STATISTICAL ANALYSIS PLAN

Study: UP0071

Product: Padsevonil

A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, SINGLE-CENTER, CROSS-OVER STUDY TO INVESTIGATE THE PHARMACODYNAMIC, PHARMACOKINETIC, SAFETY, AND TOLERABILITY PROFILES OF PADSEVONIL IN HEALTHY STUDY PARTICIPANTS RECEIVING EITHER ETHANOL OR CANNABIDIOL

PHASE 1

SAP/Amendment Number	Date
Final SAP v1.0	27 Jan 2020

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LIST OF ABBREVIATIONS

AE(s)	adverse event(s)
AED	antiepileptic drug
ALT	alanine aminotransferase
ALQ	above the limit of quantification
AST	aspartate aminotransferase
AUCτ	area under the curve over a dosing interval (12 hrs)
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
CBD	cannabidiol
CI	confidence interval
CL/F_{ss}	apparent total clearance at steady-state
C_{max}	maximum observed plasma concentration
C_{trough}	predose plasma concentration
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DEM	data evaluation meeting
ECG	electrocardiogram
EOS	End of Study
ES	Enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
geoCV	geometric coefficient of variation
ICF	Informed Consent form
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IPD	important protocol deviation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MHD	Mono Hydroxy Derivate
n	number of study participants number of available observations
PD	Pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PKS	Pharmacokinetic Set
PK	Pharmacokinetic(s)
PR	pulse rate
PSL	Padsevonil
PT	preferred term

QTcF	QT corrected for heart rate using Fridericia's formula
RR	respiratory rate
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SFU	Safety Follow-up
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures and listings
t_{max}	time to maximum concentration
ULN	upper limit of normal
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of UP0071. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP is based on the final protocol amendment 1, dated 25 July 2019.

Unless specified in the sections below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if analysis definitions must be modified or updated prior to database lock, a SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale.

The content of this SAP is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003).

UCB is the Sponsor and ICON PLC is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives and endpoints

2.1.1 Part A

Objectives	Endpoints
Primary	
To evaluate the PD interaction between steady-state treatment with PSL and ethanol	• Smooth pursuit (%) to assess eye movement coordination and attention
Secondary	
To evaluate the PK interaction between steady-state treatment with PSL and ethanol	• Ethanol dose infused over time • $C_{max,ss}$ and $AUC_{\tau,}$ obtained from the plasma concentration-time profiles for PSL and its metabolites
To evaluate the PD interaction between steady-state treatment with PSL and ethanol	• Saccadic peak velocity (degrees/sec) to assess sedation • Adaptive tracking (%) to assess visuo-motor control and vigilance • Body Sway to assess postural stability
To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol	• Adverse events (AEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study

Other	
To evaluate the safety and tolerability of PSL in study participants receiving concomitant ethanol	• Vital signs (pulse rate, respiratory rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) • 12-lead electrocardiogram (ECG) parameters • Physical examination findings • Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)
To evaluate the PD interaction between steady-state treatment with PSL and ethanol	• Visual analogue scales (VAS) Bond & Lader to assess alertness, mood, and calmness • VAS feeling high, internal and external perception (Bowdle) • VAS for alcohol intoxication to assess the effects of ethanol
To evaluate the PK interaction between steady-state treatment with PSL and ethanol	• t_{max} and C_{trough} obtained from the plasma concentration-time profiles for PSL and its metabolites
To collect and store blood for potential ADME genotype (if needed)	• Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL (and metabolite) PK analyses
To collect urine samples for additional PK analyses depending on the outcome of PSL (and metabolite) PK analyses, if needed	• Urine sample PK analysis

2.1.2 Part B

Objectives	**Endpoints**
Primary	
To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $C_{max,ss}$ and AUC_{τ} obtained from the plasma concentration-time profiles for PSL and CBD
Secondary	
To evaluate the PK interaction between steady-state treatment with PSL and CBD	• $t_{1/2}$, and $CL_{ss/F}$ obtained from the plasma concentration-time profiles for PSL and CBD
To evaluate the PD interaction between steady-state treatment with PSL and CBD	• Smooth pursuit (%) to assess eye movement coordination and attention

	• Saccadic peak velocity (degrees/sec) to assess sedation • Adaptive tracking (%) to assess visuo-motor control and vigilance • Body Sway to assess postural stability
To evaluate the safety and tolerability of PSL in study participants receiving concomitant CBD	• Adverse events (AEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to discontinuation of the study
Other	
To evaluate the safety and tolerability of PSL in study participants receiving concomitant CBD	• Vital signs (pulse rate, respiratory rate, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) • 12-lead electrocardiogram (ECG) parameters • Physical examination findings • Clinical laboratory test results (hematology, clinical chemistry, and urinalysis)
To evaluate the PD interaction between steady-state treatment with PSL and CBD	• Visual analogue scales (VAS) Bond & Lader to assess study participant alertness, mood, and calmness • VAS feeling high, internal and external perception (Bowdle)
To evaluate the PK interaction between steady-state treatment with PSL and CBD	• t_{max} and C_{trough} obtained from the plasma concentration-time profiles for PSL and CBD • $C_{max,ss}$, AUC_{τ}, $t_{1/2}$, $t_{max,}$ and metabolite/parent ratio (based on $C_{max,ss}$ and AUC_{τ}) obtained from the plasma concentration-time profiles for PSL metabolites and CBD active metabolite
To evaluate the plasma PK of single dose of CBD (Treatment Period 1)	• C_{max}, AUC_{0-t}, AUC, t_{max}, $t_{1/2}$ and CL/F
To collect and store blood for potential ADME genotype (if needed)	• Possible ADME genotyping for drug metabolizing enzymes (depending on the outcome of PSL (and metabolite) PK analyses
To collect urine samples for additional PK analyses depending on the outcome of PSL (and metabolite) PK analyses, if needed	• Urine sample PK analysis

2.2 Study design and conduct

2.2.1 Overall study design

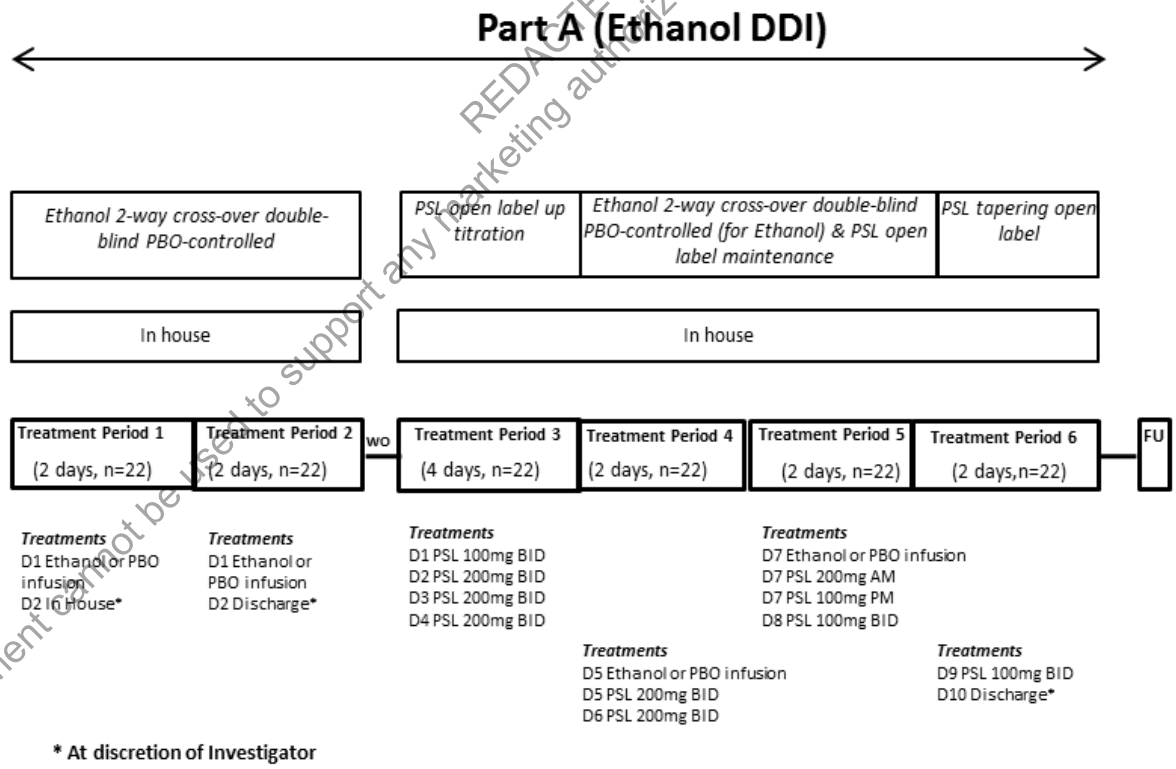
This is a Phase 1, double-blind, randomized, placebo-controlled, single-center, cross-over study to evaluate the PK, PD, safety, and tolerability of steady state treatment of PSL in healthy study participants receiving either ethanol (Part A) or steady-state treatment of CBD (Part B). Study participants that participate in Part A of the study are not eligible to participate in Part B; similarly, study participants that participate in Part B are not eligible to participate in Part A.

