A single center, open label study to assess the pharmacokinetics of cannabidiol inhaled via a Hemp Heat-not-Burn (HHnB) device in healthy participants

Protocol Number: VFC224-101

Study product:	Cannabidiol (CBD) inhaled via an HHnB device
Brief Title	An open label study to assess the pharmacokinetics of inhaled cannabidiol in healthy participants via HHnB device
Clinical Phase:	Phase 1
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Approval Date:

Sponsor Signatory:

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Investigator Signature Page

The undersigned has read and understood the study protocol version 2.0 detailed above and agrees to conduct the study in compliance with the protocol.

Milko Radicioni
Milko Radicioni (May 13, 2025 13:42 GMT+2)

Milko Radicioni, MD	**Date**
Principal Investigator	

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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List of Abbreviations and Definitions of terms

$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from the time of the last observed concentration to infinity, calculated, if feasible, as $[1 – (AUC_{0\text{-}t}/AUC_{0\text{-}inf})] \times 100$
ADE	Adverse device effect
AE	Adverse event
AESI	AE of special interest
ALT	Alanine aminotransferase
ASADE	Anticipated serious adverse device effect
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero until the last observed concentration
BLQL	Below the lower quantification limit
BMI	Body mass index
CBD	Cannabidiol
CFR	Code of Federal Regulations
CL/F	Apparent clearance
C_{max}	Maximal observed concentration
eCRF	Electronic case report form
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CRO	Contract research organization
C-SSRS	Columbia suicidality severity rating scale
CV	Coefficient of variation
CYP	Cytochrome P450
DD	Device deficiency
DMP	Data Management Plan
DVP	Data Validation Plan
ECG	Electrocardiogram
eCRF	Electronic case record form
EDC	Electronic Data Capture
EOS	End of study
ET	Early termination
ETV	Early termination visit
FAS	Full analysis set
FCOHb	Fractionated Carboxyhemoglobin
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen

HCV	Hepatitis C virus
HHnB	Hemp Heat-not-Burn
HIV	Human immunodeficiency virus
HnB	Heat-not-Burn
HPT	Human puffing topography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional review board
K_{el}	Terminal elimination rate constant
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
OMAS	Oral Mucositis Assessment Scale
OTC	Over-the-counter
PCP	Phencyclidine
PK	Pharmacokinetic(s)
PKPP set	Pharmacokinetics per protocol set
PT	Preferred term
PTAEs	Pre-treatment adverse events
RBC	Red blood cell
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SIB	Suicidal ideation and behavior
SD	Standard deviation
SoA	Schedule of Activities
SOC	System organ class
SOP	Standard operation procedure
SPA-M	Smoking Puff Analyser – Mobile
SUSAR	Suspected, unexpected, serious adverse reaction
$T_{½\ el}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
T_{max}	Time when the maximal concentration is observed
ULN	Upper limit of normal

USADE	Unanticipated serious adverse device effect
V_z/F	Apparent volume of distribution

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A single center, open label study to assess the pharmacokinetics of cannabidiol inhaled via a Hemp Heat-not-Burn (HHnB) device in healthy participants

Brief Title:

An open label study to assess the pharmacokinetics (PK) of inhaled cannabidiol in healthy participants

Rationale:

There is limited data available to date on cannabidiol (CBD) absorption following CBD inhalation via a Hemp Heat-not-Burn (HHnB) device in humans. This Phase 1 clinical study will evaluate the PK, safety and tolerability of CBD administered via an HHnB device according to two different regimens, i.e. a standardized (fixed number of puffs) puffing dosing and a non-standardized (*ad libitum*) administration (as desired by the participant). In addition, subjective effects (through a product effect questionnaire), and human puffing topography will be evaluated to provide further insights on product acceptance and use.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the PK of inhaled CBD, administered as standardized regimen (fixed number of puffs) and administered as non-standardized puff regimen (i.e. *ad libitum*) in healthy adult male and female participants.	PK Parameters for CBD: • Plasma CBD $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{ext}$, C_{max}, T_{max}, $T_{½\ el}$, K_{el}, CL/F, Vz/F
Secondary	
Pharmacokinetics: • To assess the PK of CBD metabolites (7-OH-CBD and 7-COOH-CBD), as well as tetrahydrocannabinol (THC) and its metabolites (11-OH- THC and	PK parameters for CBD metabolites (i.e. 7-OH-CBD and 7-COOH-CBD), for THC and for THC metabolites (i.e. 11-OH-THC and 11-COOH-THC):

Objectives	Endpoints
11-COOH-THC) following standardized (fixed number of puffs) and non-standardized (*ad libitum*) administration.	• Plasma $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{ext}$, C_{max}, T_{max}, $T_{½\ el}$ and Kel
Safety and Tolerability: • To evaluate the safety and tolerability of CBD inhaled via an HHnB device, following standardized (fixed number of puffs) and non-standardized (*ad libitum*) administration.	• Incidence and frequency of treatment-emergent adverse events (TEAEs), and AE of special interest (AESI) • Vital signs measurements changes from baseline (blood pressure, heart rate, respiration rate, and body temperature (ear measurement)) • Cough assessment (number, duration, intensity of cough) • Change from baseline in overall hematological/biochemistry parameters • Liver function (liver enzymes, total bilirubin, phosphatase alkaline) • 12-lead electrocardiogram (ECG) recordings • Respiratory (spirometry, FCOHb, exhaled CO) • Change from baseline in Visual oral inspection (OMAS score)
Exploratory Objectives	
• To assess product effect and perception. • To assess the remaining CBD in the stick and mouthpiece after use. • To assess human puffing topography parameters. • Evaluate variability in puffing pattern across dosages.	• Product effect evaluation, using a Product Effect Questionnaire • Remaining amount of CBD in stick and mouthpiece after use • Human puffing topography measured with a SPA-M device

Overall Design Synopsis:

This is a single center, Phase 1, open-label study to assess the PK, safety and tolerability of CBD (up to 20% CBD/stick) inhaled via an HHnB device.

Forty (40) male or female participants who are occasional users of cannabis will receive CBD (1 stick for each administration) in a standardized followed by a non-standardized (*ad libitum*) manner.

The study will include a screening visit which will take place between Day -14 and Day -2. Eligible participants will be admitted to the clinic on Day -1 and receive the study product in a standardized manner on Day 1 and in a non-standardized way on Day 4 (*ad libitum*). Washout period between administrations will be Day 2 and Day 3. Participants will be confined to the clinic until Day 5 (End of Study).

This study design includes no masking.

Brief Summary:

The purpose of this Phase 1 study is to obtain PK, safety and tolerability information on CBD in hemp sticks when inhaled via an HnB device. Exploratory endpoints on the usage, effect, and consumption pattern of the inhaled HHnB CBD will also be assessed.

After signing the informed consent form, at least 40 healthy adult male or female participants will undergo screening assessments, during an outpatient visit between Day -14 and Day -2. The results of these assessments will determine if the participants can be included in the study. Eligible participants will be admitted to the Phase 1 unit the day before the first administration of the study product (Day -1). For the next 5 days (Day 1 to Day 5), participants will remain at the site overnight and will be discharged on Day 5.

All participants will receive the same study product as follows:

- Standardized administration of HHnB CBD (1 stick): Day 1
  and
- Non-standardized administration of HHnB CBD (1 stick): Day 4

One stick of CBD will be administered via an HHnB device under standardized conditions and under non-standardized conditions (i.e. *ad libitum*) on two different study days separated by a wash out period (Day 2 and Day 3).

Assessments will include but not limited to physical examination, vital signs, urinalysis, blood draws for safety laboratory and PK, ECG, spirometry, and pregnancy tests. Participants will also be provided with a questionnaire to assess the effects of the inhaled CBD and more in general their CBD consumption habits. Safety and tolerability of the study product will be assessed throughout the study.

PK assessments will be performed from pre-dose up to 72 h after the start of standardized dosing (Day 1) and from pre-dose up to 6 h after the start of non-standardized dosing (Day 4).

Study Product and Product Form:

The study product will be administered in the form of a hemp stick using an HnB device. The main substance of the study product is up to 20% CBD, whereas THC is present at less than 1%.

Condition/Disease:

Healthy volunteers.

Study Duration:

Maximum study duration for each participant will be 19 days (including a maximum of 13 days for the screening visit, 1 day for admission and 5 days for the study procedures).

Each study participant will undergo the following phases and procedures:

- **Screening and admission phase**
  - Screening (Visit 1): between Day -14 and Day -2
  - Admission (Visit 2): Day -1
- **Interventional phase**
  - Standardized administration (Visit 3): Day 1
  - Assessments and washout (Visit 4): Day 2 and Day 3
  - Non-standardized administration (Visit 5): Day 4
- **Final phase**
  - Discharge and end of study (Visit 6): Day 5. In case of early discontinuation, discontinued participants will undergo an early termination visit (ETV).

Visit Frequency:

Each participant will attend a total of 6 visits (one outpatient screening visit and 5 in-patient visits from Day -1 to Day 5).

After a screening visit and confirmation of eligibility, participants will be confined for 5 continuous nights to the Phase 1 unit, from Day -1 until discharge on Day 5.

Number of Participants:

The number of participants to be enrolled in the study (N= 40) was selected to allow PK data interpretation, considering the anticipated high interindividual variability both for CBD metabolism and for vaping patterns. No sample size calculation was performed due to the exploratory nature of this study.

1.2. Schema

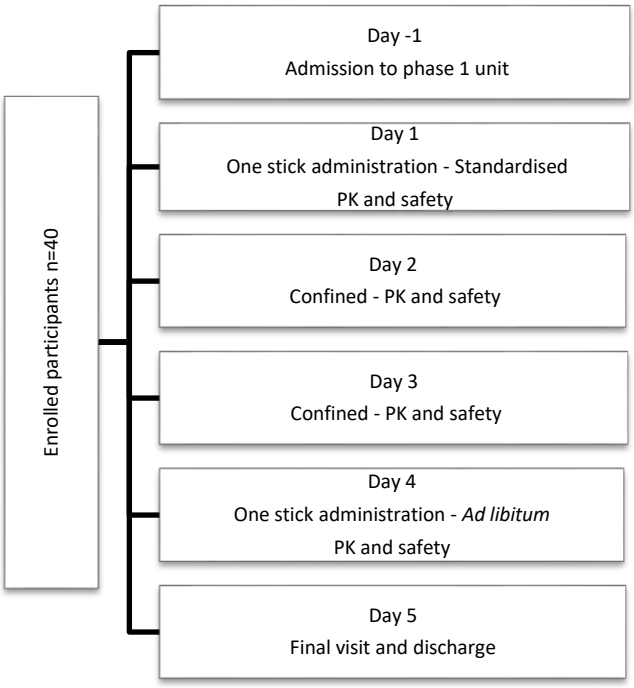


Figure 1. Study Flow Chart

1.3. Schedule of Activities (SoA)

Table 1. Schedule of Assessments

	Study Stage	Screening	Admission	Standardized product administration					Non-standardized product administration			Final visit /ETV
	Study Day	-14 to -2	-1	1			2	3	4			5
				Before	Adm	After			Before	Adm	After	
1	Informed consent	x										
2	Inclusion/exclusion criteria	x	x									
3	Demographic data/Lifestyle/Medical and surgical history	x										
4	History of cannabis use	x										
5	Prior medications	x										
6	Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
7	Admission in Phase 1 unit		x									
8	Discharge from Phase 1 unit											x
9	Ambulatory visit	x										
10	Physical examination	x										x
11	Body measurements (height, weight, BMI)	x										x (BW only)
12	C-SSRS	x										x
13	Serology tests	x										
14	Clinical laboratory tests (hematology and biochemistry)	x										x
15	Urinalysis	x										
16	Pregnancy test serum	x										
17	Pregnancy test urine		x									
18	Visual oral inspection/OMAS			x		x	x	x	x		x	x
19	Vital signs full	x	x									x
20	Vital signs brief			x		x	x	x	x		x	
21	Urine drugs test	x	x									
22	Alcohol saliva test	x	x									
23	Eligibility evaluation		x									
24	Enrolment		x									
25	Training in product use		x									
26	Standardized product administration				x							
27	Non-standardized product administration									x		
	PK and Safety											
28	PK sample collection			x	x	x	x	x	x	x	x	
29	12-lead ECG	x				x						x
30	Carboxyhemoglobin fraction			x		x	x	x	x		x	

31	**Exhaled air CO**			**x**		**x**			**x**		**x**	
32	**Spirometry**	**x**	**X (see Note 32 below)**	**x**		**x**	**x optional**		**x**		**x**	
33	**Cough assessment**				**x**	**x**				**x**	**x**	
34	**Collection of used devices**					**x**					**x**	
35	**Adverse events**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
	Exploratory											
36	**Puffing topography**				**x**							
37	**Product Effect Questionnaire**					**x Part 1**					**x Part 1 & 2**	

Abbreviations: AE = adverse event; BMI = body mass index; CBD = Cannabidiol; C-SSRS = Columbia suicidality severity rating scale; ECG = electrocardiogram; EOS = end of study; ETV = early termination visit; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; OMAS = Oral Mucositis Assessment Scale; PK = pharmacokinetic; EOT= end of treatment (prematurely); EOS= end of study (as per protocol).

10	Physical examination	Complete physical exam as per protocol at screening.
13	Serology tests	Serology tests include HBsAg, HCV antibody, and HIV antigen and antibody.
16	Pregnancy test serum	A serum pregnancy test will be performed at screening for all female participants
19	Vital signs full	Blood pressure, heart rate, respiration rate, and ear temperature.
20	Vital signs brief	Blood pressure, heart rate only. On days 1 and 4 at pre-dose and at 2, 4 and 6 h post-dose.
28	PK sample collection	PK sampling to be performed as follows: • Day 1: pre-dose (within 30 min of dosing) and 1, 3, 6, 10, 15, 20, 30 minutes, 1, 2, 4, 6, 8, 12, 24, 48 and 72 h after the start of the first standardized administration • Day 4: pre-dose (corresponding to the 72 h post-dose above) and at 1, 3, 6, 10, 15, 20, 30 minutes, 1, 2, 4, 6 h after the start of the first non-standardized administration
29	12-lead ECG	ECG must be done before spirometry and after the use of the stick within approximately 15 minutes.
30	CarboxiHb fraction	On day 1 and 4: before product administration and approx. 10 min and 30 min after complete use of the stick. On day 2 and 3 must be done before PK sampling,
31	Exhaled air CO	On day 1 and 4: before product administration and at approx. 10 and 30 min after complete use of the stick
32	Spirometry	Spirometry includes the reversibility test only for inclusion at screening. The test will not be repeated on Day -1, if done between Day -7 and Day -2 of screening. If the spirometry is repeated on Day -1, no reversibility test will be done. Spirometry on Day 2 is optional and should be repeated only if abnormal on Day 1 after the standardized study product administration.

