STATISTICAL ANALYSIS PLAN

For:

Camino Pharma, LLC

PROTOCOL No. SBP-9330-101

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIRST-IN-HUMAN STUDY TO ASSESS SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE AND MULTIPLE ASCENDING DOSES OF SBP-9330 (WITH A NESTED FOOD-EFFECT ARM) AFTER ORAL ADMINISTRATION IN HEALTHY SUBJECTS

Altasciences Project No. CNO-P5-319

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Version: Final 1.1

Date: 2023/03/10

STATISTICAL ANALYSIS PLAN APPROVAL

We have carefully read this statistical analysis plan and agree it contains the necessary information required to handle the statistical analysis of study data.

Ramadevi

17MAR2023

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Date

Olivier Vachon

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On behalf of the Sponsor:

Vijay Hingorani

16-Mar-2023

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VERSION CONTROL

Version	Date	Author	Description of Changes
Final v1.0	2022/02/11	Ramadevi Vemuri/ Olivier Vachon	Not Applicable
Final v1.1	2023/03/10	Ramadevi Vemuri/ Olivier Vachon	Added Part C details

TABLE OF CONTENTS

TABLE OF TABLES

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
DSMB	Data safety monitoring board
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
ICH	International Council for Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
WHO-DDE	World health organization drug dictionary- enhanced

1 INTRODUCTION

SBP-9330 is a potent and selective $mGlu_2$ positive allosteric modulator (PAM) with excellent drug-like properties including oral bioavailability and metabolic stability. Importantly, SBP-9330 reduces nicotine self-administration and cue-induced nicotine reinstatement in rats without affecting natural food reward. In addition, SBP-9330 was well-tolerated and safe in pivotal (good laboratory practice [GLP]) 14-day toxicology studies in rats and dogs.

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from protocol SBP-9330-101. Pre-planning of analyses reduces the potential for bias and often reduces disputes between sponsor and the regulatory authority regarding the validity of the results. The same principles apply to supportive and/or sensitivity analyses. These analyses must be prospectively specified. (Good Review Practice: Clinical Review of Investigational New Drug Applications, December 2013).

The analyses described in the SAP are based upon the final protocol version 4.0, Amendment 3 dated 2022/09/14.

2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 1.

Table 1: Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To assess the safety and tolerability of single and multiple ascending oral doses of SBP-9330 in healthy nonsmokers and healthy smokers	• Incidence and severity of adverse events (AEs) for subjects administered SBP-9330 compared to placebo • Changes in vital signs, physical examination findings, ECG findings, C-SSRS questionnaire results, and clinical laboratory results for subjects administered SBP-9330 compared to placebo	Refer to Section 8
Secondary		
To determine single and multiple oral dose pharmacokinetics (PK) of SBP-9330 in healthy nonsmokers and healthy smokers	Pharmacokinetic (PK) parameters, where appropriate, will be determined for SBP-9330 from individual concentration-time profiles in plasma. The following PK parameters will be evaluated for each study phase: <u>Part A (SAD Phase):</u> • C_{max}, T_{max}, AUC_{0-24}, AUC_{0-T}, $AUC_{0-\infty}$, T_{half}, CL/F, and V_Z/F <u>Part B (MAD Phase) and Part C (Smoker Phase):</u> • Day 1: C_{max}, T_{max}, AUC_{0-24}, AUC_{0-T} • Days 7, 11, 12, and 13: C_{trough} • Day 14: C_{trough}, C_{max}, T_{max}, C_τ, AUC_τ, AUC_{0-T}, effective T_{half}, T_{half}, CL/F_{ss}, V_Z/F_{ss}, $R_{AC}(C_{max})$, R_{AC}(AUC) For all study parts, additional PK parameters will be estimated for supportive purposes.	Refer to Section 7
To explore the effect of food on the single oral dose PK of SBP-9330 in healthy nonsmokers	Main PK parameters will be determined to assess the effect of food after a single oral dose of 600 mg SBP-9330. For Cohort A3 (Food Effects) only, the PK parameters specified above for Part A will be estimated on Day 1 and Day 8. Inferential statistical analysis will be performed on the following main PK parameters: • C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$ In addition, T_{max} will be summarized descriptively	Refer to Section 7

Exploratory		
To explore the effect of SBP-9330 on smoking-related assessments	• Expired carbon monoxide (ECO) level • Plasma cotinine level • Number of cigarettes smoked (smoking log) • Minnesota Nicotine Withdrawal Scale (MNWS) responses • Questionnaire on Smoking Urges – Brief version (QSU-Brief) responses	