2.2.2 Part A

Treatment Periods 1 and 2, and 4 and 5 are 2-way cross-over, placebo-controlled, ethanol-clamping periods with a washout of at least 2 days between Treatment Periods 2 and 3; PSL is not administered in Treatment Periods 1 and 2. Treatment Period 3 is an open-label PSL up-titration period toward a maintenance level of 200mg BID and is immediately followed by Treatment Period 4 and Treatment Period 5. Treatment Period 6 is the PSL tapering open-label period. A detailed schematic diagram of Part A of the study is provided in Figure 2-1.

The objectives of Part A are to evaluate the: plasma PK, safety and tolerability of PSL and its metabolites in the presence and absence of ethanol; metabolizing capacity of ethanol in the presence and absence of PSL; effect of PSL on PD parameters in the presence and absence of ethanol; effect of ethanol on PD parameters in the presence and absence of PSL.

Figure 2-1: Study schematic – Part A



BID=twice daily; CBD=cannibidiol; D=day; FU=Follow-up Period; PBO=placebo; PSL=padsevonil; W=week
Note: Follow up will occur between 7 to 10 days after the final dose of PSL.
Note: A WO of at least 2 days will occur between Treatment Period 2 and Treatment Period 3.

Study participants will be randomized to one of four treatment sequences:

Table 2-2: Treatment Sequences – Part A

Sequence ID	Randomization Sequence	Sequence in Full
1	Ethanol(TP1)/Placebo(TP2)/ Ethanol(TP4)/Placebo(TP5)	Ethanol (TP1)/Placebo (TP2)/PSL(TP3)/ PSL+Ethanol (TP4)/PSL+Placebo (TP5)/PSL(TP6)
2	Ethanol(TP1)/Placebo(TP2)/ Placebo(TP4)/Ethanol(TP5)	Ethanol(TP1)/Placebo(TP2)/PSL(TP3)/ PSL+Placebo (TP4)/PSL+Ethanol(TP5)/ PSL(TP6)
3	Placebo(TP1)/Ethanol(TP2)/ Ethanol(TP4)/Placebo(TP5)	Placebo(TP1)/Ethanol(TP2)/PSL(TP3)/ PSL+Ethanol(TP4)/PSL+Placebo(TP5)/PSL(TP6)
4	Placebo(TP1)/Ethanol(TP2)/ Placebo(TP4)/Ethanol(TP5)	Placebo(TP1)/Ethanol(TP2)/PSL(TP3)/ PSL+Placebo(TP4)/PSL+Ethanol(TP5)/ PSL(TP6)

TP=Treatment Period.

2.2.3 Part B

Treatment Period 1 of Part B will be conducted in a sentinel cohort of healthy study participants in order to evaluate CBD safety and PK exposure under a single dose of CBD 10mg/kg (fasted conditions).

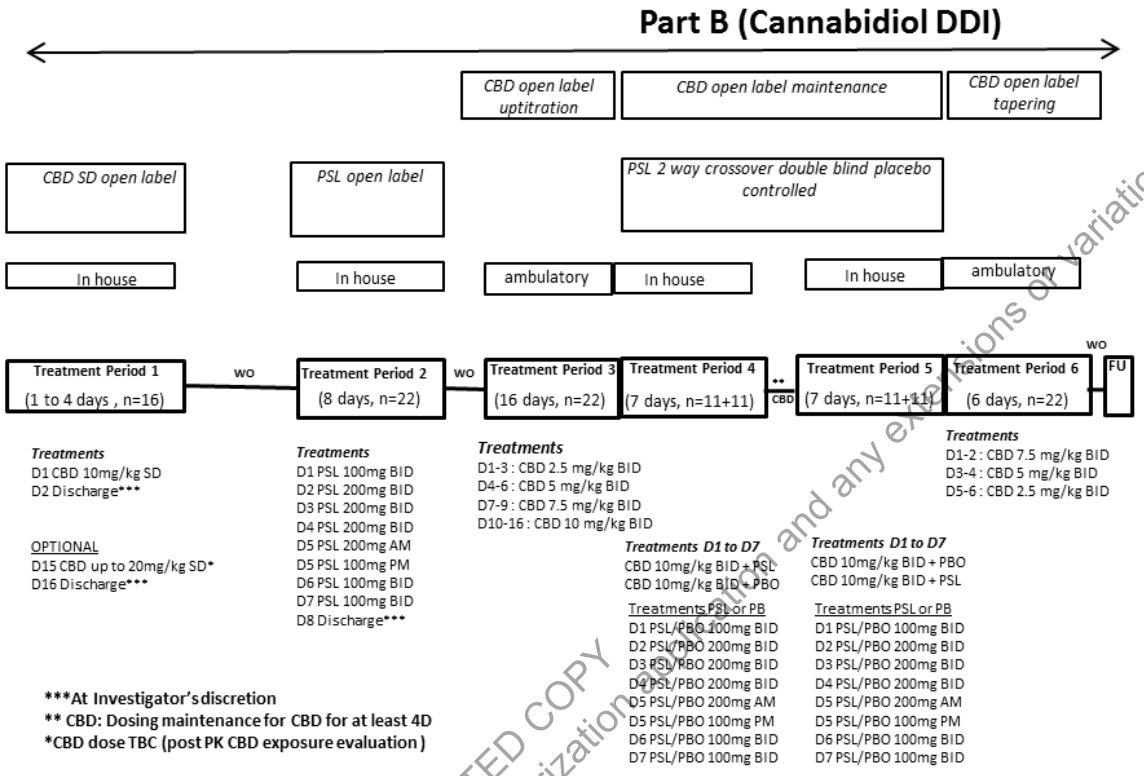
A washout of at least 6 days will occur between Treatment Period 1 and Treatment Period 2. Treatment Period 2 will include 7 days of treatment with open-label PSL treatment. Treatment Period 3 starts after a washout of minimally 6 days for all study participants and includes an ambulatory open-label CBD up titration of 16 days toward a maintenance level of 10mg/kg BID.

Treatment Periods 4 and 5 is a 2-way cross-over, double-blind and placebo-controlled periods with PSL up titrated to a maintenance level of 200mg BID through Day 5 and subsequent down titration until Day 8. A maintenance dose of 10mg/kg BID CBD will occur in-house between Treatment Periods 4 and 5. Cannabidiol down titration starts in Treatment Period 6.