2. Introduction

2.1. Study Rationale

There is limited data available to date on cannabidiol (CBD) absorption following CBD inhalation via a Hemp Heat-not-Burn (HHnB) device in humans. This Phase 1 clinical study will evaluate the PK, safety and tolerability of CBD administered via an HHnB device according to two different regimens, i.e. a standardized puffing dosing and an *ad libitum* administration (as desired by the participant). In addition, subjective effects (through a product effect questionnaire), and human puffing topography will be evaluated to provide further insights on product acceptance and use.

2.2. Background

CBD is a phyto-cannabinoid discovered in 1940 and is one of more than 110 identified cannabinoids in cannabis plants, including tetrahydrocannabinol (THC). Whilst CBD and THC come from the same plant, there are numerous differences with respect to receptor binding, target engagement and physiological effects [Stella, 2023]. To gain the benefits of CBD without the physiological effects of THC, which leads to intoxication (feeling high), cannabis products from plants with a high level of CBD and low level of THC, are potential options.

In particular, THC is psychoactive, meaning it produces the "high" associated with cannabis use. This effect occurs because THC binds to CB1 receptors in the brain and nervous system, affecting mood, perception, and cognition. It can also cause anxiety or paranoia in some users, especially at higher doses. CBD, on the other hand, is non-psychoactive. It doesn't produce a "high" and is not intoxicating.

Many cannabinoids, including THC and CBD, exhibit their physiological and pharmacological effects by engaging the endogenous cannabinoid (endocannabinoid) system. However, some cannabinoids such as CBD, have low binding affinity for these endogenous receptors and, instead, act also outside of the endocannabinoid system [Legare *et al.*, 2022; Rock *et al.*, 2012]. CBD has a broad pharmacological effect due to its interaction with many G-protein coupled receptors, including the endocannabinoid system, which are expressed on various cell types, like immune cells, osteocytes, glia, and neuronal cells [Stella, 2023]. Because of such a broad mode of action, an impact on many physiological processes, including cognition, appetite regulation, pain, mood, immune functions, and reproductive function is expected.

Following the initial focus on neurological diseases, currently CBD effects are subject of research for many diseases, (e.g. anxiety, pain, etc.) [Bilbao and Spanagel, 2022].

Currently, there are several CBD products for adult use (recreational). Various formats (tablets, cookies, gummies, lozenges, oils, vapes, etc.) are available but have limited PK characterization [MacCallum *et al.* 2023].

To date most products available on the market have utilized either an oral, topical or an inhaled route via smoking or vaporization. A previous Phase 1 clinical study [Devinsky *et al.*, 2021] reported that the maximum CBD plasma concentration for the inhaled CBD was reached between 2.5 to 5 minutes. CBD inhalation is characterized with a quick onset of action of 5–10 min, lasting an average of 1–4 h [MacCallum *et al.*, 2022].

Heat-not-burn (HnB) technology represents a significant innovation in the field of tobacco and cannabis/hemp consumption compared to smoking and e-vaporizers. Traditional smoking methods involve combustion, that produces a range of toxic substances [Graves *et al.*, 2020].

Vaporizers typically heat a synthetic fluid (e-juice or e-liquid) composed of propylene glycol (PG) or vegetable glycerin (VG), flavoring agents, and nicotine or cannabinoids producing harmful by-products [e.g. Muthumalage *et al.*, 2020; Love *et al.*, 2023].

In contrast, products based on heated hemp use organic matter without additives, lead to fewer harmful by-products upon heating at lower temperatures. Thus, HnB technology may offer a potentially safer experience for cannabis use compared to smoking or vaporizing. Research on the safety of HnB devices in general remains limited, with only a few studies available, mostly on tobacco use [e.g. Abrams *et al.*, 2007; Loffredo *et al.*, 2021].

The sponsor is developing an inhaled version of CBD delivered through an HnB device for non-medical use.

2.3. Benefit/Risk Assessment

CBD has been administered in clinical studies, as a medicine and in consumer products, thus its overall safety profile has been established [WHO CANNABIDIOL (CBD) Critical Review Report, 2018]. CBD has been administered via different routes, with inhalation being common.

The study aim is to develop a product that offers a safer and improved option for cannabis users. The sponsor of this study has developed an HnB technology that potentially offers a non-combustion approach by heating cannabis at lower temperatures and potentially producing fewer harmful by-products such as carbon monoxide.

Despite the promising aspects of HHnB products, there is a need for clinical studies to validate their safety. Clinical studies are essential to understand pharmacokinetics (PK) and to assess the safety aspects of the administration.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of CBD HHnB are available in the current investigator brochure.

2.3.1. Risk Assessment

Study Product

The product to be assessed in the study is CBD delivered through an HHnB device. HnB devices heat the material to a temperature that releases active compounds without burning them. At least for tobacco products, this process is believed to generate fewer harmful by-products,

potentially offering a safer alternative for users [Simonavicius *et al.*, 2019]. The risks associated with the study product are mainly associated with the potential device malfunctioning.

However, this risk is minimal and it is monitored throughout the study with appropriate study procedures in place.

Dose

The CBD dose administered in this study (up to 20 %/stick) via an HHnB device is low compared to the dose in approved CBD products (100 mg/mL) [Epidiolex SmPC, 2024]. According to the simulated data at the doses used in this study protocol, the systemic exposure after use of one stick is expected to stay within safety margins [Data on file, HnB simulation modelling January 2025]. It is expected that systemic exposures resulting from the use of one hemp stick (containing a maximum of 20 % CBD), delivered via inhalation through an HHnB device, will not exceed the daily exposures achieved with a 150 mg twice daily dose of the approved product Epidiolex®).

Active substance

The main substance of the study product is CBD, whereas the THC is present at less than 1%.

Increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed with oral administration of CBD. The present study will include healthy participants (i.e. without clinically significant illnesses) and will exclude participants with clinically significant abnormal laboratory values at screening and more specifically with elevation of AST, ALT, total bilirubin and alkaline phosphatase. Laboratory values will be monitored throughout the study duration.

Drowsiness and sedation have been reported in other clinical studies with CBD formulations [Devinsky *et al*., 2021]. In the current clinical study, participants will be confined at the Phase I clinical site during the entire study, thus will not be at risk due to driving. Participants with previous suicidal ideation and other psychiatric illnesses will be excluded. Participants will be monitored for AEs throughout the study duration.

Formulation and delivery

Dry powder formulations have been used in a number of respiratory diseases to deliver therapies to the lungs but also systemically, with an overall acceptable safety profile [Ye *et al.*, 2022]. However, there is an expected risk of cough, following inhaled formulations, and potentially bronchospasm [Chang *et al.*, 2020]. Therefore, participants with asthma and other respiratory diseases are excluded from the clinical study.

Inhalation of CBD was assessed in another study using a purified CBD extract and reported a favorable safety profile and good tolerability [Devinsky *et al.*, 2021].

Study Procedures

Standard blood sample collections will be performed to assess the primary endpoint. Blood sampling will be carried out by professional members of the clinical staff. The total volume of

blood to be withdrawn is approximately 305 mL and will not exceed the levels of a standard blood donation. The risks related to blood sampling are low and could include bleeding, dizziness, fainting, hematoma.

Procedures associated with the assessment of the eligibility criteria are commonly used in medical practice. Spirometry is performed with reversibility testing at screening, salbutamol is used as bronchodilator in this test. Salbutamol is generally well-tolerated, but like all medications, it may cause side effects. Common side effects include feeling shaky, increased or uneven heart rate, and increased blood flow to the extremities. Uncommon side effects may include headaches. Rare side effects can include muscle cramps, mouth and throat irritation, and allergic reactions such as swelling, rash, or low blood pressure.

For compliance and safety reasons, the participants of this study will be confined to the Phase 1 unit for the entire investigational period and until the assessments on the day of discharge are completed.

The administration of the study product will be conducted under direct investigator supervision. A thorough training on the use of the HHnB device and inhalation process will be performed to participants the day before first administering the study product. Re-training for the participants is foreseen in case of need.

Developmental Risks

There are no adequate data on the developmental risks associated with the administration of CBD oral solution in pregnant women. However, the administration of CBD to pregnant rats demonstrated evidence of developmental toxicity including increased embryofetal mortality and decreased pup weight. Additionally, there are no available data on the presence of CBD or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production [Ujváry and Hanuŝ, 2016].

Although blood exposure is expected to be low considering the low CBD dose administered in this study, pregnant or lactating women are excluded from the study. Fertile women, male participants with a fertile female partner and female partners of male participants must use an adequate birth control method (see Section 5.1.1).

2.3.2. Benefit Assessment

There may be no immediate benefits anticipated for the participants in this study following the 2 administrations (on Day 1 and Day 4) of a low dose of CBD. The participants will benefit from medical assessment and complete physical and laboratory check-ups as part of the study procedures. In addition, the data from this study will contribute to the understanding of the PK profile of CBD when inhaled through an HHnB device for non-medical use.

2.3.3. Overall Benefit Risk Conclusion

Taking into account the low risks related to the administration of low doses of CBD and the measures applied to minimize risk to participants in this study, the overall benefit / risk of the study is deemed positive.

3. Objectives and Endpoints

The objectives and their corresponding endpoints are given in Table 2.

Table 2. Overview on Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PK of inhaled CBD, administered as standardized regimen (fixed number of puffs) and administered as non-standardized puff regimen (i.e. *ad libitum*) in healthy adult male and female participants.	PK Parameters for CBD: • Plasma CBD $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{ext}$, C_{max}, T_{max}, $T_{½\ el}$, K_{el}, CL/F, Vz/F
Secondary	
Pharmacokinetics: • To assess the PK of CBD metabolites (7-OH-CBD and 7-COOH-CBD), as well as THC and its metabolites (11-OH- THC and 11-COOH-THC) following standardized (fixed number of puffs) and non-standardized (*ad libitum*) administration.	PK parameters for CBD metabolites (i.e. 7-OH-CBD and 7-COOH-CBD), for THC and for THC metabolites (i.e. 11-OH-THC and 11-COOH-THC): • Plasma $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{ext}$, C_{max}, T_{max}, $T_{½\ el}$, Kel
Safety and Tolerability: • To evaluate the safety and tolerability of CBD inhaled via an HHnB device, following standardized (fixed number of puffs) and non-standardized (*ad libitum*) administration.	• Incidence and frequency of treatment-emergent adverse events (TEAEs), and AE of special interest (AESI) • Vital signs measurements changes from baseline (blood pressure, heart rate, respiration rate, and body temperature (ear measurement)) • Cough assessment (number, duration, intensity of cough) • Change from baseline in overall hematological/biochemistry parameters

Objectives	Endpoints
	• Liver function (liver enzymes, total bilirubin, phosphatase alkaline) • 12-lead electrocardiogram (ECG) recordings • Respiratory tests (spirometry, FCOHb, exhaled CO) • Change from baseline in Visual oral inspection (OMAS scores)
Exploratory Objectives	
• To assess product effect and perception. • To assess the remaining CBD in the stick and mouthpiece after use. • To assess human puffing topography parameters. • Evaluate variability in puffing pattern across dosages.	• Product effect evaluation, using a Product Effect Questionnaire • Remaining amount of CBD in stick and mouthpiece after use • Human puffing topography measured with a SPA-M device

4. Study Design

4.1. Overall Design

This is a single center, Phase 1, open-label study to assess the PK of CBD (up to 20% CBD/stick) inhaled via an HHnB device. This is a single-arm study, where all participants will receive the same study product for the duration of the study. The aims of the study are to evaluate the PK, safety and tolerability of CBD and THC and their metabolites. Exploratory objectives will also be assessed, evaluating the product effect, remaining amount of CBD in devices and human puffing topography.

The study will include 40 healthy male and female volunteers who are occasional users of cannabis.

All participants will receive the same study products as follows:

- Standardized administration of CBD (1 stick): Day 1
  and
- Non-standardized administration of CBD (1 stick): Day 4

No control is foreseen for this descriptive PK study. Randomization is therefore not applicable.

The study will include a screening visit between Day -14 and Day -2. After signing the informed consent and meeting the eligibility criteria for the study, participants will come to the clinic on Day -1, will be confined to the clinic for 5 nights and be discharged on Day 5 in the morning (Final visit).

One stick of hemp will be administered via an HnB device under standardized and one stick under non-standardized conditions (i.e. *ad libitum*) on two different study days. PK will be performed from pre-dose (Day 1) up to 72 h after the start of standardized administration and up to 6 h after the start of the non-standardized administration (Day 4).

Safety and tolerability of the study product will be assessed throughout the study.

Maximum study duration for each participant will be 19 days (including a maximum of 13 days for the screening visit, 1 day for admission and 5 days study procedures).

A flow chart for the study is given in Figure 1.

Details of the schedule of assessments (SoA, Section 1.3) are given in Section 8.

4.2. Scientific Rationale for Study Design

This is an exploratory study to assess the PK of CBD when inhaled via an HHnB device in healthy participants. The product which will be tested contains less than 1% THC and could be marketed legally in Switzerland [Swissmedic, 2023].

The primary objective of the study is to characterize the PK and safety profile of CBD when inhaled via an HHnB device according to two different administration regimens. The PK of CBD metabolites as well as THC and its metabolites is being evaluated as a secondary objective.

The number of participants to be enrolled in the study (N= 40) was selected to allow PK data interpretation, considering the anticipated high interindividual variability both for CBD metabolism and for vaping patterns. No sample size calculation was performed due to the exploratory nature of this study.

The study will enroll healthy volunteers, in line with the standard population for a Phase 1 study, taking also into consideration the risks possibly linked to first time exposure to CBD inhalation. A risk assessment is presented in Section 2.3.

Study participants must be occasional smokers of cannabis in order to avoid including cannabis naive participants or participants that developed tolerance to the effects of cannabis (chronic users).

Up to approximately 20 % is the amount of CBD in one stick. Two regimens i.e. standardized (fixed number of puffs) and non-standardized (*ad libitum*) are investigated.

The standardized regimen with consistent inhaling procedure among participants is applied to minimize variability in the context of this early phase study. The *ad libitum* inhaling procedure will provide information on CBD PK when participants inhale CBD via the HHnB device as desired (according to their personal choice) until the device will switch off. The *ad libitum* cohort is introduced in order to assess PK, safety and tolerability when the device is used closer to a real-world setting.