3 STUDY DESIGN

3.1 General Description

This is a single-center, first-in-human, randomized, double-blind, placebo-controlled, single- and multiple-dose escalating study incorporating a food-effect cohort.
The study will include 3 parts:

- Part A: SAD phase with a nested food-effect cohort
- Part B: MAD phase
- Part C: Smoker phase

Each cohort will receive SBP-9330 in an ascending dose order.
Part A – SAD phase with nested food-effect cohort will include approximately 40 subjects (up to 5 cohorts of 8 subjects) and Part B – MAD phase will include approximately 40 subjects (up to 4 cohorts of 10 subjects), and Part C – Smoker phase will include approximately 30 subjects (up to 3 cohorts of 10 subjects). Therefore, up to 110 subjects will be included in the study.
All subjects who complete the study and those terminating early will be required to complete the End of study (EOS)/Follow up procedures.

3.1.1 Part A – SAD Phase with Nested Food-Effect Cohort

Screening of participants will occur within approximately 28 days of the first scheduled administration of study medication. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria and who consent to participation will be admitted to the CRU for baseline evaluations before dosing (Day -1). All baseline safety evaluation results should be available prior to dosing and continued eligibility confirmed. Subjects in Cohort A3 will have eligibility confirmed for Day -1 for fasted dose (Period 1) only and not for the fed dose (Period 2).

Eligible subjects will be randomized to SBP-9330 or placebo in 1 of the 5 ascending dose cohorts (8 subjects per cohort) to have a total of 6 subjects receiving SBP-9330 and 2 subjects receiving placebo. All cohorts in the fasting state will be dosed according to a sentinel dosing design to ensure optimal safety. Initially, 2 subjects will be dosed; 1 subject will be dosed with SBP-9330 and 1 subject with placebo. If the safety and tolerability results of the first 24 hours following dosing for the initial subjects are acceptable to the Investigator, the other 6 subjects (5 active and 1 placebo) may be dosed approximately 24 hours after dosing of the sentinel group. Furthermore, one single-dose, two-period, crossover, food-effect cohort will be integrated into a SAD cohort (Cohort A3).
The proposed SAD design and planned escalation are presented in Table 2.

Table 2: Part A – SAD Phase with Nested Food-Effect Cohort Design and Dose Levels

Cohort	N (active:placebo)	Dose (mg)	Drug administration
A1	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects])	150 mg (1 × 150-mg SBP-9330 capsule or matched	Single oral dose administration of SBP-9330 or placebo under fasting

Cohort	N (active:placebo)	Dose (mg)	Drug administration
		placebo)	conditions on Day 1.
A2	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects])	300 mg (1 × 300-mg SBP-9330 capsule or matched placebo)	Single oral dose administration of SBP-9330 or placebo under fasting conditions on Day 1.
A3[1]	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects] for Period 1 only)	600 mg (2 × 300-mg SBP-9330 capsule or matched placebo)	Single oral dose administration of SBP-9330 or placebo under fasting conditions on Day 1 of Period 1 and fed conditions on Day 1 of Period 2. Washout between the 2 periods will be at least 7 to 14 days.
A4	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects])	1200 mg (4 × 300-mg SBP-9330 capsule or matched placebo)	Single oral dose administration of SBP-9330 or placebo under fasting conditions on Day 1.
A5	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects])	2400 mg (6 × 300-mg SBP-9330 capsule or matched placebo)	Single oral dose administration of SBP-9330 or placebo under fasting conditions on Day 1.

[1] 2-period, food-effect cohort

For Cohorts A1, A2, A4, and A5, each subject will receive the assigned treatment (SBP-9330 or placebo) under fasting conditions.

For Cohort A3 (2 period food-effect cohort), each subject will receive the randomly assigned treatment (SBP-9330 or placebo) under fasting conditions in Period 1. After a 7- to 14-day washout period, they will receive the same single dose of SBP-9330 or placebo in a fed state in Period 2, 30 minutes after the start of an FDA High-Fat and High-Calorie Breakfast. Escalation to Cohort A4 will be based only on the fasting period safety and PK and may proceed in parallel to the A3 fed period.

All cohorts in the fasting state will be dosed according to a sentinel dosing design to ensure optimal safety. Initially, 2 subjects will be dosed; 1 subject will be dosed with SBP-9330 and 1 subject with placebo. If the safety and tolerability results of the first 24 hours following dosing for the initial subjects are acceptable to the Investigator, the other six subjects (5 active and 1 placebo) may be dosed approximately 24 hours after dosing of the sentinel group.