A detailed schematic diagram of Part B of the study is provided in Figure 2-2.

The objectives of Part B are to evaluate the: plasma PK, safety and tolerability of PSL and its metabolites in the presence and absence of CBD; plasma PK of CBD and its metabolites in the presence and absence of PSL; effect of PSL on PD parameters in the presence and absence of CBD; effect of CBD on PD parameters in the presence and absence of PSL.

Figure 2-2: Study schematic – Part B



Note: Follow up will occur between 7 to 10 days after the final dose of CBD.
Note: A WO of at least 6 days will occur following Treatment Period 1 and Treatment Period 2.
BID=twice daily; CBD=cannabidiol; D=day; FU=Follow-up Period; PBO=placebo for PSL; PSL=padsevonil; SD=single dose; W=week

Study participants will be randomized to one of two treatment sequences:

Table 2-2: Treatment Sequences – Part B

Sequence ID	Randomization Sequence	Sequence in Full
1	CBD 10mg/kg BID+PSL(TP4)/ CBD 10mg/kg BID+Placebo(TP5)	PSL(TP2)/CBD(TP3)/ CBD 10mg/kg BID+PSL(TP4)/ CBD 10mg/kg BID+Placebo(TP5)/ CBD(TP6)
2	CBD 10mg/kg BID+Placebo(TP4)/ CBD 10mg/kg BID+PSL(TP5)	PSL(TP2)/CBD(TP3)/ CBD 10mg/kg BID+Placebo(TP4)/ CBD 10mg/kg BID+PSL(TP5)/CBD(TP6)

TP=Treatment Period.

2.3 Determination of sample size

Based on the study PK and PD objectives, the total planned number of healthy study participants will be 44, including 22 evaluable participants for Part A and 22 evaluable participants for Part B.

For Part A, the sample size is based on pragmatic considerations and the ability to detect an ethanol effect on PD assessments (CNS variable). A sample size of 22 evaluable study participants provides 80% power to detect an ethanol effect in a difference in means of 3.96 (% points) for the smooth pursuit test, which is the most sensitive CNS variable to ethanol effects, assuming a SD of difference of 6.0 (% points) based on previous ethanol clamp interaction studies and using a paired t-test 2-sided with a 0.05 significance level. This sample size is also valid for the CBD effect assessment (Part B). The sample size calculation performed does not assess the difference in means between PSL+Ethanol effect vs PSL+Placebo, as the expected difference between the interaction is unknown but similarly a difference of 3.96 (% points) could be detected.

For Part B, a sample size of 22 evaluable study participants is needed to assess the PK interaction between PSL and CBD, and to estimate the mean PSL AUC_τ ratio of with/without CBD of 1.5 with a half-width of the CI of 0.3. This sample size has been evaluated with a conditional probability of 90%, assuming an inter-participant coefficient of variation of 45% of PSL AUC_τ (observed in study UP0057), correlation of 0.5, 2-sided and $\alpha = 0.05$. A sufficient number of healthy study participants (up to 20) will be selected to have 16 completed study participants.

Regarding the assessment of the single dose formulation of CBD (under fasted conditions) in Part B (study formulation vs Epidiolex formulation from literature data), 16 healthy study participants are required to assess the similarity of the 2 formulations (equivalence range of 50 to 200% based on the high variability of CBD) with a 80% power and assuming an expected geometric mean ratio of AUC and C_{max} between 0.8 and 1.3, and inter-participant CV of 80% (based on CBD literature) and correlation of 0.5.

Sample size computations were performed using SAS version 9.4 (Proc Power).

Drop outs will be replaced at the discretion of the Investigator and Sponsor.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Each study part will be summarized and analyzed separately.

Statistical evaluation will be performed by ICON PLC with the exception of PD which will be conducted to UCB. The datasets will follow the UCB analysis data model (ADaM) data specifications.

All analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, United States). The PK noncompartmental analysis (NCA) will be performed using Phoenix WinNonlin®v6.3 or higher (Certara L.P., Princeton, NJ, USA) for pharmacokinetics parameters estimation. All non-PD TFLs will be produced by ICON PLC SAS programming (Early Phase).

Continuous variables will be summarized by phase (defined in Section 3.5), treatment and timepoint (where applicable) including number of study participants (n), mean, standard deviation (SD), median, minimum, maximum and 95% confidence intervals (CI) for the mean. Geometric coefficient of variation (geoCV), geometric mean and 95% confidence interval (CI) for the geometric mean will also be presented in the descriptive statistics for the PK concentration data and PK parameters of; PSL and its metabolites ([redacted] and

[redacted]), and CBD and its active metabolite. In all outputs the confidence limits will be restricted to the possible values that the variable can take.

Categorical variables will be summarized by phase, treatment and timepoint (where applicable) with frequency counts and percentages.

3.2 General study level definitions

3.2.1 Study day

For Part A, study day consist of Day -1 (prior to Treatment Period 1) to approximately Day 16 (last day of Treatment Period 6).

For Part B, study day consists of Day -1 (prior to Treatment Period 1) to approximately Day 53 (last day of Treatment Period 6).

Relative day will not be used in this study. Instead refer to Section 3.2.1 for use of Study Day.

3.3 Definition of Baseline values

Measurement-specific Baseline timepoints are presented in Table 3–1.

Table 3–1: Definition of Baseline

Measurement	Definition of Baseline
Hematology, serum chemistry, urinalysis	For Part A, baseline is defined as the visit at which study participants were randomized to one of the four treatment sequences i.e. Day -1 prior to Treatment Period 1. For Part B, baseline is defined as Day -1 prior to Treatment Period 2. For both study parts, if Day -1 is missing or multiple assessments occur, the last measure prior to dosing will be used.
Vital Signs	For Part A, baseline is defined as predose on Day 1 of Treatment Period 1. For Part B, baseline is defined as predose on Day 1 of Treatment Period 2. For both study parts, if predose on Day 1 is missing or multiple assessments occur, the last measure prior to dosing will be used.
ECG	For Part A, the mean of the last three measurements predose on Day 1 of Treatment Period 1 will be taken as baseline. For Part B, the mean of the last three measurements predose on Day 1 of Treatment Period 2 will be taken as baseline. For both study parts. if less than three replicates are available predose, the mean of the available replicates (predose) will be taken as baseline.
C-SSRS	For both study parts, separate baseline questionnaire for C-SSRS.

Measurement	Definition of Baseline
PD variables	For both study parts, baseline for change from baseline summaries and tables is defined as the average of the two values measured at predose of given day. Baseline definition for the model is defined in Section 10.1.2.

The change from Baseline to any subsequent post-Baseline visit will be calculated as the simple difference between that post-Baseline visit's value and the Baseline visit value, as below:

$$Post\ Baseline\ Visit\ Value - Baseline\ Visit\ Value$$

3.4 Protocol deviations

Important protocol deviations (IPD) are deviations from the protocol which potentially could have a meaningful impact on study conduct or on either the primary outcome or key secondary outcome for an individual study participant. The criteria for identifying such protocol deviations will be defined within the protocol deviation specifications document.

Important protocol deviations will include the following categories:

- Inclusion/exclusion criteria deviations
- Administration of prohibited concomitant medications
- Deviations relating to withdrawal criteria
- Visit schedule deviations
- Study drug administration deviations (including incorrect treatment received, handling and storage deviations and incorrect dosage received) and any vomiting episode(s) (that could impact PK concentrations)
- Procedural noncompliance
- Missing data

All IPDs will be reviewed as part of the ongoing data cleaning process and data evaluation. After all data have been verified/coded/entered into a database, a data evaluation meeting (DEM) will be performed.