Sampling timepoints for determination of CBD concentrations were selected to ensure reliable estimation of PK parameters. Frequent sampling during the first 15 minutes will allow to assess T_{max} which is expected to be around 2.5-5 minutes. The washout period between the two administration regimens was calculated based on the inhaled plasma CBD estimated half-life (i.e. 2 h) [Data on file, HnB simulation modelling January 2025].

CBD is metabolized by CYP2C19 and 3A4 enzymes, therefore, participants who consume any drug known to induce or inhibit hepatic drug metabolism are excluded from the study.

The participants of this study will be admitted to the Phase 1 Unit for the entire investigational period and until the assessments on the day of discharge are completed.

The administration of the study products will be conducted under investigator supervision.

4.2.1. Patient Input into Design

This is an early phase study with a standard design, for a product intended for consumer use. Therefore, no patient input was sought.

4.3. Justification for Dose

The study product is not intended to provide a therapeutic effect, hence a therapeutic dose justification is not applicable. A dose of up to 20 % of CBD has been considered sufficient to provide a satisfactory experience with an HHnB device and is anticipated to lead to plasma blood levels which are within safety margins.

4.4. End-of-Study Definition

The end of the study (EOS) is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if the participant has completed the two dosing periods including the EOS (or final) visit.

5. Study Population

It is planned to enroll 40 eligible male or female healthy participants in this study.

5.1.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Sex, Age, BMI, tobacco use

1. Male or female non-tobacco smokers or mild tobacco smokers (1-10 cigarettes or nicotine e-cigarette per day) that are willing to comply with the study restrictions related to smoking.
2. Age ≥18 and ≤55 years of age.
3. BMI ≥ 18.5 and ≤ 30.0 kg/m^2.

Type of Participant and Disease Characteristics

4. Occasional smokers of cannabis (i.e. individuals who smoked cannabis products maximum once a week in the past 3 months) willing to refrain from cannabis products for 2 weeks prior to Day -1.
5. Healthy participants, defined as:
    - The absence of clinically significant illness and surgery within 4 weeks prior to dosing.
    - The absence of clinically significant history of neurological, endocrine, cardiovascular, dermatological, hematological, immunological, psychiatric (e.g., history of major depression or (C-SSRS) score above Type 1 ideation), gastrointestinal, renal, hepatic, and metabolic disease (e.g. diabetes) as well as any other medical history event considered clinically significant in the opinion of the Investigator.
    - The absence of clinically significant history of respiratory (e.g., significant history of acute or chronic bronchospastic) disease (including asthma and chronic obstructive pulmonary disease treated or not treated).
    - The absence of any history of diagnosis of any other pulmonary disease that in the judgment of the investigator is likely to be exacerbated by inhalation of CBD from the device.

Sex and Contraceptive/Barrier Requirements

6. Female participants of childbearing potential must have a negative pregnancy test result before administration of the study product and must agree not to donate ova (or egg(s)) for at least 30 days after the last dose of study product administration.

7. Female participants of non-childbearing potential must be:
    a. At least 12 months of spontaneous amenorrhea; or
    b. postsurgically sterile (documented bilateral oophorectomy with or without hysterectomy) for at least 3 months prior to dosing.
8. Female participants of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized for at least 3 months prior to dosing) must be willing to use two of the following acceptable contraceptive methods throughout the study and for 30 days after the last dose:
    a. simultaneous use of hormonal contraceptive (e.g., oral, patch, depot injection, implant, vaginal ring, intrauterine device) or non-hormonal intrauterine device used for at least 4 weeks prior to dosing (must agree to use the same contraceptive throughout the study) and condom for the male partner;
    b. simultaneous use of diaphragm or cervical cap with spermicide and condom for the male partner, started at least 21 days prior to dosing.
    c. True abstinence (i.e., refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), lactational amenorrhea, and withdrawal are not acceptable.
9. Male participants who are not vasectomized for at least 3 months prior to dosing, and who are sexually active with a female partner of childbearing potential must be willing to use one of the following acceptable contraceptive methods from the first dose and for 90 days after the last dose:
    a. simultaneous use of condom and hormonal contraceptive (e.g., oral, patch, depot injection, implant, vaginal ring, intrauterine device) or non-hormonal intrauterine device used for at least 4 weeks prior to sexual intercourse for the female partner;
    b. simultaneous use of condom and a diaphragm or cervical cap with spermicide for the female partner.
10. Male participants (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from the first dose until 90 days after the last dose.
11. Male participants must be willing not to donate sperm from the first dose until 90 days after the last dose.

Informed Consent

12. Able to understand the study procedures, restrictions and visit schedule and provide signed informed consent to participate in the study.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Any clinically significant abnormal finding at physical examination at screening that could interfere with the objectives of the study.
2. Clinically significant abnormal laboratory test results which in the opinion of the investigator could prevent participation in the study, at screening.
3. Positive serology test results for HBsAg, HCV antibody, or HIV antigen and antibody at screening
4. Positive pregnancy test (at screening or Day -1) or lactating female participant.
5. Positive urine drug (including cannabis related substances) screen and alcohol saliva test at screening or Day -1.
6. Participant with abnormal lung function defined by spirometry testing such as: FEV1 < 80% of predicted normal value OR FEV1/FVC ratio < 0.70 at screening OR with post-bronchodilator FEV1 ≥ 12% increase from pre-bronchodilator values (Reversibility testing).
7. Clinically significant ECG abnormalities at screening.
8. Clinically significant vital signs abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, resting diastolic blood pressure lower than 50 or over 90 mmHg, or resting heart rate less than 50 or over 100 bpm) at screening.
9. History of cannabis use disorder (i.e. mental health condition in which there is a problematic pattern of cannabis use that causes distress or impairs life) within 1 year prior to screening or of hard products (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening.
10. History of alcohol use disorder (defined as a problematic pattern of alcohol use leading to clinically significant life impairment or distress) within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%).
11. Known allergic reaction to CBD, or other related products, or to any excipient in the formulation.

12. Any of the following laboratory parameters above 1.5 x upper limit of normal (ULN) at screening or baseline (Day -1): aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin. Analyses may be repeated once for confirmation.
13. History of liver disease or hepatic dysfunction (including cirrhosis), hyperbilirubinemia, jaundice, or elevated liver enzymes.
14. History of epilepsy, major depression, schizophrenia or any other psychotic disorders.

Prior/Concomitant Therapy

15. Use of medications for the timeframes specified below, except for medications exempted by the investigator on a case-by-case basis because they are judged unlikely to affect the PK profile of the study product or participant's safety (e.g., topical drug products without significant systemic absorption):
    a. current use of clobazam or valproate sodium, or use within 4 weeks prior to dosing; no other prescription medication from 14 days and over the counter (OTC) products from 7 days prior to dosing and throughout the study;
    b. depot injection or implant within 3 months prior to dosing (excluding depot injection for contraception);
    c. any product known to induce or inhibit CYP3A4, CYP2C9 or CYP2C19 mediated hepatic drug metabolism, including St. John's wort and cytochrome p450 (CYP) substrates of CYP1A2 (e.g., theophylline) and CYP2B6 (e.g., bupropion, efavirenz), CYP2C8 (e.g., montelukast), CYP2C9 (e.g. phenytoin), CYP2C19 (e.g., diazepam) and uridine 5' diphospho-glucuronosyltransferase (UGT) substrates of UGT1A9 (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) within 30 days prior to dosing until the last PK blood draw;
    d. any vaccine, including COVID-19 vaccine, within 14 days prior to dosing;
    e. OTC medications and natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to dosing, with the exception of the occasional use of paracetamol (acetaminophen) (up to 2 g daily);
    f. any food or beverages containing grapefruit, starfruit, Seville orange, pomegranate, pineapple, or pomelo from 7 days prior to dosing until the last PK blood draw;
    g. any food containing poppy seeds from 24 hours prior to admission until the last PK blood draw;

h. any alcohol-based products from 24 hours prior to admission until the last PK blood draw;

Prior/Concurrent Clinical Study Experience

16. Participation in the evaluation of any investigational product for 3 months before this study. The 3-month interval is calculated as the time between the first calendar day of the month that follows the last visit of the previous study and the first day of the present study.

Other Exclusion Criteria

17. Blood donations for 3 months before screening.
18. Any reason which, in the opinion of the investigator, would prevent the participant or make him/her inappropriate from participating in the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

A standard diet will be provided for the participants for the whole confinement period. Participants are not allowed to bring their own food or beverages to the investigational site.

Meals will be served according to the schedules provided here.

On Day -1 (admission) evening all participants will receive a standardized low-fat dinner.

On Day 1 and Day 4, participants will be allowed to have a low-fat breakfast at approximately 1 to 2 hours before they start using the study product. Standardized lunch and dinner will be served at approximately 5 h and 12 h post-dose.

On Days 2 and 3, standardized breakfast, lunch and dinner will be served at about 08:00, 13:00 and 20:00, respectively.

Additional light snacks, fruits, and raw vegetables can be distributed to the participants without restrictions at any time during confinement (except during the product use periods) as long as they comply with the standard diet. Consumption of water is allowed as desired. In addition, on Days 1 and 4, in order to maintain adequate hydration, the participants will be encouraged to drink at least 150 mL of mineral water every 2 h for 5 h post-dose, starting at 1 h post-dose.

One cup of coffee or tea will be allowed after each meal only. Any other coffee, tea or food containing xanthines (i.e. cola, chocolate, etc.) will be prohibited during confinement. Decaffeinated and non-theine products are allowed.

Alcohol based products and food containing poppy seeds will not be allowed from 24 h prior to admission until the end of confinement.

Participants should refrain from ingesting food or beverages containing grapefruit, starfruit, Seville-type (sour) oranges, pomegranate, pineapple or pomelo from 7 days before dosing until study end. Consumption of quinine-containing drinks (e.g., tonic water) is not allowed.

The same menu and meal schedule will be administered uniformly for all participants.

5.3.2. Drugs, Nicotine and Alcohol

Participants will be required to fulfill the requirements listed under exclusion criteria in Section 5.2.

Electronic cigarettes with nicotine will be considered as conventional cigarettes and similarly managed. Electronic cigarettes without nicotine will be forbidden during confinement.

On dosing days (Day 1 and Day 4), smoking is not allowed from 12 hours before dosing until the last study assessment of the day.

On the other study days at the Phase I Unit, one cigarette after each meal will be allowed.

5.3.3. Activity

Participants will abstain from vigorous activity from 3 days before admission to the clinic until the end of confinement. During confinement, routine ambulant daily activities will be recommended, except for at least 2 hours after each study product use (see Section 5.3.4).

5.3.4. Other Restrictions

During the study, the participants will be confined in the clinical Phase 1 unit from the evening prior to dosing (study Day -1; Admission) until the morning of Day 5.

For safety reasons, participants are recommended to remain seated or semi-reclined and avoid lying down or sleeping for at least 2 h after each study product use. Failure of the participant to comply with these requirements will not constitute a deviation from the protocol if it is medically necessary, required for procedures, or for physiological needs. When appropriate, participants will be accompanied by a staff member while walking.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently enrolled in the study (see definitions in Section 10.2).

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure (screen failure details), eligibility criteria, and any AE or SAE reported after signing ICF.

Individuals who do not meet the criteria for participation in this study during the first screening period may be considered for rescreening only after consultation with the sponsor. Only a single rescreening of previous screen failures is allowed.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Product

Not applicable.

6. Study Product and Concomitant Therapy

6.1. Study Product Administered

Study product: CBD HHnB stick with up to 20% CBD.

Details of the study product for this study are given in Table 3 and Table 4. More details about the study product are available in the Investigator's Brochure (IB).

Table 3. Study Products Administered

Product Label	**Inhaled CBD**
Product Name	Cannabidiol Hemp Heat-not-Burn (HHnB)
Product Description	Cannabidiol (CBD) for inhalation via HHnB device
Type	Cannabis, product-device combination
Dose Formulation	1 stick of up to 20 %
Unit Dose Strength(s)	Up to 20 % CBD/stick
Dose regimens	Day 1: standardized inhalation (see Table 4) Day 4: non-standardized (*ad libitum*) inhalation (see Table 4)
Route of Administration	Oral inhalation
Use	Experimental
IP	Study product: CBD HHnB stick with up to 20% CBD
Sourcing	Product and device will be provided by the sponsor
Device	Hemp Heat-not-Burn (HHnB)
Packaging and Labeling	Study product will be provided as bulk and labelled according to country regulations
Current/ Former Name(s) or Alias(es)	The heating device is a Hemp Heating Device (HHnB device) to electrically heat hemp product (or stick)

Table 4. Study Product Standardized and Non-standardized Administration

Day	Standardized	Non-standardized
Day 1	Inhalation for 10 times (10 puffs) with 30 sec breaks between puffs	Not applicable
Day 4	Not applicable	*Ad libitum* inhalation until the device shuts down (6 minutes from start)

Participants will be instructed on how to use the CBD HHnB study product. Administration will be supervised by the clinical staff.

For the standardized administration:

- The participants will be asked to inhale 10 times (10 puffs) with 30 sec breaks between puffs.
- Each puff will consist of a slow steady draw of 5 seconds (similarly to smoking a cigarette) followed by 30 seconds of pause between puffs.
- The device will automatically shut down at 6 minutes.
- A Smoking Puff Analyzer - Mobile (SPA-M) will be associated with the stick for measuring the topography.

For non-standardized administration:

- The participants will be asked to inhale from the stick *ad libitum*.
- The participants will be allowed to inhale from the stick as desired without restrictions (e.g. no limitation on the duration of the inhalation or pause between puffs) until the device shuts down at 6 minutes.

6.1.1. Hemp Heat not Burn (HHnB) device

The device in this study is a re-usable HHnB device for investigational use.

The device works by inserting a stick in the device. Once the HHnB device is switched on, it reaches the operating temperature within 20 sec. The device will switch off automatically after 6 minutes of use. All device deficiencies (including malfunction, use error and inadequate labelling) will be documented and reported by the investigator throughout the clinical study and appropriately managed by the sponsor. The process of recording and reporting device deficiencies for the site staff is detailed in the pharmacy manual.

An inhaler use training will be performed by the sponsor/sponsor representatives to the site staff (details will be found in the training manual). The investigator and/or site staff will train the participants in the study. Retraining of the participants is foreseen in case of need.

6.2. Preparation, Handling, Storage, and Accountability

The Sponsor must confirm that appropriate conditions (e.g., temperature) have been maintained during transit for all study products delivered, and any discrepancies are reported and resolved before authorizing the Investigator use of the study product.