Escalation to the next higher dose will only proceed if none of the stopping criteria have been reached and when the safety and tolerability and plasma PK analysis of the previous dose,

including delayed emergence of significant AEs in earlier cohorts, are acceptable to the Investigator, Sponsor and DSMB.

The SAD phase will have a maximum of 5 cohorts. The number of cohorts may be changed at the discretion of the Sponsor depending on the emerging safety and plasma PK data from the previous cohorts. The dose levels proposed for SAD cohorts may be adjusted during the course of the study based on preliminary safety and plasma PK data but escalation will not be more than 3-fold the previous dose.

For Cohorts A1, A2, A4, and A5:

- Subjects will be confined to the CRU from at least 10 hours prior to drug administration until approximately 48 hours after study drug administration. Subjects will therefore be confined for 4 days and 3 nights (Day -1 to Day 3). However, they may be advised to stay longer at the CRU for safety reasons, if judged necessary by an Investigator.
- Subjects will return for a follow-up visit approximately 5 days after the last PK blood sample/discharge (Day 8±1).
- Total study duration: up to 38 days (including Screening)

For Cohort A3 (food-effect cohort):

- In each period, subjects will be confined to the CRU from at least 10.5 hours prior to drug administration until approximately 48 hours after study drug administration. Subjects will therefore be confined for 4 days and 3 nights (Day -1 to Day 3) in each period. However, they may be advised to stay longer at the CRU for safety reasons, if judged necessary by an Investigator.
- Washout period between treatment administrations: at least 7 to 14 calendar days
- Subjects will return for a follow-up visit approximately 5 days after the last PK blood sample/discharge (Day 8±1) of Period 2.
- Total study duration: up to 46 days (including Screening)

3.1.2 Part B - MAD Phase

Screening of participants will occur within approximately 28 days prior to the first scheduled administration of study medication. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria and who consent to participation will be admitted to the CRU for baseline evaluations before dosing (Day -1). All baseline safety evaluation results should be available prior to dosing and continued eligibility confirmed.

Subjects will be randomized to SBP-9330 or placebo in 1 of the 3 ascending dose cohorts (10 subjects per cohort in 4:1 [SBP-9330:placebo] ratio) to have a total of 8 subjects receiving SBP-9330 and 2 subjects receiving placebo. An additional MAD cohort (Cohort B4) may be added at the discretion of the Sponsor depending on emerging safety and PK data from previous cohorts.

The proposed MAD design and planned escalation are presented in Table 3.

Table 3: Part B - MAD Phase Design and Dose Levels

Cohort	N (active:placebo)	Dose	Drug administrations
B1	8:2	adaptive	Once daily oral administrations of SBP-9330 or placebo for 14 consecutive days (Days 1 to 14) under fasting conditions
B2	8:2	adaptive	Once daily oral administrations of SBP-9330 or placebo for 14 consecutive days (Days 1 to 14) under fasting conditions
B3	8:2	adaptive	Once daily oral administrations of SBP-9330 or placebo for 14 consecutive days (Days 1 to 14) under fasting conditions
Additional B4	8:2	adaptive	Once daily oral administrations of SBP-9330 or placebo for 14 consecutive days (Days 1 to 14) under fasting conditions

Each subject will receive once daily oral administration of the assigned treatment and dose under fasting conditions (SBP-9330 or placebo) for 14 consecutive days.

The MAD phase of the study may commence in parallel to the SAD or thereafter. The decision on how early the MAD phase of the study may be started and the doses to be administered will be determined by the Sponsor after consultation with the DSMB based on emerging safety and PK data. The first MAD daily dose will be less than or equal to an already well-tolerated SAD dose for which complete safety and PK data are available.

All relevant safety and available plasma PK data will be reviewed by the DSMB before any dose escalation. The dose levels proposed for MAD cohorts may be adjusted during the course of the study based on preliminary safety and PK data. The dosing frequency may also be changed from once daily to twice daily, without changing the total daily dose outlined in the protocol.

The MAD phase will have a maximum of 4 cohorts. The number of cohorts may be changed at the discretion of the Sponsor depending on the emerging safety and PK data from the previous cohorts. The increase from one dose level to the next dose level will not be more than 3-fold. A MAD daily dose level cannot be higher than the highest dose level tested in SAD.

Subjects will be confined to the CRU from at least 10 hours prior to drug administration until approximately 48 hours after last study drug administration. Subjects will therefore be confined for 17 days and 16 nights (Day -1 to Day 16).