At least one DEM will be performed at the following time:

- Prior to the final analysis after all data have been verified/coded/entered into the database

Additional DEMs may be conducted as deemed necessary.

The purpose of these DEM reviews will be to review all protocol deviations, define the analysis sets, and check the quality of the data. The reviews will also help decide how to manage problems in the study participants' data (e.g. missing values, withdrawals and protocol deviations).

Accepted deviations from scheduled time points will be described in the appropriate documents and included in the Study Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions (including inclusion into each of the analysis sets) at the final DEM, the database will be locked.

3.5 Analysis Sets

The following analysis sets apply and will be created separately for each study part.

3.5.1 All Study Participants

All Study Participants will consist of all participants who have signed the Informed Consent form (ICF). This set was previously referred to as Enrolled Set in the Study Protocol.

3.5.2 Safety Set

The Safety Set (SS) will consist of all study participants who are randomized and have received at least 1 dose (any amount) of study medication. Safety variables will be analyzed using the SS.

It is expected that study participants will receive treatment as randomized; hence, safety analyses will be based on the randomized treatment group. However, if after unblinding it is determined that study participants received the incorrect treatment (i.e. not as per the randomization schedule), then for safety analyses study participants will be allocated to the actual treatment they received (as-treated) for the data summaries.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) consists of all study participants that were randomized, received study medication, and had at least one valid post-baseline primary PD assessment observation. It is intended that study participants will be classified according to the treatment which was actually received.

3.5.4 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) consists of all study participants that received at least one dose of active study drug and have at least one observable PK measurement. If a study participant in the PK set is missing individual timepoints or are otherwise unobservable will be included in the PK set but those timepoints will be omitted from the PK summaries, as appropriate.

3.6 Treatment assignment and treatment groups

3.6.1 Part A

For all analyses (where applicable) the results will be presented by phase and treatment. For summary tables, results from Treatment Period 3 and 6 will be presented by PSL. Sequence in full will be used where applicable (defined in Section 2.2.2).

Phase, phase day, treatment (for listings and tables) and the corresponding treatment period and day from the protocol are defined in Table 3-2.

Table 3–2: Definition of Phase - Part A

Protocol Treatment Period	Protocol Treatment Period Day	Phase	Phase Day	Treatment for Listings	Treatment for Tables
Screening	-28 to -2	Screening	-28 to -2	N/A	N/A
1	-1 to 2	Ethanol Phase	-1 to 2	Ethanol/Placebo	Ethanol/Placebo
2	1 to 2	Ethanol Phase	3 to 4	Ethanol/Placebo	Ethanol/Placebo
Washout Period	-	Ethanol Phase	5 to 6	Ethanol/Placebo	Ethanol/Placebo
3	-1	Interaction Phase	-1	Ethanol/Placebo	Ethanol/Placebo*
3	1	Interaction Phase	1	PSL up-titration	PSL
3	2 to 4	Interaction Phase	2 to 4	PSL maintenance	PSL
4	5	Interaction Phase	5	PSL+Ethanol/PSL+Placebo	PSL+Ethanol/PSL+Placebo
4	6	Interaction Phase	6	PSL maintenance	PSL
5	7	Interaction Phase	7	PSL+Ethanol/PSL+Placebo	PSL+Ethanol/PSL+Placebo
5	8	Interaction Phase	8	PSL tapering	PSL
6	9 to 10	Interaction Phase	9 to 10	PSL tapering	PSL
Follow-up	-	Follow-up	17 or 20	N/A	N/A

- = Day not specified in protocol; * If assessments are summarized by treatment, phase and day, then data will be presented as: PSL, Interaction Phase, Day -1. If assessments are summarized by treatment, then data from Day -1 will attribute to either Ethanol or Placebo e.g. if an AE occurs on Day -1, then the AE will be summarized where treatment is Ethanol or Placebo since this is the most recent treatment received.

3.6.2 Part B

For all analyses (where applicable) the results will be presented by phase and treatment. For summary tables, results from Treatment Period 3 and 6 will be presented by CBD. Listings will also include phase day. Sequence in full will be used where applicable (defined in Section 2.2.3).

Phase, phase day, treatment (for listings and tables) and the corresponding treatment period and day from the protocol are defined in Table 3-3.

Table 3–3: Definition of Phase - Part B

Protocol Treatment Period	Protocol Treatment Period Day	Phase	Phase Day	Treatment for Listings	Treatment for Tables
Screening	-28 to -2	Screening	-28 to -2	N/A	N/A
1	-1 to 2 (optional 15-16)	CBD Phase	-1 to 2 (optional 15-16)	CBD SD	CBD
Washout Period	-	CBD Phase	3 to 8 (or 17 to 22)	CBD SD	CBD
2	-1	PSL Phase	-1	CBD SD	CBD[a]
2	1 to 8	PSL Phase	1 to 8	PSL	PSL
Washout Period	-	PSL Phase	9 to 14	PSL	PSL
3	-1	Interaction Phase	-1	PSL	PSL[b]
3	1 to 16	Interaction Phase	1 to 16	CBD up-titration	CBD
4	1 to 7	Interaction Phase	17 to 23	CBD+PSL/CBD+Placebo	CBD+PSL/CBD+Placebo
CBD Dose Maintenance	-	Interaction Phase	24 to 27[c]	CBD maintenance	CBD
5	1 to 7	Interaction Phase	28 to 34	CBD+PSL/CBD+Placebo	CBD+PSL/CBD+Placebo

Protocol Treatment Period	Protocol Treatment Period Day	Phase	Phase Day	Treatment for Listings	Treatment for Tables
6	1 to 7	Interaction Phase	35 to 41	CBD tapering	CBD
Follow-up	-	Follow-up	47 or 50	N/A	N/A

- = Day not specified in protocol; [a] If assessments are summarized by treatment, phase and day, then data will be presented as: PSL, PSL Phase, Day -1. If assessments are summarized by treatment, then data from Day -1 will attribute to CBD. [b] If assessments are summarized by treatment, phase and day, then data will be presented as: CBD, Interaction Phase, Day -1. If assessments are summarized by treatment, then data from Day -1 will attribute to PSL.
[c] CBD dose maintenance will occur for at least 4 days. If dosing is maintained for more than 4 days, the phase day will need to be changed accordingly;

3.7 Center pooling strategy

This is a single center trial.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 22.1). Medications will be coded according to the World Health Organization Drug Dictionary (WHODD) (Version SEP/2017). Medical procedures will not be coded.

3.9 Changes to protocol-defined analyses

- Due to changes in ClinPharm Standards, Enrolled Set has been changed to All Study Participants Set, Pharmacokinetic Per-Protocol Set has been changed to Pharmacokinetic Set and Pharmacodynamic Per-Protocol Set has been removed.
- For Part A and B, period has been removed from the mixed analysis of variance (ANOVA) in the cases where it is confounded with treatment for PK and PD.
- For Part B, analysis of metabolite to parent ratio based on AUC$_\tau$ has been included for completeness.
- For Part A and B baseline by time interactions have been added.
- The following parameters were intended but omitted from the protocol and are included for completeness:
  - For Part A, t_{max} and C_{trough} have been included as PK parameters for PSL and its metabolites
  - For Part A, $C_{max,ss}$ and AUC_τ have been included as PK parameters for PSL metabolites
  - For Part B, C_{trough} has been included as PK parameters for PSL and CBD
  - For Part B, C_{max}, AUC_{0-t}, AUC, t_{max}, $t_{1/2}$ and CL/F have been included as PK parameters for the single dose of CBD within Treatment Period 1

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

For the analysis of PD parameters, the within study participant baseline and between study participant baseline (defined in Section 10.1.2) will be included in the model as a covariate.

4.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data unless otherwise stated below. Missing data will be handled as described in the sections below for safety laboratory and PK results. No other imputations will be performed.