Only participants included in the study will receive the study product and only authorized site staff may supply, prepare or administer the study product.

All study products must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, or authorized site staff is responsible for the study product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records) at site.

All used and unused study products (sticks and HHnB devices) and all used and unused SPA-M devices (including their accessories if any) will be returned to the sponsor after completion of the study.

6.3. Assignment to Study Product

This is a one arm study. All participants will be assigned to the same study product throughout the study. Randomization is therefore not applicable.

6.4. Blinding

This study will be an open-label study, with no blinding necessary. The open-label design is not expected to bias the study objectives, due to the objective nature of the PK assessments.

6.5. Study Product Compliance

Each individual study product for the participants will be prepared at the site from a bulk supply of hemp sticks and HnB devices and the preparation of each dose will be confirmed by a second member of the study site staff.

Participants will be provided with the study product by the investigator or designee and will self-administer the product at the site under supervision of the clinical staff.

When participants are dosed at the site under standardized or non-standardized conditions, they will receive the study product directly from the investigator or designee, under medical supervision, therefore compliance is expected unless safety issues will arise that will require study product interruption.

For standardized administration, the time of start and end of the inhalation process (i.e. time of initiation of the first puff and last puff) will be recorded by the SPA-M device and reported in the eCRF from the source data. For non-standardized administration, the time of start and end of the inhalation process (i.e. time of initiation of the first puff and last puff) will be recorded by the study staff and the number of puffs will be recorded by the participant and reported by study staff in the eCRF from the source data. Further information on the SPA-M device functioning and timing recording in the source data will be provided in the training manual for the site staff. If any temporary or permanent interruption, this should be recorded alongside the time of the interruption and the reason for the interruption or discontinuation alongside the number of puffs until the point of interruption. These data will be recorded both in the source data and eCRF.

A record of the quantity of the HnB devices and hemp sticks dispensed to each participant must be maintained and reconciled with the study product received in the compliance records.

6.5.1. Post-use Device Assessment

The used HnB device and hemp stick will be collected and placed into individual pre-labelled polyethylene bags for shipment to the sponsor's assigned facility for assessment.

Post-use device assessment will be performed by the sponsor to confirm product delivery (by assessing device post use, capsules post use, etc.).

6.6. Dose Modification

No dose modification is expected in this study.

6.6.1. Retreatment Criteria

No retreatment is expected in this study.

6.7. Continued Access to Study Product after the End of the Study

There will be no access to the study product after the end of the study.

6.8. Treatment of Overdose

There is no expected overdose due to the controlled administration of the study product by the site staff and the low dose of CBD administered.

Participants will be monitored for AE/SAE and laboratory abnormalities throughout the study.

6.9. Prior and Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) as specified in the eligibility criteria and, with the exception of the occasional use of paracetamol (acetaminophen) (up to 2 g daily).

No other concomitant medications will be allowed during the study, with the exception of:

- hormonal contraceptives,
- medications required for the medical management of an AE, and
  medications exempted by the investigator on a case-by-case basis that are judged unlikely to affect the PK profile of the study product or participant safety (e.g., topical drug products without significant systemic absorption).

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Medications taken in the previous 3 months prior to signing the informed consent and no longer ongoing at the time of ICF signature will be documented as prior medications. Any medication continued or newly initiated after informed consent signature will be documented as concomitant medication. Any prior or concomitant medication use, other than the allowed medications stated above, will be reviewed and evaluated on a case-by-case basis by the investigator (in consultation with the sponsor, if needed) to determine if they affect a participant's eligibility or continued participation in the study, or for potential impact on the study results.

6.9.1. Rescue Medicine

No rescue medication is foreseen in this study.

7. Discontinuation of Study Product and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Product

In rare instances, it may be necessary for a participant to permanently discontinue the study product. If the study product is permanently discontinued, the participant should, if possible, remain in the study to be evaluated for the remaining assessments until the final visit at Day 5 or if not possible an early termination visit (ETV) will be performed as early as possible except in case of informed consent withdrawal (See the SoA in Section 1.3 for data to be collected at the ETV). If the study product is discontinued due to safety reasons, this must be recorded as an AE.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of the study product for abnormal liver tests is required by the investigator in the presence of abnormal liver chemistries if the investigator believes that it is in the best interest of the participant.

For further information please refer to Section 9.2.6.

7.1.2. QTc Stopping Criteria

Not applicable in this study.

7.1.3. Temporary Discontinuation

Not applicable.

7.1.4. Rechallenge

Not applicable.

7.1.4.1. Study Product Restart or Rechallenge After Liver Stopping Criteria Are Met

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted.

The participant will be permanently discontinued from the study product and the study at that time.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up, if the participant fails to return for scheduled visits and the site is unable to contact the participant.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source documents.
- Should the participant continue to be unreachable, the participant will be considered lost to follow-up.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA, Section 1.3. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Unless otherwise specified, study procedures will be conducted in accordance with clinical site SOPs. From screening through EOS, participants will undergo study procedures at pre-defined times as specified in the SoA (Section 1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.

A written informed consent will be obtained before any study assessment or procedure. The first participant first visit (FPFV) is defined as the first date the first participant signs his/her first informed consent to participate in activities that are protocol directed interventions. The last participant last visit (LPLV) is defined as the last visit of the last participant, i.e. the last visit at the clinical site (or telephone follow-up, if applicable), independently of the fact that the participant is a completer or a withdrawn participant.

Each participant will attend a total of 6 visits (one outpatient visit and 5 in-patient visits). Each study participant will undergo the following phases and procedures:

- **Screening and admission phase**
  - Screening (Visit 1): between Day -14 and Day -2
  - Admission (Visit 2): Day -1
- **Interventional phase**
  - Standardized administration (Visit 3): Day 1
  - Assessments and washout (Visit 4): Day 2 and Day 3
  - Non-standardized administration (Visit 5): Day 4
- **Final phase**
  - Discharge and end of study (Visit 6): Day 5.

In case of early discontinuation, discontinued participants will undergo an ETV.

During the study the following **blood volumes** will be collected from each participant:

For routine safety laboratories analyses:
Screening visit: 12 mL
Final visit/ETV: 12 mL

For PK analysis:
28 samples x up to 10 mL = up to 280 mL

For venous COHb analysis: 6 samples x 100 µL = 600 µL

The maximum amount of blood collected from each participant over the duration of the study, will not exceed approximately **305 mL** (not exceeding a normal blood donation).

8.1. Administrative Procedures

Participants must provide voluntary written informed consent prior to initiation of any study procedures, including screening assessments.

The investigator or designee will be on site on Day 1 and Day 4 for the administration of the study product and until 4 hours post-dose and will be available on call for the remainder of the study. If necessary, the investigator or designee at the clinical site or a healthcare professional in a nearby hospital will administer treatment for any AE(s) as per medical need. A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

After signing the informed consent form, patients will undergo the screening investigations and procedures as detailed in the SoA (Section 1.3) and in the sections below.

8.2. Efficacy Assessments

No efficacy assessments are foreseen in this study.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA. Participants will be monitored for AEs by the clinical staff throughout the study.

Safety assessments scheduled during the study will be repeated according to the clinical site SOPs or upon request from the investigator or designee. Any abnormal repeated measurement will be evaluated and repeated, if judged necessary. Further action may be taken upon the investigator or designee's request.

Significant findings/illnesses, identified during any of the safety assessments described in this section after commencement of study product that meet the definition of an AE (see Section 9.2), will be recorded in the participant source documents and eCRF.

8.3.1. Physical Examinations

A complete physical examination will include assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

Information about the physical examination will be recorded by the investigator. Any abnormalities will be recorded.

Significant findings/illnesses, reported after the start of the study and that meet the definition of an AE (see Section 9.2), will be recorded in the participant source documents.

Date of the physical examination, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) will be reported in the individual CRFs.

8.3.2. Body Measurements

Participants will be weighed (kg) lightly clothed without shoes.

Height will be measured at screening only and BMI will be recorded at screening. BMI will be calculated as weight [kg]/(height [m] x height [m]).

8.3.3. Vital Signs

Vital signs will be measured at the timepoints specified in the SoA, after 5 minutes rest in a supine position at all times.

Vital signs for full assessment will include: systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature (ear measurement).

Vital signs for brief assessment will include: systolic and diastolic blood pressure and heart rate.

8.3.4. Electrocardiograms

ECGs must be done before spirometry measurement, when applicable.

Standard triplicate 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

Date/time of the ECG recording, parameter recordings, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) will be reported in the individual CRFs. All clinically significant abnormalities after the screening visit will be recorded as AEs. ECG recordings will be kept as source data at the site.

8.3.5. Clinical Safety Laboratory Tests

Two samples of blood (total volume 12 mL) and one sample of urine for clinical laboratory assessments will be collected at the time points specified in Section 1.3.

The following laboratory analyses will be performed:

HAEMATOLOGY

- Leukocytes and leukocyte differential count, erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, thrombocytes.

BLOOD CHEMISTRY

- **Electrolytes:** sodium, potassium, calcium, chloride, inorganic phosphorus
- **Enzymes:** alkaline phosphatase, γ-GT, AST, ALT
- **Substrates/metabolites:** total bilirubin, creatinine, glucose, urea, uric acid, total cholesterol, triglycerides
- **Proteins:** total proteins

SERUM VIROLOGY

- **Hepatitis B** (HBs antigen), **Hepatitis C** (HCV antibodies), **HIV 1/2** (HIV Ag/Ab combo)

URINE ANALYSIS

- **Urine chemical analysis** (stick)**:** pH, specific weight, appearance, color, nitrites, proteins, glucose, urobilinogen, bilirubin, ketones, hematic pigments, leukocytes
- **Urine sediment** (analysis performed only if positive): leukocytes, erythrocytes, flat cells, round cells, crystals, cylinders, mucus, bacteria, glomerular erythrocytes

OTHER ANALYSES

- **Serum Pregnancy test** – all women

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study will be subject to investigator decision if they need to be repeated or not.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

The laboratory analyses listed above will be performed at Unilabs SA, Switzerland.

The following tests will be performed at the clinical site:

- Urine pregnancy test for all women

- Urine drug screening test, including cannabis related substances
- Alcohol saliva test

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Assessment of suicidal ideation, intensity of ideation and suicidal behavior (SIB) will be performed using the Columbia Suicidality Severity Rating Scale (C-SSRS) (Section 11.9, Appendix 9), a suicidal ideation and behavior rating scale to evaluate suicide risk.

The C-SSRS *baseline lifetime scale* will be used to assess SIB at screening for eligibility assessment. The C-SSRS *since last visit* scale will be used to assess SIB at the other visits as per SoA (Section 1.3).

The scale will be administered by an authorized member of the clinical team to the participant and completed on paper. Data will be transcribed in the eCRF.

Participants will be confined at the clinical site throughout the treatment period and will be monitored appropriately and observed closely for SIB or any other unusual changes in behavior. If the investigator determines that a participant is at risk of suicide or self-harm, appropriate measures to ensure the participant's safety and obtain mental health evaluation must be implemented. In such case, the participant must immediately be discontinued from the study product. The event should be recorded as either an AE or a SAE, as determined by the investigator, and reported appropriately (within 24 h, if SAE) to the sponsor.

8.3.7. Respiratory Tests

Spirometry, carboxyhemoglobin (COHb) and exhaled CO will be performed at the time points specified in the SoA, Section 1.3.

Blood samples for venous COHb analysis (100 µL) will be collected from a forearm vein of each participant using a syringe for hemogas analysis.

COHb and exhaled CO will be measured using specific instruments.

In particular, for COHb the instrument will measure FCOHb (also commonly referred to as COHb), i.e. the fraction of total hemoglobin (ctHb) which is present as COHb. By convention the fraction is expressed as a percentage (%), thus: FCOHb(%) = cCOHb/ctHb x 100.

8.3.8. Visual Oral Inspection

Participants will undergo checks for mucosal irritation, which will be quantified using the Oral Mucositis Assessment Scale (OMAS) presented in Table 5, at the timepoints indicated in Section 1.3. The scoring system uses the methods outlined in Sonis *et al.*, 1999.

Table 5. Oral Mucositis Assessment Scale (OMAS)

Location	Ulceration/Pseudo membrane				Erythema		
Upper Lip	0	1	2	3	0	1	2
Lower Lip	0	1	2	3	0	1	2
Right Cheek	0	1	2	3	0	1	2
Left Cheek	0	1	2	3	0	1	2
Right ventral and lateral tongue	0	1	2	3	0	1	2
Left ventral and lateral tongue	0	1	2	3	0	1	2
Floor of mouth	0	1	2	3	0	1	2
Soft palate/fauces	0	1	2	3	0	1	2
Hard palate	0	1	2	3	0	1	2

Ulceration/Pseudo membrane: 0 = no lesion, 1 = < 1 cm^2, 2 = 1 to 3 cm^2, 3 = > 3 cm^2; Erythema: 0 = none, 1 = not severe, 2 = severe

A dedicated observer will check and record local mucosal reactions at the administration site. If possible, the same evaluator will follow the participant throughout the study. If more than one evaluator is required to follow the participant, then every precaution should be taken to limit the number of evaluators.

In the event of development of an oral reaction, an AE will be reported. Up to investigator and depending on the severity of the reaction, a digital photograph of the reaction may be taken. If the investigator deems it necessary, additional visits for visual inspections may be requested.

8.3.9. Human Puffing Topography

Human puffing topography (HPT) involves the measurement of each participant's unique way of using the HHnB device. The SPA-M device consists of a special sample holder with a mechanical adapter and a data logger. Both the sample holder and the mechanical adapter are associated before starting the HHnB use.

The SPA-M device has to be used for every HHnB use for all participants on Day 1, i.e. during standardized (fixed number of puffs) use. For each participant, one SPA-M device will be assigned at Day 1. A replacement device will be provided in case of malfunction of the device assigned. Any malfunction of the SPA-M device will be documented in the appropriate log.

A training manual will be provided describing the SPA-M device (including its use). Storage requirements for both the SPA-M and HHnB devices will be reported in the pharmacy study

manual. The sponsor will provide training on the use of the SPA-M device to the site staff members responsible for the HPT assessment. All devices will be returned to the sponsor after completion of the study.

The SPA-M device measures and records the flow rate and other per-puff parameters (listed in Section 11.10, Appendix 10). Per-product use experience parameters, representing average or total values per product, will be derived from the per-puff parameters.

Data collected with the SPA-M device will be assessed prior to interpretation. More information will be provided in the Statistical Analysis Plan.