Subjects will return for a follow-up visit approximately 5 days after the last PK blood sample/discharge (Day 21±1).

3.1.3 Part C - Smoker Phase

Screening of participants will occur within approximately 28 days prior to the first scheduled administration of study medication. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria and who consent to participation will be admitted to the CRU for baseline evaluations before dosing

(Day -1). All baseline safety evaluation results should be available prior to dosing and continued eligibility confirmed.

Subjects will be randomized to SBP-9330 or placebo in 1 of the 2 planned Smoker cohorts (10 subjects per cohort in 4:1 [SBP-9330:placebo] ratio) to have a total of 8 subjects receiving SBP-9330 and 2 subjects receiving placebo. An additional Smoker cohort (Cohort C3) may be added at the discretion of the Sponsor depending on emerging safety and PK data from previous cohorts.

Table 4: Part C - Smoker Phase Design and Dose Levels

Cohort	N (active:placebo)	Dose	Drug administrations
C1	8:2	adaptive	Once daily oral administrations for 14 consecutive days
C2	8:2	adaptive	Once daily oral administrations for 14 consecutive days
Optional C3	8:2	adaptive	Once daily oral administrations for 14 consecutive days

Each subject will receive once daily oral administration of the assigned treatment and dose under fasting conditions (SBP-9330 or placebo) for 14 consecutive days.

The Smoker phase of the study may commence after completion of dosing the MAD phase of the study. The Smoker cohort daily dose will be less than or equal to highest MAD dose for which complete safety and PK data are available.

All relevant safety and available plasma PK data will be reviewed by the DSMB before any dose escalation. The DSMB will be provided the randomization code to aide in the review for Part C. The dose levels proposed for Smoker cohorts may be adjusted during the course of the study based on preliminary safety and PK data.

The Smoker phase will have a maximum of 3 cohorts. The number of cohorts may be changed at the discretion of the Sponsor depending on the emerging safety and PK data from the previous cohorts.

Subjects will be confined to the CRU from at least 10 hours prior to drug administration until approximately 48 hours after last study drug administration. Subjects will therefore be confined for 17 days and 16 nights (Day -1 to Day 16).

Subjects will return for a follow-up visit approximately 5 days after the last PK blood sample/discharge (Day 21±1).

3.2 Determination of Sample Size

Sample size is based on the estimate of the number of subjects necessary to obtain a clinical assessment regarding the drug's safety profile over the planned dose range and was not based on statistical considerations.

3.3 Study Treatments

The following investigational products (IPs) will be administered according to the outlined dose levels in Table 2 and Table 3.

- Test product: SBP-9330 75-mg, 150-mg and 300-mg capsules
- Placebo: Placebo to match SBP-9330 75-mg, 150-mg and 300-mg capsules

3.4 Study Procedures

For complete details on the study assessments to be performed for each study period, refer to APPENDIX A.

3.5 Randomization and Unblinding Procedures

The CRU will generate the randomization code for each cohort with a computer program according to the study design, the number of subjects and the treatment to be administered. Once generated, the randomization code will be final and will not be modified.

Subjects enrolled in the SAD sentinel groups will be randomized 1:1 to receive SBP-9330 or matching placebo while the rest of the subjects in the cohort will be randomized 5:1 to receive SBP-9330 or matching placebo. Subjects enrolled in the MAD and Smoker cohorts will be randomized 8:2 to receive SBP-9330 or matching placebo.

Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study treatment may be replaced. Subjects who sign the ICF, are randomized and received at least 1 dose of the study treatment, and are withdrawn prematurely from the study, may be replaced by an equal number of newly enrolled subjects. A new unique randomization number will be assigned to the replacement subject. The replacement list will be provided and will be identical to the original randomization scheme.

This study is double-blind. Treatment assignments (active or placebo) will be blinded to the investigator, subjects and all clinical and research staff for the entire study, with the exception of designated pharmacy staff who will remain unblinded in order to dispense active drug or placebo.

The study blind will be broken upon completion of the clinical study and after the study database has been locked.

During the study, the randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by the qualified investigator for further treatment to the subject, to assess cohort stopping rules or to complete a SAE report. Randomization information will be held by designated individual(s). When possible, the qualified investigator should discuss the emergency with the Sponsor prior to unblinding. The date and reason for breaking the blind must be recorded.