4.2.1 Pharmacokinetics

The 95% CI lower and 95% CI upper should be left blank if the SD (or equivalently, the geometric CV) is 0. Measurements of PK concentrations that are below the limit of quantification (BLQ) and which are occurring prior to t_{max} will be imputed with half of the lower

limit of quantification (LLOQ/2), except for embedded BLQ values (between two measurable data points) which will be treated as missing, for the purpose of calculating the geometric mean and its 95% CI, the geometric CV, the arithmetic mean and SD for summaries and figures. Post-t_{max}, BLQ values will be treated as missing. Descriptive statistics of concentrations will be calculated if at least 2/3rd of the individual data points are quantifiable (≥LLOQ).

For all individual PK concentration figures any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with "LLOQ/2" for linear scale plots.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as "(BLQ)" in the listings
- Descriptive statistics of plasma and dried blood concentrations will be calculated if more than 2/3rd of individual data points are quantifiable (>=LLOQ) at the given time-point. Values that are BLQ will be replaced by the numerical value of the LLOQ/2 in this instance.

However, if n<3, then only n, minimum and maximum will be presented, and the median will also be presented if n=3. The other descriptive statistics will be left blank.

- For t_{max}, only N, median, minimum and maximum will be displayed into the summary statistics
- For plasma concentrations, all BLQ values occurring prior to t_{max} will be replaced by "LLOQ/2", except for embedded BLQ values (between two measurable data points) which will be treated as missing. Post- t_{max}, BLQ values will be treated as missing. The Pharmacokinetic analysis will be performed in accordance to the Guideline on performing NCA analysis dated 08 Nov 2017.
- For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of predose BLQ measurements which will be imputed with "LLOQ/2" for linear scale plots.
- If no study participants have data, only n=0 will be presented. The other descriptive statistics will be left blank.
- The geometric CV will be calculated using the following formula where SD is the standard deviation from the log-transformed data:

$$\text{Geometric CV (\%)} = \text{sqrt}[(\exp(\text{SD}^2) - 1)] \times 100$$

4.2.2 Safety laboratory data

The rules for handling values that are BLQ or above the limit of quantification (ALQ) in the safety laboratory data will be the same as those described for PK data in Section 4.2.1.

4.2.3 Electrocardiogram data

For the 12-lead ECG data, all calculations of changes from Baseline and descriptive statistics will be based on the mean of the triplicate assessments at each timepoint. In the event that there are not 3 available measurements at a given timepoint, the mean will be calculated based on the number of measurements for which data are provided.

4.3 Interim analyses and data monitoring

Treatment Period 1 of Part B will be conducted in a sentinel cohort of healthy study participants in order to evaluate the PK exposure under a single dose of CBD 10mg/kg (fasted conditions). The results of the PK analysis from the first dose of CBD in Treatment Period 1 (Part B) will be compared to published PK data of CBD (dose of 750mg in fasted conditions) obtained in similar conditions with Epidiolex® (Taylor et al, 2018). The UCB study team will determine whether it is appropriate to proceed to Treatment Period 2, to proceed with the second single dose of CBD 20mg/kg or to terminate Part B of the study.

If the observed CBD exposure matches the data from the literature, then study will proceed directly to Treatment Period 2 of Part B (no second dosing of CBD will be required). A difference between the PK results in the present study and the literature findings requiring a >2-fold dose adjustment will be considered as not manageable and would result in termination of Part B of the study. If a dose adjustment ≤2-fold is needed, then there may be a second dose of CBD administered to a cohort of healthy study participants within Treatment Period 1 in Part B.

If the second dose is required, the results of the PK analysis from the second dose of CBD will be compared to published PK data of CBD. The UCB team will determine whether it is appropriate to proceed to Treatment Period 2 or to terminate Part B of the study.

Treatment Period 2 cannot commence until the PK results from Treatment Period 1 are assessed.

Pre-programming on the PD data has the potential to unblind study personnel. Hence the programming of SDTM (ICON) and ADaM and TFLs (UCB) will be done by teams independent to the study team.

No interim analysis or data monitoring are planned in this study.

4.4 Multicenter studies

Not applicable.

4.5 Multiple comparisons/multiplicity

Multiple comparisons will not be accounted for.

4.6 Use of an efficacy subset of study participants

Not applicable.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Participant disposition

Study participant disposition will be listed by treatment sequence for All Study Participants and will include the following information: study participant status (screen failure, study completed or discontinued, study drug completed or discontinued, study drug discontinued, but study

continued), date of informed consent, date of randomization, date of first and last dose of study drugs, date of premature study and/or study drug termination (if applicable) and primary reason for study and/or study drug termination (if applicable). The listing will also include the date and reason for breaking the randomization code (if applicable) as well as the date of final contact for the study participant and the previous study participant number, if a study participant was re-screened.

Study participant disposition will be summarized overall for All Study Participants Screened including the reasons for screen failure, the number of study participants re-screened, the number of study participants randomized, reasons for discontinuation of study and/or study drug and the number of study participants with premature termination of study drug but not early withdrawn from the study.

The number and percentage of study participants included in each of the analysis sets will be summarized for All Study Participants by treatment sequence. Percentages will be calculated based on All Study Participants for the purpose of this summary.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types in the IPD document. A listing of all IPDs identified at the DEM will be presented for all study participants by phase based on the FAS and will include the deviation type and description.

6 DEMOGRAPHICS

A listing of demographics by study participant and treatment sequence will be presented for All Study Participants. This will include the year of birth, age (in years), sex, race, ethnicity, height (cm), weight (kg) body mass index (BMI, in kg/m2). The body weight will be the measurement obtained at Screening.

Body mass index (kg/m2) is calculated based on the height (m) and the weight (kg) using the following formula:

$$BMI\ (kg/m^2) = weight(kg)/[height(m)]^2$$

The BMI will be reported to 1 decimal place.

All demographic characteristics (except for date of birth) will be summarized for the SS by sequence and overall. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years

- ≥65 years

6.1 Medical history and concomitant diseases

Medical history and ongoing medical conditions will be listed and summarized for the SS by treatment sequence, MedDRA system organ class (SOC) and preferred term (PT). The reported term will be included in the listing. The summary will include the number and percentage of study participant and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Study Participants' column.

6.2 Concomitant medications

Concomitant medications will be listed and summarized for the SS by treatment sequence and will include WHODD Anatomical Main Group [Level 1 term text], Pharmacological Subgroup [Level 3 term text] and PT. The reported term will be included in the listing. Separate tabulations will be presented for prior medications and concomitant medications. All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Study Participants' column.

7 MEASURES OF TREATMENT COMPLIANCE

As dosing is performed in-house by the investigator or member of staff, no specific assessment or compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR. Administration of study medications will be listed.

8 EFFICACY ANALYSES

Not applicable.

9 PHARMACOKINETICS

The calculation of the PK parameters of PSL and its metabolites ([redacted]), CBD and its metabolite (7-hydroxy-CBD) will be performed by the Quantitative Clinical Development Department, ICON PLC.

Pharmacokinetic concentrations and parameters will be summarized by phase and treatment using the PKS. Figures of summaries will be based on the PKS and figures of individual concentrations will be based on the FAS.

Pharmacokinetic parameters of PSL, CBD and metabolites will be calculated using the actual blood sampling times. $C_{max,ss}$ and t_{max} will be determined from the observed concentration and time data. When two or more identical peak concentrations are observed, t_{max} will be defined as the time of the first occurrence. AUCτ will be computed using the linear trapezoidal rule.

For Part A, the PK variables used for PSL and its metabolites are: $C_{max,ss}$, AUCτ, t_{max} and C_{trough}; and for ethanol, total ethanol dose will be used.