9. Cough Assessment

During and for at least 5 minutes after each administration of CBD inhaled using the HHnB device on Day 1 and 4, the participants will be monitored for coughing. Observation time could be prolonged, if needed (e.g. in case of prolonged cough). Cough assessments timepoints are reported in the SoA, Section 1.3. The information detailed below is to be reported for the cough assessments of Day 1 and Day 4 only.

As per CTCAE v.5.0, cough is defined as a disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.

The study staff will assess the cough for:

- time of occurrence,
- duration and pattern,
- severity,
- number of coughs,
- water needs.

This information will be recorded in the source documents and in the eCRF. The investigator will report an AE/SAE for any episode of mild or higher severity cough. Clearing throat episodes or short cough after inhalations will not be reported as AEs but will be captured in the source documents and cough specific eCRF page.

The data reported in the following Sections 9.1.1.1 to 9.1.1.5 will be collected in the source documents and eCRF for the cough assessments of Day 1 and Day 4 only.

9.1.1.1. Occurrence

Cough /coughing reflex will be observed, and occurrence will be recorded as:

- During inhalation
- After inhalation

9.1.1.2. Duration and Pattern

- Seconds and non-repetitive
- Continuous, below 1 minute
- Continuous, more than 1 minute

9.1.1.3. Severity

- Clearing throat/short cough after inhalation
- Mild Cough (non-prescription intervention indicated)
- Medium/Severe Cough/choking episodes

9.1.1.4. Number of Coughs

The number of cough bouts (repeated sequential coughs) will be recorded.

9.1.1.5. Water Needs

Water needs (as requested by participant and not offered proactively by study personnel) will be recorded.

9.1.1. Product Effect Questionnaire

The Product effect questionnaire is a questionnaire provided to the participants to rate their overall experience with the HHnB device and in general their CBD consumption habits and preferences. The Product effect questionnaire is appended to the protocol (Section 11.8, Appendix 8). The questionnaire will be administered in two parts by an authorized member of the clinical team at the timepoints specified in the SoA, Section 1.3, and completed on paper by the participant. Data will be also reported in the eCRF.

9.2. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 11.3, Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs or SAEs (see Section 7). Adverse Events reported by the participant will be assessed for adequate reporting.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 11.3.

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the signing of the ICF until the EOS or ET visit at the timepoints specified in the SoA, Section 1.3.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 11.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obliged to actively seek information on AEs or SAEs, which begin after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study product or study participation, the investigator must promptly notify the sponsor.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESI (as defined in Section 9.2.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 11.3.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor (or delegate, e.g. CRO) of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants under clinical investigation are met. Further details on the safety reporting process is described in the safety management plan.

The sponsor (or delegate, e.g. CRO) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study product under clinical investigation. The Sponsor (or delegate, e.g. CRO) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and Investigators.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it in the Investigator's Study File and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

9.2.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study product and 30 days after the last dose.

Participants need to inform the site if a pregnancy occurred within 30 days after the participant ended the study. If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The pregnant participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.

Any poststudy pregnancy-related SAE considered reasonably related to the study product by the Investigator will be reported to the sponsor as described in this section. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue the study product and if possible, will undergo an ETV to assess safety. Please also refer to Section 11.3.

9.2.6. Adverse Events of Special Interest

An adverse event of special interest (AESI) refers to an AE that is of particular concern or interest in a clinical study or medical study due to its potential seriousness, unpredictability, or association with the study product.

Particular attention will be posed to the following events indicating abuse potential:

- Euphoric mood; Elevated mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination; Inappropriate affect
- Disturbance in attention, cognition (such as cognitive disorder), and mood (such as Mood altered, Mood swings, Depressed mood), Somnolence.
- Dissociative/psychotic terms: Dissociative disorder, Psychotic disorder; Aggression; Confusional state and Disorientation

The following AEs must be reported as AESI:

- ALT or AST greater than or equal to 5 x ULN
- Total bilirubin equal or greater than 2 x ULN (if ALT is equal or greater than 3 x ULN)
- ALP equal or greater than 2 x ULN (if the source of the ALP increase is the liver)

Investigators will closely monitor participants for the occurrence of AESIs throughout the course of the study. Any relevant clinical signs and symptoms and detailed information on the timing and severity of the events will accompany the information.

9.2.7. Device Deficiencies

The study product investigated in this study (Hemp inhaled through a HnB device) is **not** classified as a medical device according to relevant regulations (ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research), however device deficiencies will be defined, collected, processed and reported to the sponsor as per device training manual.

9.3. Pharmacokinetics

Blood samples for PK analyses for the measurement of concentrations of CBD, its major metabolites (7-OH-CBD, 7-COOH CBD), THC and its metabolites (11-OH-THC and 11-COOH-THC) (up to 10 mL of blood for each blood sampling) will preferably be collected via in-dwelling IV catheter or by direct venipuncture.

The planned venous blood sampling time points together with the allowed time windows are presented in Table 6 for the standardized (fixed number of puffs) administration and in Table 7 for the non-standardized (*ad libitum*) administration.

Actual sampling times for each participant will be recorded in the individual source documents and reported in the eCRFs. The reference time for the PK blood sampling (related to both standardized and non-standardized administration) will be taken in relation to the time of the start of the first puff.

The actual sampling times should not exceed the recommended tolerance ranges presented in the tables below. Any deviation outside the recommended ranges will be verified through automatic clarifications and, if confirmed, will be reported as protocol deviations, although it will not automatically lead to the exclusion of the concerned subjects from the PK set or PKPP set.

Table 6. Time Points for PK Blood Samples and Allowed Time Windows – Standardized (fixed) use

Day	Time points CBD inhaled ± tolerance range
Day 1	Pre-dose (within 30 minutes prior to dosing)
	Post-dose • 1 min (after 2 puffs) ± 20 sec • 3 min (after 6 puffs) ± 30 sec • 6 min (after 10 puffs) ± 1 min • 10 min ± 2 min • 15 min ± 3 min • 20 min ± 3 min • 30 min ± 5 min • 1 h ±5 min • 2 h ±10 min • 4 h ±15 min • 6 h ±15 min • 8 h ±30 min • 12 h ±1 hour
Day 2	• 24 h ±1 hour
Day 3	• 48 h ±2 hours
Day 4	• 72 h ±4 hours (same as the pre-dose for the ad libitum administration)

Table 7. Time Points for PK Blood Samples and Allowed Time Windows – Non-standardized (ad libitum) Use

Day	Time points CBD inhaled ± tolerance range
Day 4	Pre-dose (corresponding to 72 h post-dose in Table 6 above)
	Post-dose • 1 min ± 20 sec • 3 min ± 30 sec • 6 min ± 1 min • 10 min ± 2 min • 15 min ± 3 min • 20 min ± 3 min • 30 min ± 5 min, • 1 h ±5 min • 2 h ±10 min • 4 h ±15 min • 6 h ±15 min

Blood samples for PK analysis will be collected using an indwelling catheter with switch valve. Details on samples collection, processing, labeling, storage and transport to the analytical laboratory will be given in the study manual.

If any clinical assessment, such as vital signs measurement or ECG recording is foreseen at the same time-point as blood sampling for PK analysis, blood collection will be performed at the scheduled time. However, vital signs and ECG parameters can be influenced by the blood sampling. Therefore, these assessments can be performed within 30 min before the scheduled PK time-points (Table 8).

Table 8. Tolerance Ranges for the Safety Assessments in Relation to Blood Sampling Times

Blood sampling time	Vital signs tolerance range
Pre-dose (0)	Within 30 minutes before blood sampling
Post-dose	Within 30 minutes before blood sampling

Any deviations outside the recommended time will be verified.

However, since vital signs measurements and ECG recordings will be performed for safety reasons, deviations from the planned time schedule will be listed but considered not important.

9.3.1. Samples storage and transport

At the Phase 1 Unit, the samples will be stored at ≤ -70° C (brief fluctuations up to -60° C are possible when freezers are opened).

At the end of each collection day, at the clinical site, P1 aliquots will be stored in one freezer, whereas P2 and P3 aliquots will be stored in another freezer.

All P1 aliquots, packed in sufficient solid CO_2, will be shipped by an authorized courier from CROSS Research S.A. Phase I Unit, Switzerland, to the analytical laboratory, Syneos Health Clinique Inc., Canada.

The counter-samples (P2 and P3 aliquots) will remain stored at CROSS Research S.A., Switzerland, for up to 5 years. These samples could either be:

- sent to the laboratory for reanalysis should this become necessary for analytical reasons or if any problems occur during the delivery of P1 (or P2) aliquots, or
- destroyed at an authorized site, or
- transferred to the sponsor upon written request, or sent to a different laboratory for reanalysis should this become necessary for bioanalytical reasons.

All aliquots received by Syneos Health Clinique Inc., Canada, will remain stored at the bioanalytical laboratory for 3 months after the finalization of the bioanalytical report. After that period, the aliquots stored could either be destroyed or returned to Cross/Sponsor or stored for an additional period, according to specific Sponsor agreement with the bioanalytical laboratory.

More details, if applicable, will be given in the study manual.

No bioanalyses different from those stated in this protocol and agreed by the participants when signing the informed consent form will be performed unless new informed consent and new approval from the Ethical Committee (EC) is obtained. The participants may ask to destroy their own samples at any time.

9.3.2. Bioanalytical Methods

Plasma concentrations of CBD, its metabolites 7-OH-CBD and 7-COOH-CBD, TCH and its metabolites 11-OH-THC and 11-COOH-THC, will be measured at Syneos Health Clinique Inc., Canada, using fully validated LC-MS/MS methods.

Analyses will be performed according to the general principles of GLP and GCP.

Details of the bioanalytical method will be present in the bioanalytical plan. The method validation report and the analytical report will be attached to the final clinical study report.

9.4. Pharmacodynamics

Not applicable.

9.5. Genetics

Genetics are not evaluated in this study.

9.6. Biomarkers

Biomarkers are not evaluated in this study.

9.7. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

9.8. Health Economics OR Medical Resource Utilization and Health Economics

Health economics OR Medical resource utilization and health economics parameters are not evaluated in this study.

9.9. Measurement of remaining CBD on stick, mouthpiece and device after use

All subjects' sticks including mouthpiece and device will be collected as specified in the study manual.

Remaining CBD on the stick and mouthpiece after use will be analyzed by the sponsor.

10. Statistical Considerations

10.1. Statistical Hypothesis

There is no statistical hypothesis to be tested for this study.

10.1.1. Multiplicity Adjustment

Not applicable.

10.2. Analysis Sets

A participant will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures.

A participant will be defined as eligible if he/she meets all the inclusion/exclusion criteria. Otherwise, he/she will be defined as a screen failure.

A participant will be defined as enrolled in the study if he/she is included in the interventional phase of the study. The enrolment will be performed through non-randomized allocation to the study intervention.

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	**Description**
Enrolled set	All enrolled participants. This analysis set will be used for demographic, baseline and background characteristics.
Safety set (SAS)	All participants, who are exposed to at least one dose of study product. This analysis set will be used for the safety analysis.
PK analysis set (PK set)	All participants from the safety population who have at least one quantifiable post-dose PK concentration (≥ lower limit of quantification [LLOQ]). This analysis set will be used for the PK analysis.
PK per protocol analysis set (PKPP Set)	All participants from the PK set, who completed the use of the study product as per protocol and who have at least one PK parameter and who have not experienced any major protocol deviation or other circumstances that may affect study results. This analysis set will be used for the PK (sensitivity) analysis

A data review meeting will take place before database lock. During the Data Review Meeting (DRM), before database lock, the study team will make the final decision on which subjects will be included in the Safety set, the PK set and the PKPP set. Details on the study team participating in the DRM will be given in the statistical analysis plan.

Reasons for exclusion of the subjects from the analysis sets will be detailed in the statistical analysis plan.

10.3. Statistical Analyses

10.3.1. General Considerations

The statistical analysis plan will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The data documented in this study and the parameters measured will be evaluated and compared using classic descriptive statistics, i.e. geometric mean (PK data only), arithmetic mean, SD, CV (%), minimum, median and maximum values for quantitative variables, and frequencies for qualitative variables.

Not available data will be evaluated as “missing values”.

The statistical analysis of demographic and safety data will be performed using SAS® version 9.3 (TS1M1), or higher (the actual versions will be stated in the final report).

The statistical analysis of PK parameters will be performed using Phoenix WinNonlin™ version 8.3.5 or higher and SAS® version 9.3 (TS1M1), or higher.

10.3.1. Demographic, baseline and background characteristics

Critical demographic characteristics will be examined according to qualitative or quantitative data. Qualitative data will be summarized in contingency tables. Quantitative data will be summarized using classic descriptive statistics.

10.3.2. Study Endpoint Analyses

10.3.2.1. Definition of endpoints

See also Section 3.

The primary endpoints are the following PK parameters:

- CBD $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{extra}$, C_{max}, T_{max}, $T_{1/2\ el}$, K_{el}, CL/F, Vz/F

The secondary endpoints for PK are the following parameters:

- $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $\%AUC_{extra}$, C_{max}, T_{max}, $T_{1/2\ el}$, K_{el}, for:
  - 7-OH-CBD and 7-COOH-CBD (CBD metabolites)
  - THC
  - 11-OH-THC and 11-COOH-THC (THC metabolites)

The secondary endpoints for safety are:

- Incidence and frequency of treatment-emergent adverse events (TEAEs), and AE of special interest (AESI)
- Vital signs measurements changes from baseline (blood pressure, heart rate, respiration rate, and body temperature (ear measurement))
- Cough assessment (number, duration, intensity of cough)
- Change from baseline in overall hematological/biochemistry parameters
- Liver function (liver enzymes, total bilirubin, phosphatase alkaline)
- 12-lead electrocardiogram (ECG) recordings
- Respiratory tests (spirometry, FCOHb, exhaled CO)
- Change from baseline in Visual oral inspection (OMAS scores)

The exploratory endpoints are:

- Product effect evaluation, using a Product Effect questionnaire
- Remaining amount of CBD in stick and mouthpiece after use
- Human puffing topography measured using SPA-M device

10.3.2.2. Main Analytical Approach

The following PK parameters will be measured and/or calculated for CBD (primary endpoints) and its metabolites and THC and its metabolites (secondary endpoints), as applicable, using the validated software Phoenix WinNonlin™ version 8.3.5, or higher (actual version will be stated in the final report):

C_{max}:	Maximal observed plasma concentration
T_{max}:	Time when the maximal concentration is observed
K_{el}:	Terminal elimination rate constant
$T_{1/2\ el}$:	Terminal elimination half-life
AUC_{0-t}:	Area under the concentration-time curve from time 0 until the last observed concentration time t, calculated with the linear trapezoidal method
AUC_{0-inf}:	Area under the concentration-time curve extrapolated to infinity
$\%AUC_{extra}$:	Percentage of AUC_{0-inf} due to extrapolation from the time of the last observed concentration to infinity, calculated, if feasible, as $[1 – (AUC_{0-t}/AUC_{0-inf})] \times 100$
CL/F:	Apparent clearance – only for CBD
Vz/F	Apparent volume of distribution – only for CBD

Other PK parameters could be calculated, if applicable.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$.

