and $AUC_{0\text{-}120}$ 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.

10.3.2 Subjective Effects Measures

Where applicable, responses to the questionnaires recorded as VAS scores or Likert scales will be treated as continuous variables and summarized descriptively by study product and time point for each questionnaire item using means, standard deviations (SD), medians, and ranges.

The PES 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 Questions 11, 13, 14, 15, and reversed for Question 20 (i.e., not at all = 7, extremely = 1);
e) Questions 17, 19, 21 will be summarized as individual item scores.

The maximum response (E_{max}) and time to maximum response (TE_{max}) will be determined for the Urge to Smoke questionnaire.

Responses and parameters will be listed by subject and summarized by study product using descriptive statistics.

10.3.3 Puff Topography

The following topography parameters will be assessed:

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

Summary statistics of puff topography parameters will be presented, including means, SD, medians, and ranges.

10.3.4 Mass Loss

The difference in weights before and after each product use session will be summarized by study product using descriptive statistics.

10.3.5 Safety

All clinical safety data will be summarized 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 summarized. 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 summarized and sorted by system organ class. Frequencies of subjects with study product use-emergent serious AEs will be likewise summarized. Frequencies of study product use-emergent AEs will be summarized by severity and relationship to study product.

All concomitant medications recorded will be listed by subject.

11. STUDY ADMINISTRATION

11.1 Ethics

11.1.1 Institutional Review Board

This protocol will be reviewed by the Advarra IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines, and may be reached at:

Advarra IRB
6100 Merriweather Dr., Suite 600
Columbia, MD 21044
Phone: 410.884.2900

11.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

11.1.3 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 summarizing the discussion prior to Screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

11.2 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.

11.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at LA Clinical Trials, LLC relevant to the quality of this study. Designated personnel of LA Clinical Trials, LLC 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.

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 will be made prior to database lock.

11.4 Direct Access to Source Data/Documents

LA Clinical Trials, LLC will ensure that the sponsor, IRB 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.

11.4.1 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).

11.5 Reporting for the Study

11.5.1 Case Report Forms

LA Clinical Trials, LLC 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 LA Clinical Trials, LLC and the sponsor (e.g., compact disc, flash drive, secure file transfer protocol). This will be documented in the Data Management Plan (if applicable).

AEs will be coded using MedDRA®. Coding will be completed by qualified members of LA Clinical Trials, LLC staff.

11.5.2 Report Format

According to the ICH Harmonized 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).

11.5.3 Record Keeping

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by LA Clinical Trials, LLC 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.

11.6 Confidentiality

All clinic sites and vendors will have signed confidentiality agreements with LA Clinical Trials, LLC. By signing this protocol, the investigator and LA Clinical Trials, LLC staff will regard all information provided by the sponsor and all information obtained during the course of the study as confidential.

Neither the clinic site nor LA Clinical Trials, LLC will supply to the sponsor any subject names, initials, date of birth (except year), or other personal identifiers in compliance with 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, social security details etc. may be released to the sponsor. The subjects will be informed during the consenting process that representatives of the sponsor, IRB, 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.

11.7 Publication Policy

All unpublished information given to LA Clinical Trials, LLC 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.

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13. APPENDICES

13.1 Appendix 1. COVID-19 Screening

Questions for **Screening**:

At any time <u>during the past 14 days</u> have you…(check yes or no for each)	**Yes**	**No**
Felt like you had a fever?		
Had a new or worsening cough?		
Had difficulty breathing?		
Had chills?		
Had a sore throat?		
Experienced body aches or muscle aches?		
Experienced a change in your ability to smell things?		
Experienced a change in your ability to taste things?		
Close contact with someone who is sick with suspected or confirmed COVID-19?		

Before **every Visit**:

Temperature:_____ Note: Fever = a temperature of 100.4° F (38° C) or greater

Questions **at every reminder call** and **every Product Use Visit**:

At any time since <u>your last clinic visit</u> have you…(check yes or no for each)	**Yes**	**No**
Felt like you had a fever?		
Had a new or worsening cough?		
Had difficulty breathing?		
Had chills?		
Had a sore throat?		
Experienced body aches or muscle aches?		
Experienced a change in your ability to smell things?		
Experienced a change in your ability to taste things?		
Close contact with someone who is sick with suspected or confirmed COVID-19?		

13.2 Appendix 2. Nicotine Use and Subjective Effects Questionnaires

13.2.1 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)
      v.
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_____

13.2.2 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 others ☐
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 ☐

Subject Initials_____ Date _____

13.2.3 Product liking questionnaire

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

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

13.2.4 Urge to smoke questionnaire

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

No Urge Very Strong Urge

The Urge to Smoke questionnaire will be completed up to 30 seconds prior to the scheduled blood draw; however, if necessary, the blood draw will take precedence over completing the questionnaire.

13.2.5 Intent to use product again questionnaire

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

Definitely would not Definitely would

13.2.6 Product Evaluation Scale

	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?							