For Part B, the following PK variables used for PSL and CBD:

- Primary: $C_{max,ss}$ and AUCτ
- Secondary: CLss/F and $t_{1/2}$
- Other: t_{max}

In addition, the other PK variables (for Part B) used are:

- C_{max}, AUC_{0-t}, AUC, t_{max}, $t_{1/2}$ and CL/F for the single dose of CBD (Treatment Period 1)
- $C_{max,ss}$, AUCτ and t_{max} for PSL metabolites and CBD metabolite
- The metabolite to parent ratio (based on $C_{max,ss}$ and AUC_{τ}) obtained from the plasma concentration-time profiles for PSL metabolites and CBD active metabolite

Metabolite to parent ratios will be corrected for molecular weight. The molecular weight (MW) of: PSL is 432.8; metabolite [redacted] is [redacted]; metabolite [redacted] is [redacted]; CBD is 314 and 7-hydroxy-CBD is 330.

For both study parts, depending on the outcome of the PK analyses of PSL and its metabolites, urine samples for additional PK analyses will be collected for measurement of urine concentrations of PSL and its metabolites if needed.

9.1 Analysis of pharmacokinetics variables

Pharmacokinetic variables will be analyzed separately for each study part.

9.1.1 Descriptive figures and summaries

The PK plasma concentrations and the PK parameters of PSL, CBD and metabolites will be summarized by phase, treatment and nominal sampling times using descriptive statistics (number of available observations [n], arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming lognormally distributed data]). Any samples that are obtained outside the tolerance window permitted at the specified time point will be discussed at the DEM and any possible exclusion from analysis will be documented accordingly. Values below the LLOQ will be reported with a clear sign (flag variable in the dataset) indicating that they were below the LLOQ. The plasma trough concentrations of PSL, CBD and metabolites will be summarized separately.

Individual participant concentration-time profiles of PSL and CBD by treatment (For Part A: PSL+Ethanol and PSL+Placebo, for Part B: CBD (single dose from Treatment Period 1), CBD+PSL and CBD+Placebo) will be displayed graphically in linear and semi-logarithmic scale.

Combined individual (spaghetti) plots will be displayed by treatment with all participants overlaid on the same plot (linear and semi-logarithmic scale).

Geometric mean profiles of plasma concentrations for PSL and CBD over time will be presented, with all treatments overlaid on the same plot, in both linear and semi-logarithmic scale. For the linear scale plot only, the lower and upper 95% confidence interval (CI) for the geometric mean will be displayed.

All plasma concentration figures will include the LLOQ on the semi-logarithmic scale plots and will be based on scheduled times.

Individual breath ethanol concentration-time data will be summarized by phase, treatment and nominal sampling times presenting the number of observations, geometric mean, lower and upper limit of the 95% CI for the geometric mean, geoCV(%), arithmetic mean, SD, median, minimum, and maximum. Individual participant breath ethanol concentration-time profiles will be displayed graphically in linear scale. Total ethanol dose will also be summarized by treatment.

The amount of urinary excretion of PSL (mg) per time interval after oral administration of PSL will be summarized by phase and treatment if measured.

9.1.2 Statistical analysis of pharmacokinetics variables

The log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of PSL, CBD and metabolites, metabolite to parent ration based on AUC_{τ} (for Section 9.1.2.3 and Section 9.1.2.4 only) and total ethanol dose will be analyzed separately by a mixed analysis of variance (ANOVA) with period, treatment and sequence as fixed effects and study participant by period and study participant as the random effects.

Due to the confounding of treatment within period within the design only the periods of interest will be included in any given comparison. For example, if the comparison is within the interaction phase then only Periods 4 and 5 will be kept in the model.

Period should be removed from the model statement due to confounding with treatment in any comparisons where either test or reference period only contains one treatment option. It will be left in the random statement as period is synonymous with treatment.

The PK parameter, t_{max}, of PSL, CBD and metabolites will be analyzed separately with the non-parametric Hodges-Lehmann method to compute point estimates and associated 90% confidence intervals for the median of differences ((PSL+CBD) – CBD, and (PSL+CBD) – PSL).

9.1.2.1 Ethanol interaction on PSL (Part A)

The log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of PSL and its metabolites will be analyzed separately by a mixed ANOVA with period (Treatment Period 4 and 5) and treatment (PSL+Ethanol and PSL+Placebo) as fixed effects and study participant as the random effect to assess the effects of ethanol on PSL.

Point estimates for the ratio of geometric means with and without ethanol (PSL+Ethanol vs PSL+Placebo) and the respective 2-sided 90% CIs will be computed using the least squares means and the root mean squares of error from the mixed effects model, based on the log-transformed data with subsequent exponential transformation.

Lack of ethanol effect on PSL will be concluded if the 90% CI of the ratio between PSL+Ethanol and PSL+Placebo of the least squares means for the log transformed AUC_{τ}, and $C_{max,ss}$ is within the conventional acceptance range of 80% to 125%.

9.1.2.2 PSL interaction on ethanol (Part A)

The individual metabolizing capacity will be characterized by calculating the total ethanol dose, i.e. the total amount of ethanol infused during Treatment Period 1/2 and Treatment Period 4/5.

Total ethanol dose will be analyzed by the model specified in Section 9.1.2, where period includes Treatment Periods 1 or 2 and 4 or 5, and treatment includes PSL+Ethanol and Ethanol, to assess potential differences of metabolizing capacity between treatments. The ratio of the least squares means with and without PSL (PSL+Ethanol vs Ethanol), and its 90% CI will be calculated.

9.1.2.3 CBD interaction on PSL (Part B)

The log-transformed PK parameters ($C_{max,ss}$, AUC_{τ}) of PSL and its metabolites, and the metabolite to parent ratio based on AUC_{τ} (no transformation required) will be analyzed

separately by a mixed ANOVA with treatment (PSL (Treatment Period 2) and CBD+PSL (Treatment Period 4/5)) as a fixed effect and study participant as the random effect to assess the effects of CBD on PSL. The SAS code stated in Section 9.1.2 will be used with period removed.

Point estimates for the ratio of geometric means with and without CBD (CBD+PSL vs PSL) and the respective 2-sided 90% CIs will be computed using the least squares means and the root mean squares of error from the mixed effects model, based on the log-transformed data with subsequent exponential transformation.

9.1.2.4 PSL interaction on CBD (Part B)

The log-transformed PK parameters ($C_{max,ss}$, AUC_τ) of CBD and its metabolite, and the metabolite to parent ratio based on AUC_τ (no transformation required) will be analyzed by the model specified in Section 9.1.2, where period includes Treatment Periods 4 and 5 and treatment includes CBD+PSL and CBD+Placebo, to assess the effects of PSL on CBD.

Point estimates for the ratio of geometric means with and without PSL (CBD+PSL vs CBD+Placebo) and the respective 2-sided 90% CIs will be computed using the least squares means and the root mean squares of error from the mixed effects model, based on the log-transformed data with subsequent exponential transformation.

10 PHARMACODYNAMICS

Pharmacodynamic parameters (absolute values and change from Baseline) will be summarized by phase, treatment, phase day and timepoint using the FAS. Figures of summaries and individual assessments will be based on the FAS.

The PD parameters include:

- Smooth Pursuit Eye Movements
- Body Sway
- VAS Mood and Alertness (Bond & Lader)
- VAS feeling high, internal and external perception (Bowdle)
- Saccadic eye movements
- Adaptive tracking
- VAS alcohol intoxication (Part A only)

For the derivation of VAS feeling high, internal and external perception (Bowdle) and VAS Mood and Alertness (Bond & Lader) see Appendix 14.1 and Appendix 14.2 respectively. The raw values of VAS alcohol intoxication will be presented, and any derivation required will be outlined in CSR.