A descriptive PK will be presented for each product use (standardized and non-standardized). The results will be displayed and summarized in tables and figures. Individual and mean curves (+SD at sampling times), indicating inter-participant variability, will be plotted. Data below the lower quantification limit (BLQL) will be considered as 0 in the calculations and presented as BLQL in listings and tables. As a consequence of BLQL (i.e. 0) values, calculated geometric means (if requested) could be null. For this reason, in the presence of any null value, the geometric mean will be reported as not calculated (NC).

From individual plasma concentrations, PK parameters will be estimated using a standard non-compartmental method. Actual sampling times will be used to determine PK parameters.

Descriptive statistics, which include but is not restricted to mean, SD, CV%, median, minimum, and maximum, interquartile ranges will be calculated for each PK parameter. Comparisons between standardized and non-standardized product use regimens for the analytes PK parameters might be performed.

10.3.3. Exploratory Endpoints Analysis

10.3.3.1. Product Effect Questionnaire

Product effect scores from the questionnaire will be listed and summarized by standardized and non-standardized product use and questionnaire part using descriptive statistics and/or score frequency, as applicable. Comparisons between product use regimens might be performed.

10.3.3.2. Puffing topography results

HPT parameters will be listed and summarized for standardized product use regimen using descriptive statistics (arithmetic means, arithmetic CV, and 95% CIs). Comparisons between product use regimens might be performed, when applicable.

Descriptive statistics will be applied for the data on the outputs generated by topography SPA-M device.

10.3.3.3. Remaining CBD on stick and mouthpiece after use

Remaining CBD on the stick and mouthpiece after use will be listed and summarized by descriptive statistics.

The correlation between the remaining CBD product in the HHnB device (overall remaining quantity after each product use regimen) and the corresponding CBD blood levels after the standardized and the non-standardized inhalation, respectively, will be analyzed using Pearson or Spearman coefficients for each product use regimen."

10.3.3.4. Additional PK analysis

If feasible, data from this study will be used for additional analysis of untransformed k_{el} and $t_{1/2}$. A comparison of untransformed k_{el} and $t_{1/2}$ between standardized and ad libitum regimen will be

performed by means of Paired T test or Wilcoxon Signed rank test, depending on the data distribution. Results from this additional analysis will be presented in the clinical study report.

10.3.4. Safety Analyses

Safety and tolerability of CBD will be evaluated through the assessment of AEs (i.e., seriousness, severity, relationship to the study product, outcome, duration, time to onset and management), vital signs, 12-lead ECGs, clinical laboratory tests, spirometry and physical examinations.

Safety and tolerability data will be reported using descriptive statistics including number of non-missing values, mean, median, SD, minimum and maximum for continuous variables and number and percentage for categorical variables.

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version will be specified in the clinical study report.

AEs will be classified as pre-treatment AEs (PTAEs) and treatment-emergent AEs (TEAEs), according to the period of occurrence, as follows:

- PTAEs: all AEs occurring before the first dose of the study product
- TEAEs: all AEs occurring or worsening after the first dose of the study product

Individual PTAEs and TEAEs will be listed in participant data listings. No summary table will be provided for PTAEs. TEAEs will be summarized by treatment and overall. The number and percentage of participants with any TEAE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity. AESI will also be listed and summarized separately. AESI will also be listed and will be summarized with the other TEAEs as well as separately.

10.3.4.1. Physical examination

Date of the physical examination, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed.

10.3.4.1. C-SSRS

C-SSRS scores will be listed and summarized by standardized and non-standardized product use regimen using score frequency. Change from baseline will be calculated if possible. Comparisons between product use regimens might be performed.

10.3.4.2. Laboratory data

Date/time of samples collection, overall Investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant findings (if any) will be listed. All laboratory results will be listed and a table of all the abnormal values will be presented. The overall Investigator's interpretation will be summarized using tables of

frequency. Changes in clinical laboratory tests from baseline to post-dose time points will be summarized.

10.3.4.1. Body weight

Body weight values at screening and final visit/ETV will be listed and summarized by descriptive statistics. Changes in body weight from baseline to final visit/ETV will be summarized.

10.3.4.2. Vital signs

Vital signs (blood pressure, heart rate, respiration rate and body temperature) values will be listed and summarized by descriptive statistics. Changes in vital signs from baseline to post-dose timepoints will be summarized.

10.3.4.3. ECG

Date/time of ECG recording, overall investigator's interpretation (as normal or abnormal and, if abnormal, clinically significant or not clinically significant) and clinically significant abnormalities (if any) will be listed. The overall investigator's interpretation will be summarized using tables of frequency. ECGs results as well as changes from baseline will be listed and summarized.

10.3.4.4. Visual oral inspection analyses

Visual oral inspection (OMAS) scores will be listed and summarized by standardized and non-standardized product use regimen using score frequency. Change from baseline will be calculated, when possible. Comparisons between product use regimens might be performed.

10.3.4.5. Cough assessment

Cough assessment results will be listed and summarized by product use regimen using descriptive statistics and/or score frequency, as applicable. Potential comparisons between product use regimens might be performed.

10.3.4.1. Respiratory parameters

Spirometry parameters, FCOHb and exhaled CO values will be listed and summarized by descriptive statistics. Changes in the parameters' values from baseline to post-dose time points will be summarized, as applicable.

10.3.5. Other Analyses

Not applicable.

10.4. Interim Analysis

Not applicable.

10.5. Sample Size Determination

The sample size was not powered on the basis of statistical hypothesis testing considering the descriptive nature of this study.

The sample size of 40 participants was selected to allow data interpretation, keeping in mind the anticipated high individual variability both for CBD metabolism and vaping pattern. Discontinued subjects will not be replaced.

11. Supporting Documentation and Operational Considerations

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., questionnaires) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Non-substantial amendments will be notified to the Authorities according to the current regulations.

The investigator will be responsible for the following, as applicable:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently, if applicable, in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

11.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3. Material Supplied to the Clinical Center

The CRO in charge of the clinical study will provide the investigator(s) with paper format of all the scales used in the study. Moreover, before the start of the study, the investigator(s) will be provided or the Sponsor will ensure availability at site of the following documents: ICH guidelines, confidentiality agreement (if applicable), protocol amendments (if any), declaration of Helsinki, insurance statement, SAE forms, financial agreement (if applicable), confidential subject identification code list form, drug accountability forms, investigator and site delegation and signatures log form.

11.1.4. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The study source documents must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Participants will be provided with information prepared in the local language, regarding the processing of personal data according to the Swiss Federal Act on Data Protection (Law 235.1 of 25 September 2020 and subsequent updates) and the European General Data Protection Regulation (GDPR, EU Regulation n 2016/679).

To ensure medical confidentiality and data protection, the signed informed consent forms will be stored in the investigator's study file according to the regulatory requirements. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IRB/IEC members and regulatory authorities. He/She will confirm, by signing and dating the forms, that informed consent has been obtained.

11.1.1. Insurance Policy

An insurance cover has been issued in favor of the participants participating in this clinical study. The insurance is in compliance with the local regulation and with the requirements of the Health Authorities.

11.1.2. Recruitment Strategy

Study participants will be recruited from the volunteers' database maintained by the CRO. This database contains a pool of volunteers that are contacted whenever necessary to enroll participants in a new study. Before the start of the new study, the principal investigator and other relevant staff discuss with the volunteers' recruiter the study recruitment needs and specific requirements. On the basis of this information, the volunteers' recruiter queries the database, contacts potential participants to propose the study and evaluate their interest and availability. In addition to the volunteers' database, new participants often call or email the CRO asking to become a research volunteer, after hearing of the clinical site activities from other volunteers or friends or after checking the company web site.

The CRO and its clinical site have detailed SOPs on the recruitment process.

11.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their study source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

11.1.4. Committee Structure

No formal safety data committee is foreseen for this study.

11.1.4.1. Early Safety Data Review

Not applicable as no formal safety data committee is foreseen in this study.

11.1.5. Dissemination of Clinical Study Data

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. People to whom this study protocol is disclosed must be

informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the sponsor.

All information on a participant obtained during the conduct of the study will be kept confidential. Participants will be identified by a pseudonymized identifier on all samples and study records provided to the sponsor or delegate. In compliance with ICH-GCP, the sponsor's authorized representatives, monitor(s), auditor(s), IRB/IEC, and regulatory authority(ies) will be granted direct access to the participant's original study-related records for verification of clinical study procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations. Consent from the participant for disclosure of such information will be obtained in writing in the ICF. In addition, should a participant require medical care or hospitalization during the course of the study, the clinical site may contact the treating physician with the participant's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the participant's identity will remain confidential.

The clinical site will maintain adequate study records according to applicable regulatory requirements. The sponsor will be notified prior to the destruction of study records.

The publication policy for this clinical study and its results are detailed in Section 11.1.11.

11.1.6. Monitoring, Quality Control and Quality Assurance

11.1.6.1. Monitoring

The monitoring visits will be conducted by an appointed freelance CRA.

Monitoring activities, including monitoring purpose, selection and qualifications of monitors, extent and nature of monitoring, monitoring procedures, monitoring reports will comply with ICH-GCP requirements.

Adequate time and availability for monitoring activities should be ensured by the investigator and key study personnel.

Data verification is required and will be done by direct comparison with source documents, always giving due consideration to data protection and medical confidentiality. In this respect the investigator will always ensure support to the monitor.

The investigator agrees, by written consent to this protocol, to fully co-operate with compliance checks by allowing authorized individuals to have access to all the study documentation. In addition to the monitoring activities performed by the study monitor, the sponsor could perform other quality control and quality assurance activities to verify the compliance with the study procedures and the ICH-GCP guidelines.

11.1.6.2. Quality Control and Quality Assurance

The CRO has implemented and maintains a Quality System with written SOPs to ensure that the study is conducted in compliance with the protocol and all effective amendments, ICH-GCP, and the applicable regulatory requirement(s) and that data have been reliably and correctly generated, recorded, processed and reported, in agreement with the ALCOA++ principles (Attributable-Legible-Contemporaneous-Original-Accurate-Complete-Consistent-Enduring-Available-Traceable).

The clinical site(s) is responsible for implementing and maintaining quality assurance and a quality control system to ensure that the study is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

The CROs and the sponsor will be responsible for their respective activities.

The sponsor may transfer any or all the sponsor's study-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the study data always resides with the sponsor.

11.1.6.3. Applicable SOPs

The sponsor, the clinical site and the CRO will follow their respective SOPs in the conduct of the respective activities, unless otherwise stated in written agreements. SOPs will be made available for review, if required.

11.1.6.4. Data access

The investigator and the CRO will ensure that all raw data records, source documents, CRFs and all other documentation that is relevant to this study will be made accessible for monitoring activities, audits, IRB/IEC review, and regulatory inspections.

11.1.6.5. Audits and inspections

The sponsors, independent bodies acting on behalf of the sponsor and the CRO have the right to perform audits according to ICH-GCP guidelines.

The study may also be inspected by regulatory authorities.

The investigator and the CRO agree, by written consent to this protocol, to fully co-operate and support audits and inspections compliance checks by allowing authorized individuals to have access to all the study documentation.

11.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator will need to request previous medical history information from the study participants.

Definition of what constitutes source data and its origin can be found in the Source Data Location Agreement. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The sponsor or designee (e.g. CRO) will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

11.1.8. Study documentation and record keeping

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRF and in all required reports.

The investigator must keep source documents for each subject in the study. All information in the eCRF must be traceable to these source documents. The source documents should contain all demographic and medical information, including laboratory data, ECGs, etc., and the original signed informed consent forms.

Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator and the sponsor should maintain the study documents as specified in the "Essential Documents for the Conduct of a Clinical Trial" chapter 8 of ICH-GCP and as required by the applicable regulatory requirement(s).

These are documents which individually and collectively permit evaluation of a study and the quality of the data produced and include groups of documents, generated before the study commences, during the clinical study, and after termination of the study and include but are not limited to, study protocol, amendments, submission and approval of EC, raw data of subjects including lab tests and ECG tracing, insurance contracts, certificate of analysis of the investigational product, accountability records, signed informed consent forms, confidential subjects identification code, eCRF, curricula vitae of the investigator and other participants in the study, site delegation and signatures log form, monitoring reports and final study report.

The investigator and the sponsor should take measures to prevent accidental or premature destruction of these documents.

Study documents must be retained by the investigator and the sponsor as long as needed to comply with ICH-GCP, national and international regulations. By signing the protocol, the investigator and the sponsor agree to adhere to these requirements.

The investigator and the sponsor must retain all data relating to the clinical study at least for twenty years after the completion or premature termination of the clinical study.

11.1.9. Data management procedures

11.1.9.1. Data collection – eCRF

The investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the participant's source documents.

To ensure legibility, the eCRF should be filled out in English. Any correction to the eCRF entries must be carried out by the investigator or a designated member of staff. In the interest of completeness of data acquisition, the questions which are repeated in each section of the eCRF should be answered in full, even if there are no changes from a previous examination. The investigator must provide a reasonable explanation for all missing data.

Each authorized member of staff will have an individual user account with access privileges defined by the user profiles. Each user can access the Electronic Data Capture (EDC) system only through a unique combination of username and password.

The eCRF will be completed during the study and will be signed by the Principal Investigator with electronic signature (username and password) after source data verification has been performed by the monitor and all clarifications have been solved.

The site will have the possibility to insert and/or update data until the lock of the database. After the completion of data management procedures and the lock of the database, data of the eCRF will be provided to the sponsor in the preferred format and the site will file a copy of the eCRF data in PDF format. Prior to read-only access to the investigator being revoked, a copy including the audit trail should be made available to the investigator in a complete and comprehensive way.

11.1.9.2. Unique subject identifier

All the participants who sign the informed consent form for the present study will be coded with "unique subject identifiers" when data are extracted from the study database into the domains of the CDISC SDTM model. The unique subject identifier consists of the sponsor study code (i.e. VFC224-101), the 6-digit screening number (e.g., 01-001, etc., where 01 is the site number) and, if applicable, the 3-digit subject study number (e.g. 001, 002, etc.). Study code, site number, screening number and subject study number are separated by slashes ("/").