10.1 Analysis of pharmacodynamics variables

Pharmacodynamic parameters will be analyzed separately for each study part.

10.1.1 Descriptive figures and summaries

The PD parameters (absolute values and changes from baseline) will be summarized by phase, treatment and timepoint using descriptive statistics (number of available observations [n],

arithmetic mean, median, SD, minimum, maximum, geometric mean, geometric CV and 95% CI for the geometric mean [assuming lognormally distributed data]).

Individual participant profiles of PD parameters over time will be generated using the FAS.

Graphs of the Least Squares Means estimates over time by treatment will be presented with 95% confidence interval (CI) as error bars.

10.1.2 Statistical analysis of pharmacodynamics variables

For the analysis of PD variables, there will be two baselines per study participant (Kenward-Rogers, 2010):

1. Between subject baseline = mean of all predose PD parameter for each subject
2. Within subject baseline = baseline at given day – between subject baseline

The PD parameters will be analyzed separately by a repeated measures ANOVA with treatment, time, treatment by time, period and sequence as fixed effects; time as repeated measure; with subject by period and subject as random effects and within subject baseline and between subject baseline and the baseline interactions with time as covariates. Section 10.1.2.1 and Section 10.1.2.2 specify which treatments to include in the model.

Due to the confounding of treatment within period within the design only the periods of interest will be included in any given comparison. For example, if the comparison is within the interaction phase then only Periods 4 and 5 will be kept in the model.

Period should be removed from the model statement due to confounding with treatment in any comparisons where either test or reference period only contains one treatment option. It will be left in the repeated statement as period is synonymous with treatment.

The following SAS code may be used for the repeated measures ANOVA stated above:

Contrasts for each PD variable will be reported along with 95% CI. Variables will initially be analyzed without transformation, but if visual inspection of the residual plots suggest otherwise (data are not normally distributed), an appropriate transformation may be applied.

Further exploratory analyses for PD variables may be conducted by UCB.

10.1.2.1 Ethanol and PSL (Part A)

The similarity of PD parameters between treatments will be analyzed using the model specified in Section 10.1.2, where treatment includes Ethanol, Placebo, PSL+Ethanol and PSL+ Placebo.

The following contrasts will be calculated within the model:

- PSL+Ethanol (Treatment Period 4/5: Day 5/7) vs PSL+Placebo (Treatment Period 4/5: Day 5/7) (primary comparison)
- PSL+Placebo (Treatment Period 4/5: Day 5/7) vs Placebo (Treatment Period 1/2: Day 1)
- Ethanol (Treatment Period 1/2: Day 1) vs Placebo (Treatment Period 1/2: Day 1)
- PSL+Ethanol (Treatment Period 4/5: Day 5/7) vs Ethanol (Treatment Period 1/2: Day 1)

10.1.2.2 CBD and PSL (Part B)

The similarity of the PD parameters between treatment will be analyzed using the model specified in Section 10.1.2, where treatment includes CBD, PSL, CBD+PSL and CBD+Placebo.

The following contrasts will be calculated within the model:

- CBD+PSL (Treatment Period 4/5: Day 5) vs PSL (Treatment Period 2: Day 5) (primary comparison)
- CBD+PSL (Treatment Period 4/5: Day 5) vs CBD (Treatment Period 3: Day 16)
- CBD+PSL (Treatment Period 4/5: Day 5) vs CBD+Placebo (Treatment Period 4/5: Day 5)

This analysis will also be performed for PD variables measured in Treatment Period 4/5, Day 1. Any treatment effect may be compounded by time in the first and second comparison stated above. Additionally, there may be a learning effect due to study participants performing the PD assessments multiple times.

11 SAFETY ANALYSES

All safety summaries and listings will be performed using the SS.

11.1 Extent of exposure

Administration of treatments will be listed by study participant. For PSL and CBD, the listing will include the date and time of administration of the morning and evening dose, and total daily dose. For ethanol infusion, the listing will include the date of infusion, start and stop time of infusion, duration of infusion and total volume of ethanol given.

Exposure data will be listed only.

11.2 Adverse events

All AEs will be coded using the MedDRA® and characterized as pre-treatment and treatment emergent according to the intake of each treatment. Adverse events with a start date prior to the first dose of treatment will be defined as pre-treatment AEs. A treatment-emergent AE (TEAE) is defined as any AE with a start date/time on or after the first dose of treatment or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment.

Adverse events will be attributed to the most recent treatment received. Adverse events that occur during the washout periods will be assigned as treatment emergent with regards to the treatment of the previous period.

The number and percentage of participants who experience TEAEs will be summarized by MedDRA SOC, PT and treatment.

Summaries of TEAEs will include the following:

- Incidence of overall TEAEs (overview including number and percentage of study participants with any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs and TEAEs leading to death; event counts will also be included)
- Incidence of TEAEs
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by relationship
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants

Additional summary tables of fatal, serious and discontinuations due to TEAEs by relationship will be produced if more than one of these events occurs.

Summary tables will contain counts of study participant, percentages of study participants in parentheses and the number of events where applicable. A participant who has multiple events in the same SOC and PT during a given treatment will be counted only once in the participant counts for that treatment, but all events will be included.

In summaries including relationship, the following relationships will be summarized: 'Not related', 'Related'. Participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered alphabetically by SOC and decreasing frequency of PT within SOC in the group column for tables including event counts. For tables including only number and percentage of study participants, summaries will be ordered alphabetically by SOC and decreasing incidence of PT within SOC in the group column.

Listings of AEs and TEAEs will include the following:

- All AEs
- Incidence of all TEAEs
- All Serious AEs
- Discontinuation due to AEs

All listings (expect incidence of all TEAEs) will be presented by study participant and treatment sequence and will include the onset date/time and outcome date/time of the event, most recent treatment received, the event duration (derived), time to onset (derived), pattern of event, intensity, relationship, action taken, outcome and AEs that led to discontinuation, TEAEs and SAEs will be flagged.

The listing of incidence of all TEAEs will be presented by treatment and will include intensity, relationship, severity, number of study participants reporting at least one TEAE within SOC/PT, number of individual occurrences of TEAE and site-study participant number.

11.3 Clinical laboratory evaluations

All laboratory results (clinical chemistry, hematology and urinalysis) outside the normal ranges will be listed by study participant, phase, treatment sequence, timepoint and parameter including most recent treatment received, changes from Baseline for numeric variables, the reference ranges and a flag to indicate whether values are below the lower limit of the reference range or above the upper limit of the reference range. The listing will include any laboratory value out of normal range at the timepoint it occurred only.

Separate listings of clinical chemistry and hematology laboratory results outside the normal ranges will be provided. These listings will include all data for a parameter for which a participant has at least one abnormal value during the study.

Urinalysis results will be listed by study participant, phase, treatment and timepoint including changes from Baseline for numeric variables, the reference ranges and flags for values outside the normal ranges.

A separate listing for laboratory results meeting the criteria for potential drug-induced liver injury (PDILI) will be provided. The listing will present the study participant who meets one or more of the following criteria for PDILI at any time point:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN)
- Alkaline phosphatase ≥2xULN
- Total bilirubin increase ≥2xULN

Clinical chemistry and hematology parameters will be summarized by phase, treatment and timepoint for both absolute values and changes from Baseline.

Laboratory variables will be grouped according to the laboratory function panel (Table 10-1) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory. For selected variables that are identified in Table 10-1 the change in category from Baseline will be presented in shift table at all post-Baseline time points.

Any additional laboratory variables not included in the outputs described previously will be listed separately. These will include the following:

- Serology
- Alcohol breath test
- Serum pregnancy test (for women of childbearing potential)
- Urine toxicology screen

Figures of mean and mean change from Baseline may be presented for selected laboratory variables that will be identified at the DEM.

Table 11-1: Laboratory measurements

Laboratory Assessments	Parameters		
Hematology[1]	Platelet Count[2]	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils[2] Lymphocytes[2] Monocytes Eosinophils Basophils
	RBC Count		
	Hemoglobin		
	Hematocrit		

Laboratory Assessments	Parameters			
Clinical Chemistry[1]	Blood Urea Nitrogen[2] (BUN)	Potassium	Aspartate Aminotransferase[2] (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin (direct is only measured if total >1xULN)
	Creatinine[2]	Sodium	Alanine Aminotransferase[2] (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting at Screening)	Calcium	Alkaline phosphatase[2] (ALP)	
Routine Urinalysis[1]	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick. If protein or blood or leukocytes are abnormal (positive), a microscopic examination of the sediment will be performed.			
Other Screening Tests	• Follicle-stimulating hormone (at Screening only to confirm postmenopausal status in female study participants • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Breath alcohol test • Pregnancy test: Urine or serum beta human chorionic gonadotropin (hCG) test (as needed for women of childbearing potential; serum hCG test used at Screening only) • Serology (HIV 1 and 2 Ab, HBsAg, HCV-Ab)			

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBsAG=hepatitis B surface antigen; HCV-Ab=hepatitis C antibody; HIV-1/2Ab=human immunodeficiency virus-1/2 antibodies

[1] Hematology, clinical chemistry, and urinalysis assessments will be performed under fasting conditions at Screening and non-fasting conditions at all other assessments.

[2] Shift tables will be presented for these variables.

11.4 Vital signs, physical findings, and other observations related to safety

11.4.1 Vital signs

The following vital signs measurements will be assessed:

- Systolic and diastolic blood pressure
- Pulse rate

- Body temperature (aural)
- Respiratory rate

Vital signs measurements will be summarized and listed by phase, treatment sequence, position (standing (screening only) and supine) and timepoint including changes from Baseline and most recent treatment received. The listing will also include details to abnormal values. Vital signs with values below lower limit of normal and a decrease greater than the limit given in the following table or vital signs with values above upper limit of normal and an increase greater than the given value in the table will be classified as abnormal.

Table 11–2: Reference ranges for vital signs

Variable	Unit	Low[a]	High[a]
Systolic blood pressure	mmHg	Value <90 and/or ≥20 decrease from Baseline	Value >140 and/or ≥20 increase from Baseline
Diastolic blood pressure	mmHg	Value <50 and/or ≥15 decrease from Baseline	Value >90 and/or ≥15 increase from Baseline
Pulse rate	bpm	Value <45 and/or ≥15 decrease from Baseline	Value >90 and/or ≥15 increase from Baseline

11.4.2 Electrocardiogram

12-lead ECG will be recorded 3 times at each time point. The individual mean at each time point will be calculated as raw parameters for descriptive analysis. The individual mean and change from Baseline will be summarized using descriptive statistics by phase and treatment at each time point.

All standard 12-lead ECD recordings will be taken in triplicate with the study participant resting in the supine position for at least 5 minutes. The following ECG parameters will be reported:

- PR interval
- QT interval
- QRS interval
- QTc interval (QT corrected for heart rate using Fridericia's formula [QTcF])
- Heart rate

The individual measurements and the mean of the triplicate measurements will be reported in the by- participant listings including change from Baseline and most recent treatment received and will be presented by phase, treatment sequence and timepoint.

Measured values and change from Baseline will be summarized by phase, treatment and ECG variable at each timepoint (based on the mean of the triplicate values at each timepoint). The mean change for ECG parameter will also be displayed graphically. Additionally, the following cut-points in QTcF (observed data and change from Baseline), based on the mean of the triplicate data, will be summarized categorically (number and percentage of participants) by treatment group at each timepoint. For observed data:

- <450 msec
- ≥450 to <480 msec

- ≥480 to <500 msec
- ≥500 msec

Absolute change from Baseline in QTcF:

- <30 msec
- ≥30 to <60 msec
- ≥60 msec

All ECG findings for the individual triplicate measurements will be listed separately.
Any incomplete triplicate measurements at a given timepoint will be handled as described in Section 4.2.3.

11.4.3 Other safety variable(s)

11.4.3.1 Physical examination

Study participants with abnormalities in the physical examination will be listed including details of the abnormality.

11.4.3.2 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al, 2011) data will be listed by treatment sequence. Module of the questionnaire, time point, question and the associated response will be listed for all the visit days where this questionnaire is collected.

12 OTHER ANALYSES

Not applicable.

13 REFERENCES

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14 APPENDICES

14.1 Appendix 1: VAS feeling high, internal and external perception (Bowdle)

The Bowdle Visual Analogue Scale (B-VAS) evaluates psychedelic effects (Bowdle et al, 1998). It consists of 13 100-mm self-rated visual analogue scales from which two composite scales are calculated: internal perception (six items) and external perception (5 items).

The individual items of the B-VAS are listed below:

1. My body or body parts seemed to change their shape or position
2. My surroundings seemed to change in size, depth, or shape
3. The passing of time was altered
4. I had feelings of unreality
5. It was difficult to control my thoughts
6. The intensity of colors changed
7. The intensity of sound changes
8. I heard voices or sounds that were not real
9. I had the idea that events, objects, or other people had particular meaning that was specific for me
10. I had suspicious ideas or the belief that others were against me
11. I felt anxious
12. I felt high
13. I felt drowsy

The two composite scales, internal perception and external perception, are calculated as follows (Zuurmann et al, 2008):

- External perception = [$\log_{10}$(Item1+2) + $\log_{10}$(Item2+2) + $\log_{10}$(Item3+2) + $\log_{10}$(Item5+2) + $\log_{10}$(Item6+2) + $\log_{10}$(Item7+2)]/6
- Internal perception = [$\log_{10}$(Item4+2) + $\log_{10}$(Item8+2) + $\log_{10}$(Item9+2) + $\log_{10}$(Item10+2) + $\log_{10}$(Item11+2)]/5

Item 12 is the individual VAS feeling high (no derivation is required).

14.2 Appendix 2: VAS Bond-Lader

The Bond-Lader VAS evaluates mood and alertness (Bond and Lader, 1974). It consists of 16 100-mm self-rated visual analogue scales (Figure 14-1) from which three factors are calculated: alertness, calmness, and contentment.

The three factors are calculated as follows:

- Alertness = (Item1 + Item3 + Item4 + Item5 + Item6 + Item9 + Item11 + Item12 + Item15)/9
- Calmness = (Item7 + Item8 + Item13 + Item14 + Item16)/5
- Contentment = (Item2 + Item10)/2

Certain scale scores may need to be inversed prior to calculation (Bond and Lader, 1974) based on the frequency distribution of the scales.

Figure 14-1: Bond-Lader VAS

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

		Scales	
Factor 1 (nine scales)	1. Alert … … … … …	…	Drowsy
	11. Attentive … … … …	…	Dreamy
	6. Energetic … … … …	…	Lethargic
	4. Clear-headed … … …	…	Muzzy
	5. Well-coordinated … …	…	Clumsy
	9. Quick-witted … … …	…	Mentally slow
	3. Strong … … … …	…	Feeble
	15. Interested … … … …	…	Bored
	12. Proficient … … … …	…	Incompetent
Factor 2 (five scales)	13. Happy … … … …	…	Sad
	14. Amicable … … … …	…	Antagonistic
	8. Tranquil … … … …	…	Troubled
	7. Contented … … … …	…	Discontented
	16. Gregarious … … … …	…	Withdrawn
Factor 3 (two scales)	2. Calm … … … … …	…	Excited
	10. Relaxed … … … …	…	Tense

Note: Scales not to size.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the SAP or amended SAP is released for execution.

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