The last 10 digits of the unique subject identifier (enrolled participants), corresponding to the subject screening and subject study numbers separated by a slash, or the last 6 digits of the unique subject identifier (not enrolled participants), corresponding to the subject screening number, will appear as subject identifier in the individual listings and figures of the clinical study report and will be used to identify the participants in in-text tables or wording (if applicable).

11.1.9.3. Database management

Database and eCRF design will be set-up by the Biometry Unit of the CRO on the basis of the Clinical Study Protocol before the start of the study. The database will be validated to ensure it is compliant with the protocol requirements, regulatory requirements and with the user requirements.

The design and the check programming will be tested by the CRO and, if applicable, by the sponsor through User Acceptance Tests (UATs).

Validation is a complex procedure that could involve several successive tests and reworking until the eCRF responds to the requirements. A study-specific validation will be performed by the eCRF provider (Nubilaria srl) before database activation.

The eCRF provider is also responsible for the maintenance of the validation status of the EDC system through his own quality system. Refer to the eCRF provider documentation for further details about security, disaster mitigation, disaster recovery, audit trail and electronic signature features.

After the validation has been completed, the eCRF can be activated and deployed according to eCRF provider standard procedures.

Verification and cross-verification of the data entered by the study personnel will be automatically performed by the system, according to predefined nature/type of the data, value ranges and rules. All rules applied by the system to check specific items will be detailed in the Data Validation Plan (DVP).

Automatic clarifications will be generated by the system for all data found to be inconsistent, incorrect or missing. Manual discrepancies could be sent to the site in order to correct mistakes potentially present in the eCRF.

All changes performed to data inserted in the eCRF will be tracked by the system and every change will be automatically recorded. Each observation in the audit trail will contain the original value, the new value, the reason for change, date/time in which the modification was made and the user identification of the person who made the change.

Once all data are entered into the eCRF, all outstanding queries are solved and the monitor has completed the Source Data Verification (SDV), the Data Manager will verify the correctness of the answers, and the investigators will approve (sign) the data of the participants' eCRF. Data management standards and procedures will be stated in the Data Management Plan (DMP) in agreement with the sponsor.

11.1.9.4. Database lock

The clinical database will be locked after the end of the data validation procedures, the resolution of all clarifications, the finalization of the MedDRA and WHO-DD coding, the SAEs Reconciliation, the source data verification and the Principal Investigator signature of the eCRF.

The CRO and Sponsor will sign a database lock form asking the eCRF provider to proceed with the locking procedure.

Written approval from the sponsor is needed in order to update data after the lock of the database.

11.1.9.5. Database decommissioning

After the completion of all analysis and following sponsor's request, the eCRF provider will do the decommissioning following their own standard procedures. Decommissioning can occur only after the investigator has received his own certified copy of all data.

11.1.9.6. Laboratory Normal Ranges

The central safety laboratory (Unilabs SA, Switzerland) provides its own Laboratory Normal Ranges.

The CRO is responsible for managing the laboratory normal ranges into the eCRF used for remote data capture and for assuring that the association between each laboratory analysis and each participant is based on the following data inserted in the eCRF: date of sample collection, sex of the participant, age of the participant at the time of sample collection.

11.1.9.7. Coding dictionaries

Medical/surgical history and underlying diseases, clinically significant physical examination abnormalities and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™).

Previous and concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD). The version of the coding dictionaries will be stated in the data-management plan, the statistical analysis plan and the clinical study report.

11.1.9.8. SDTM and ADaM

The Biometry Unit of the CRO will extract data from the eCRF and will provide tabulation datasets according the SDTM model of CDISC and analysis datasets according to the ADaM model of CDISC.

SDTM and ADaM domains will be validated using the Pinnacle 21 Community validator. The original export of the eCRF data and the final data files will be transferred to the sponsor in the agreed format with the relevant CDISC documents (i.e., output reports for both SDTM and ADaM datasets from the Pinnacle 21 validation tool) together with all other study documentation.

11.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

The study will be considered terminated at the date of the last visit of the last participant.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study product development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

11.1.11. Publication Policy and Transparency

The sponsor agrees that the study results can be made publicly available by the investigator. If foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission to allow the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements. The study information will also be published in a primary international registry before study start. A summary of the results will be made publicly available in accordance with the Swiss regulations.

11.2. Appendix 2: Clinical Laboratory Tests

Refer to Section 8.3.5 for clinical laboratory tests.

11.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Applicable SOPs

AEs definition, classification and management will follow the CRO SOPs, based upon applicable local and international regulations. The full SOP or an operative summary will be made available to the clinical center.

A summary of AEs definition, classification and management is reported below.

11.3.2. Definitions

- **Adverse event (AE)**

Any untoward medical occurrence in a subject to whom a study product is administered and which does not necessarily have a causal relationship with the treatment.

- 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.
- An AE can include previously undetected symptoms, or the exacerbation of a pre-existing condition.
- Unless differently stated in the protocol, therapeutic failures during a study should be recorded but not be considered as AEs (except for study products used for the treatment of life-threatening diseases).

- **Adverse Drug Reaction (ADR)**

Any noxious and unintended response to a study product (i.e., a causal relationship between a study product and an AE is at least reasonably possible in the investigator's or sponsor's opinion, the relationship cannot be ruled out) resulting not only from the authorized use of a study product at normal doses, but also from medication errors and uses outside the terms of the marketing authorization, including the misuse and abuse of the study product.

- **Pre-treatment AE (PTAE)**

Any AE occurring before the first dose of a study product. The following medical occurrences and clinical investigations are the only clinically significant events which, according to the investigator’s judgement, can be defined and recorded as PTAEs:

- trauma (fractures, sprains, strains, falls, domestic accidents, car accidents, etc.) occurred after the signature of the informed consent and before the first product administration

- new measurements (vital signs, ECG, laboratory parameters, etc.), performed after the signature of the informed consent and before the first product administration, which show a clinically significant worsening in comparison with a previous (baseline) measurement performed after the signature of the informed consent
- any disease diagnosed after the anamnesis recorded at visit 1 and before the first product administration
- physical and mental status changes (pre-syncope, anxiety, dizziness, fainting, etc.) occurred after the signature of the informed consent and before the first product administration

- **Treatment-emergent AE (TEAE)**

Any AE occurring or worsening after the first dose of a product

- **Serious Adverse Event (SAE)**

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is an important medical event that may jeopardize the subject's health status or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are cancer, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse

- **Unexpected ADR**: an ADR the nature or severity of which is not consistent with the Reference Safety Information (RSI)
- **Reference Safety Information** (RSI): this is reported in the current version of the Investigator's Brochure (IB)

  The RSI may change during the conduct of a clinical study. For the purpose of reporting SUSARs the version of the RSI at the moment of occurrence of the SUSAR shall apply.

- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

An ADR that is both unexpected (the nature, severity or outcome of which is not consistent with the RSI) and also meets the definition of a SAE.

11.3.3. AEs monitoring window

- Start of monitoring: all AEs that begin or worsen immediately after the signature of the informed consent
- End of monitoring: last follow-up visit/ETV

An AE occurring after the last follow-up visit/ETV and coming to knowledge of the investigator (e.g., by spontaneous reporting by study subjects) must be recorded only if it is an ADR, according to the investigator's judgment.

SAEs that are still ongoing at the end of the investigation period must be followed until the determination of outcome (resolution or stabilization).

All SUSARs occurring in any of the subjects of the clinical study, which are identified by or come to the attention of the Principal Investigator after the end of the clinical study, shall also be reported to the authorities as required.

11.3.4. AEs recording

All AEs derived from spontaneous, unsolicited reports of the subjects, by observation and by routine open questioning should be collected and reported.

AEs should be documented in the source documents of the site, providing an adequate level of detail, sufficient to complete all the data required by the (e)CRF (for example medical charts, detailed medical narratives).

AEs must be evaluated by Medical Doctors, according to study delegations. Staff entering the AEs in the (e)CRF shall only copy information sourced from the Medical Doctors documents without any change or interpretation.

The following minimal information will be recorded for an AE (detailed explanation for each element is available in the SOP or in the operative summary made available to the clinical site) in the source documents and later transcribed into the (e)CRF:

1. Adverse Event: progressive number of the adverse event
2. Description: verbatim description of the adverse event or

   Follow-up: progressive number of follow-up of the adverse event
3. Start Date/Time: start date/time of the adverse event or

   Follow-up Date/Time: follow-up date/time of the adverse event
4. End Date/Time: end date/time of the adverse event
5. Affected Body Area: anatomical location relevant for the event
6. Whether the adverse event starts before or after the first intake of the study product or whether the adverse event has worsened or not after the first intake of the study product
7. Last Study product Administration Date/Time Before Onset: if the adverse event started after the first administration of the study product, the date/time of last administration of the study product before the onset of the adverse event or

   Last Study product Administration Date/Time Before Worsening: In case of treatment emergent adverse event, the date/time of the last administration of the study product(s) before the worsening of the adverse event.

8. Investigator's opinion about the reasonable possibility of a causal relationship with the study product.
9. Investigator's opinion about other causal relationship (e.g. non study product, concomitant therapy, study device, etc.).
10. Severity: the severity or intensity of the event
    - 1 Mild
    - 2 Moderate
    - 3 Severe
11. Pattern: Used to indicate the pattern of the event over time
    - 1 Single Event
    - 2 Continuous
    - 3 Intermittent
12. Serious Adverse Event
13. Action Taken with Study product: describes changes to the study product as a result of the event. It is specifically for actions taken with the study product
    - 1 Dose Not Changed
    - 2 Dose Increased
    - 3 Dose Reduced
    - 4 Drug Interrupted (i.e. temporary stop)
    - 5 Drug Withdrawn (i.e. definitive stop)
    - 6 Not Applicable (e.g. drug administration not started yet or completed)
    - 7 Unknown
14. Concomitant Therapy: if concomitant therapy is given, it must be reported in the specific (e)CRF forms
15. Study Discontinuation: if the adverse event causes the subject to be discontinued from the study
16. Other Action Taken: other actions taken as a result of the event that are unrelated to dose adjustments of study product
17. Outcome: Outcome of the event
    - 1 Recovered/Resolved
    - 2 Recovered/Resolved With Sequelae
    - 3 Recovering/Resolving
    - 4 Not Recovered/Not Resolved
    - 5 Fatal
    - 6 Unknown

11.3.5. SAEs reporting

The investigator must report any SAE within 24 h of becoming aware of the event to the contacts reported in Section 10.3.12.

If the investigator is initially unable to obtain all the necessary details for completing the form, he/she should in any case transmit all the available information. The investigator should provide an appropriate follow-up of SAEs to all concerned parties as soon as possible and in any case not later than 7 calendar days after the initial report (2 for fatal or life-threatening SAEs) following the awareness of the new information, unless justified.

Seriousness, severity and causality must be assessed by the investigator. Expectedness is assessed by the sponsor.

If the investigator is unable to assess the causality it is recommended to adopt a conservative approach and treat the event as a suspected adverse reaction until follow-up information is available.
The sponsor may also assess causality, independent of that of the investigator. The most conservative approach should be taken when it comes to regulatory reporting. Under no circumstances should the sponsor downgrade the investigator's opinion or put the investigator under pressure to change his/her assessment. In case of disagreement, both the opinion of the investigator and the sponsor should be provided in the report.
The sponsor will evaluate the SAE expectedness on the basis of the RSI.

When multiple SAEs are observed, the investigator should identify the primary adverse event, which is the most significant one. For any additional events listed in the same report, the investigator must determine, along with their relationship to the IMP/IP, which events are classified as serious, and which are non-serious. In all cases, the investigator is required to provide an assessment of the relationship between the observed event(s) and the IMP/IP.

11.3.6. Conditions that should not be reported as SAEs

The conditions listed below, that may require hospitalization of a study subject, are not considered to be SAE and shall not be reported as such, but only need to be recorded in the (e)CRF:

- hospitalizations for other reasons like for example:
  - hospitalizations for routine pre-planned events
  - hospitalizations planned before entry into the clinical study for a pre-existing condition that is unrelated to the indication under study and did not worsen
  - hospitalizations which are part of general care or the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition
  - hospitalizations that were planned as part of the eligibility for the study

- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs given above and not resulting in hospital admission.
- abnormal test results that do not induce clinical signs and/or symptoms and do not require intervention/therapy, i.e., are not clinically significant.
- anticipated events from disease progression.
- end-points like death in a myocardial infarction study.

11.3.7. SUSARs management

The clock for initial expedited reporting starts as soon as the information containing the minimum reporting criteria has been received by the sponsor (Day 0).

For fatal and life-threatening or potentially lethal SUSARs the concerned authorities should be informed as soon as possible and in any case within 7 days.

If the initial report is incomplete, e.g., not all the information/assessments were available, a complete report should be sent within an additional 8 days.

SUSARs which are not fatal and not life-threatening are to be reported within 15 days.

The minimum information to be reported includes:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One SUSAR
- One suspect IMP/IP (including active substance name, code)
- A causality assessment (a reasonable possibility of a causal relationship with the study product can be excluded only if there is information supporting this decision, otherwise it cannot be excluded).

In addition, in order to properly process the report electronically, the following administrative information shall be provided:

- the sender's (case) safety report unique identifier
- the receive date of the initial information from the primary source
- the receipt date of the most recent information
- the worldwide unique case identification number

If the results of an investigation show that an event not initially determined to be reportable is reclassified as reportable, the sponsor shall be informed as soon as possible, after the event has been classified as such.

11.3.8. AEs/SAEs exemption

There are no AEs/SAEs exemptions for this study

11.3.9. Pregnancy

According to the study selection criteria, women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized as explained in the relevant sections of the protocol. Women of childbearing potential are defined as fertile women, following menarche and until becoming post-menopausal unless permanently sterile.

A man is considered fertile after puberty unless permanently sterilized (e.g. vasectomy).

Women must be instructed to contact the investigator immediately if during the study they suspect they might be pregnant; in the same way, men who become aware that the partner might be pregnant, are to be instructed to contact the investigator immediately.

The investigator must report every pregnancy as soon as possible (within 24 hours of learning of the pregnancy) to the sponsor's pharmacovigilance and follow it to term agreed with the sponsor.

If pregnancy is associated with a SAE (e.g., if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be prepared and filed.

Miscarriage, stillbirth and any malformation/disease must be reported as a SAE. Any pregnancy leads to the immediate cessation of the study treatment.

11.3.10. Other events qualified for expedited reporting

Other safety issues also qualify for expedited reporting when they might materially alter the current benefit-risk assessment of the product or would be sufficient to consider changes in the product administration or in the overall conduct of the study, for instance:

- single case reports of an expected serious adverse reaction with an unexpected outcome (e.g.: a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important.
- post-study SUSARs that occur after the subject has completed a clinical study and are reported to the investigator by the subject.
- new events relating to the conduct of the study or the development of the product likely to affect the safety of the subjects, such as:
  - a SAE which could be associated with the study procedures, and which could modify the conduct of the study
  - a significant hazard to the subject population such as lack of efficacy of a product used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity) or from other clinical studies.

If immediate safety and protective measures have to be taken during the conduct of the clinical study, the investigator shall notify the IRB/IEC of these measures, and of the circumstances necessitating them, within 7 days.

11.3.11. Overdose

Not applicable in this study since the study product is administered under study staff surveillance.

11.3.12. SAEs: contacts

The clinical site can be contacted using the phone and fax numbers stated in this protocol or calling the mobile phone number +41.79.822.35.07 (operative 24-h/day, 365 days/year).

This mobile phone can be called by the study participants to communicate to the clinical staff about any SAE occurring outside the clinical facility.

The contact for reporting SAEs by the subjects is the following:

Dr. Milko Radicioni
Phone: +41.91.64.04.450
Fax: +41.91.64.04.451
Email: milko.radicioni@croalliance.com

Sponsor contact person:

Dr. Roxana Drake
Phone: +41.782168739

Email: roxana.drake@vecturafertinpharma.com

11.4. Appendix 4: Contraceptive and Barrier Guidance

The requirements with regards to contraception are detailed in Section 5.1.1, Inclusion criteria.

11.5. Appendix 5: Genetics

Genetics are not evaluated in this study.

11.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 9.2.6.

11.7. Appendix 7: Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Not applicable. The study product investigated in this study (Hemp inhaled through a Heat not burn device) is **not** classified as a medical device according to relevant regulations (ISO 14155

and the European Medical Device Regulation (MDR) 2017/745 for clinical device research). However, device deficiencies are defined, collected, processed and reported to the sponsor according to the device training manual.

11.8. Appendix 8: Product Effect Questionnaire (Part 1 and 2)

PRODUCT EFFECT QUESTIONNAIRE- PART 1 (VERSION 09MAY2025)

PARTICIPANT NUMBER: …….

Date (DD-MMM-YYYY): …….

Time of administration (hh:mm): ……

Instructions: *We are interested in your input on the cannabis product you are taking during this study. The following questions relate to onset, duration and intensity of effect, taste, texture, and ease of use. It will take about 2 minutes to complete the questionnaire.*

1. **How soon after intake did you observe an effect after the use of the product in the study?** *Check one box*

   a. After 15 min or less ☐
   b. After 15-30 min ☐
   c. After 30-60 min ☐
   d. After 60-120 min (1 to 2 hrs) ☐
   e. After 120 min and more (2hrs +) ☐
   f. I haven't observed an effect yet ☐

2. **Did you experience any of the following effects?** *Check all that apply*

   a. Stress reduction ☐
   b. Calming effects ☐
   c. Mindfulness ☐
   d. Enhanced mood ☐
   e. Increased focus ☐
   f. Improved recovery ☐
   g. Physical endurance ☐
   h. I haven't observed an effect yet. ☐

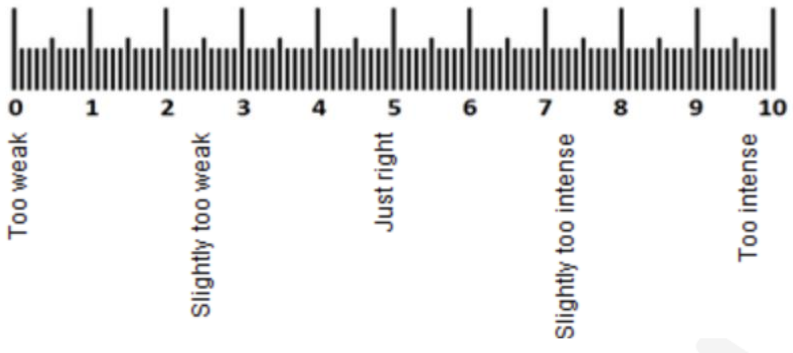
3. **How long did the effect last?** *Check one box*

   a. 1 hour or less ☐
   b. 1-3 hours ☐
   c. 3-6 hours ☐
   d. Over 6 hours ☐
   e. I haven't observed an effect yet. ☐

4. **How would you describe the effect of the product in words?** *Indicate which response best reflects your experience with this cannabis product. Check all that apply*

Cheerful ☐	**Sad** ☐	**Active** ☐	**Angry at self** ☐
Disgusted ☐	Calm ☐	Guilty ☐	Enthusiastic ☐
Attentive ☐	Afraid ☐	Joyful ☐	Downhearted ☐
Bashful ☐	Tired ☐	Nervous ☐	Sheepish ☐
Sluggish ☐	Amazed ☐	Lonely ☐	Distressed ☐
Daring ☐	Shaky ☐	Sleepy ☐	Blameworthy ☐
Surprised ☐	Happy ☐	Excited ☐	Determined ☐
Strong ☐	Timid ☐	Hostile ☐	Frightened ☐
Scornful ☐	Alone ☐	Proud ☐	Astonished ☐
Relaxed ☐	Alert ☐	Jittery ☐	Interested ☐
Irritable ☐	Upset ☐	Lively ☐	Loathing ☐
Delighted ☐	Angry ☐	Ashamed ☐	Confident ☐
Inspired ☐	Bold ☐	At ease ☐	Energetic ☐
Fearless ☐	Blue ☐	Scared ☐	Concentrating ☐
Disgusted at self ☐	Shy ☐	Drowsy ☐	Dissatisfied at self ☐

5. **How would you assess the intensity of the effect of this product?** *Answer the question, by drawing one short line (as straight as possible) that cuts across the scale to indicate your choice.*



6. How would you qualify your overall experience with this product? *Check one box*

a. Extremely dissatisfied ☐
b. Somewhat dissatisfied ☐
c. Neutral ☐
d. Somewhat satisfied ☐
e. Extremely satisfied ☐

7. **How would you rate the taste/flavour of this product?** *Please consider the following attributes when evaluating the product: intensity and type, complexity, sweetness, saltiness, sourness, bitterness. Check one box*

   a. Poor ☐
   b. Fair ☐
   c. Good ☐
   d. Very good ☐
   e. Excellent ☐
   f. Not applicable ☐

8. **How would you rate the aftertaste of this product?** *Please consider the following attributes when evaluating the product: length of after taste, how long the flavours lasted for across the chewing experience where applicable. Check one box*

   a. Poor ☐
   b. Fair ☐
   c. Good ☐
   d. Very good ☐
   e. Excellent ☐
   f. Not applicable ☐

9. **How would you rate the mouthfeel/texture of this product?** *Please consider the following attributes when evaluating the product: length of chew, resistance, bitty, elasticity, smoothness, roughness, drying, mouthwatering, tooth packing. Check one box*

   a. Poor ☐
   b. Fair ☐
   c. Good ☐
   d. Very good ☐
   e. Excellent ☐
   f. Not applicable ☐

10. **How would you rate the ease of use of this product?** *Check one box*

    a. Poor ☐
    b. Fair ☐
    c. Good ☐
    d. Very good ☐
    e. Excellent ☐

PRODUCT EFFECT QUESTIONNAIRE - PART 2 (VERSION 09MAY2025)

PARTICIPANT NUMBER: …….

Date (DD-MMM-YYYY): ……..

Time of administration (hh:mm): ……

Instructions: *We are interested in your input on the cannabis products you may have been taking in the past as well as the product taken in this study. It will take about 2 minutes to complete the questionnaire.*

2. Which CBD products have you taken in the past? *Check all that apply*

a. Oil (ingested) ☐
b. Oil (oral spray) ☐
c. Capsules/softgels ☐
d. Dissolvable lozenges ☐
e. Edibles (gummies, baked goods, beverages, etc.) ☐
f. Dried Flower (joint, vapes) ☐
g. Topical (cream, lotion, ointment, bath bombs, etc.) ☐
h. Wax/Vape Pen (extract) ☐
i. Suppository ☐
j. Other – please specify: _____

3. What is the purpose for which you have taken CBD products? *Check all that apply*

A. **Medical purposes**

a. Pain ☐
b. Sleep issues ☐
c. Anxiety or stress ☐
d. Depression or low mood ☐
e. Seizures ☐
f. Muscle spasms and stiffness ☐
g. Nausea and vomiting ☐
h. Agitation ☐
i. Appetite ☐
j. Concentration ☐
k. Migraines/headaches ☐
l. Inflammation ☐
m. Instable blood pressure ☐
n. Substance use cravings ☐

o. Other - please specify: _____

B. **Wellness purposes**

a. Stress reduction ☐
b. Mindfulness ☐
c. Relaxation – calming effects ☐
d. Restoration ☐
e. Energizing ☐
f. Focus ☐
g. Improved mood ☐
h. Physical recovery ☐
i. Physical endurance ☐
j. Creativity ☐
k. Other - please specify: _____

C. Recreational purposes ☐

4. How often do you take CBD products? *Check all that apply*

a. Occasionally, less than once per month ☐
b. Once per month ☐
c. 2-3 times every two weeks ☐
d. Once per week ☐
e. 2-3 times per week ☐
f. Daily ☐

If daily, how much do you take on average per day (in milligrams)?

i. [mg] _____
ii. Don't know ☐

5. On a scale of 0 to 10, how likely are you to take the product you tested in this study again? *Check one box*

0 (Not at all likely) ☐
1 ☐
2 ☐
3 ☐
4 ☐
5 (Neutral) ☐
6 ☐
7 ☐
8 ☐
9 ☐

10 (Extremely likely) ☐

6. **How much would you be willing to pay for the product you tested in the study (assuming a box of 30 units)?** *Answer item a and b or check one box*

   a. Minimum price willing to pay (*insert a number between 1 and 100*): _____

   b. Maximum price willing to pay (*insert a number between 1 and 100, the number entered needs to be higher than the one in the minimum price*): _____
   c. I'm not willing to pay for this product ☐
   d. Unsure if I want to use/buy it ☐

11.9. Appendix 9: Columbia Suicidality Severity Rating Scale (C-SSRS)

C-SSRS Baseline Lifetime scale

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide **(e.g., "***I've thought about killing myself***")** without thoughts of ways to kill oneself/ associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out **(e.g.,** thought of method to kill self but not a specific plan). Includes person who would say **"***I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it***"**. ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to **"***I have the thoughts but I definitely will not do anything about them***"**. ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times a week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - a few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of the time (4) 4-8 hours/most of the day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOUR *(Checkmark all that apply, as long as these are separate events; must ask about all types.)*			**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of the act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so that no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons/without ANY intention of killing yourself (such as to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe:			Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behaviour?			Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or person is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:			Yes ☐ No ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:			Yes ☐ No ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:			Yes ☐ No ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?			Yes ☐ No ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches) 1. Minor physical damage (e.g., lethargic speech, first-degree burns, mild bleeding, sprains) 2. Moderate physical damage: *medical* attention needed (e.g., conscious but sleepy, somewhat responsive, second-degree burns, bleeding of major vessel) 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body, extensive blood loss but can recover, major fractures) 4. Severe physical damage: *medical* hospitalization with intensive care required (e.g., comatose without reflexes, third-degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area) 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; lying on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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C-SSRS Since Last visit Scale

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behaviour" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it"*. ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*. ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ____ ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times a week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - a few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of the time (4) 4-8 hours/most of the day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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C-SSRS—Since Last Visit (Version 2009-01-14)

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SUICIDAL BEHAVIOUR *(Checkmark all that apply, as long as these are separate events; must ask about all types.)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of the act*. Behaviour was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behaviour or circumstances. For example, a highly lethal act that is clearly not an accident so that no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons/without ANY intention of killing yourself (such as to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behaviour without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behaviour?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (*if not for that, actual attempt would have occurred*). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or person is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Interrupted _____
Aborted Attempt: When person begins to take steps towards making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behaviour. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of Aborted _____
Preparatory Acts or Behaviour: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behaviour: Suicidal behaviour was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches) 1. Minor physical damage (e.g., lethargic speech, first-degree burns, mild bleeding, sprains) 2. Moderate physical damage: medical attention needed (e.g., conscious but sleepy, somewhat responsive, second-degree burns, bleeding of major vessel) 3. Moderately severe physical damage: *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact, third-degree burns less than 20% of body, extensive blood loss but can recover, major fractures) 4. Severe physical damage: *medical* hospitalization with intensive care required (e.g., comatose without reflexes, third-degree burns over 20% of body, extensive blood loss with unstable vital signs, major damage to a vital area) 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; lying on train tracks with oncoming train but pulled away before run over). 0 = Behaviour not likely to result in injury 1 = Behaviour likely to result in injury but not likely to cause death 2 = Behaviour likely to result in death despite available medical care	*Enter Code* _____

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11.10. Appendix 10: Human Puffing Tomography Parameters

Table 9. Per-puff Parameters

Description	Variable	Unit
Puff number	Ni	
Puff volume	Vi	mL
Puff duration	Di	s
Average flow [Vi/Di]	Qmi	mL/s
Peak flow	Qci	mL/s
Inter puff interval	Ii	s
Sum of Ii and Di	DFi	s
Peak flow position	PosQci	%
Number of peaks	Pn	

Table 10. Per-product Use Experience Parameters

Description	Variable	Formula	Unit
Total number of puffs	NPC	∑ Ni	
Total puff volume	TVOL	∑ Vi	mL
Average puff volume	AvgVi	∑ Vi / NPC, i=1 ... NPC	mL
Average puff duration	AvgDi	∑ Di / NPC, i=1 ... NPC	s
Total puff duration	TDi	∑ Di	s
Average flow	AvgQmi	∑ Qmi / NPC, i=1 … NPC	mL/s
Peak flow	AvgQci	∑ Qci / NPC, i=1 … NPC	mL/s
Total inter puff interval	TIi	∑ Ii	s
Average inter puff interval	AvgIi	∑ Qci / NPC, i=1 … NPC	s
Total puffing duration	TDFi	∑ DFi	s
Puffing Intensity	SMINT	TVOL/TDFi	mL/s
Puffing Time Index	PTI	(100*TDi)/TDFi	%
Puff Frequency	PFeq	NPC/(TDFi/60)	

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VFC224-101_Protocol Version 02_09 May 2025

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