The results of the blinded safety and available PK data will be made available to the DSMB group before proceeding with the next dose level. The bioanalytical facility will preserve the blind by reassigning alternative subject numbers to the interim data before they are made available to the PK facility and Sponsor; these alternative subject numbers will be assigned by the lab at the time of sample analysis. For the food-effect cohort (Cohort A3), the clinic will provide the lab with the meal condition for each subject, and the lab will translate this information to the corresponding alternative subject number and will provide the resulting list comprised of alternative number and associated meal condition to the PK scientist. These measures will ensure that whenever possible, the DSMB members remain blinded during their reviews and throughout the clinical part of the study. Based on review of the safety data, the DSMB may request randomization information, if necessary, to make appropriate dose escalation decisions and this unblinding will be documented.

At the request of the Sponsor, specified individuals may be unblinded and receive the randomization information prior to database lock. This unblinding will be fully documented and all unblinded individuals advised that they must not distribute randomization information to any blinded parties.

4 ANALYSIS POPULATIONS

- **Safety population:** The safety population will include all subjects who received at least 1 dose of one of either the SBP-9330 or placebo.

  The number of subjects who were included, who discontinued, and who completed the study will be tabulated. The primary reasons for discontinuation will be provided.

- **Pharmacokinetic Population:** The PK population will include all subjects who have received at least 1 dose of SBP-9330 and have at least 1 PK concentration after dosing.

  Subjects who do not complete the sampling schedule of one or more study days may be included in the PK and statistical populations for only the PK parameters that are judged not to be affected by the missing sample(s).

  Subjects with protocol deviations or adverse events (e.g., vomiting) that could be considered to have an impact on the PK results may be excluded from the PK population. Excluded subjects will be tabulated with the exclusion reason in the PK listings.

5 STUDY SUBJECTS

Disposition and protocol deviations will be summarized and listed as described in Table 5. The disposition table and listing will be presented for the randomized subjects. Protocol deviations will be presented for the safety population.

Table 5: Data presentations for study subject information

Data	Variables	Presentation
Disposition and analysis population	Subject, completion status (i.e., completed or withdrawn), reason for withdrawal, analysis population determination	Summary Table: • N of subjects randomized • N and % of subjects who completed the study • N and % of subjects discontinued from the study by primary reason for discontinuation • N and % of subjects included in each of the analysis populations T14.1.1.1 T14.1.1.2 T14.1.1.3 Listings: • Disposition and completion/discontinuation L16.2.1 • Exclusions from analysis population L16.2.3
Protocol deviations	Protocol deviations	Listings: • General deviations L16.2.2.1 • Blood sample collection time deviations L16.2.2.2 • Inclusion/Exclusion Criteria violations L16.2.2.3

5.1 Disposition

Subject disposition will be summarized for all subjects randomized in this study, and frequency (percentages) of subjects who completed the study, the reason for study discontinuation, and the

number of subjects who have been included in each study population. The percentages will be calculated using the number of subjects randomized as denominator.

A listing of subject disposition and completion/discontinuation will be provided. A listing of subjects included in each of the analysis populations will also be provided.

5.2 Protocol Deviations

A listing of all protocol deviations will be provided. Separate listings will be generated for blood sampling time deviations for SBP-9330. Samples taken outside of the windows mentioned in Altasciences SOP MAP-6014 will be captured as blood sampling time-related deviations.

Deviations will be collected in the clinic deviation tracking system (DTS) and presented as entered in a general protocol deviation listing.

For blood sampling time deviations, information will be derived programmatically.

6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, all available data will be listed and summary tables for demographics and other baseline characteristics will be presented for each analysis population as detailed in Table 6.

Table 6: Data presentations for demographic and other baseline characteristics

Data	Variables	Presentation
Demographics and baseline characteristics	Sex, age, race, height, body weight and BMI	Listing and summary tables by analysis populations L16.2.4.1 T14.1.2.1.1 T14.1.2.1.2 T14.1.2.1.3 T14.1.2.2.1 T14.1.2.2.2 T14.1.2.2.3
Medical history	All medical history findings	Listing Note: includes coded terms (system organ class [SOC] and preferred term [PT]) L16.2.4.2
Prior medications	All medications taken prior to study drug administration	Listing Note: includes coded terms (anatomic therapeutic chemical [ATC] level 1 and preferred name) L16.2.4.3

7 PHARMACOKINETIC ANALYSIS

The PK analysis will be carried out according to Altasciences Standard Operating Procedures (SOPs).

7.1 Missing Values

The lack of concentration values due to failure to collect the sample, a lost or compromised sample or due to the subject's early termination from the study will be considered "missing" in the dataset, and no imputation will be done.

If the actual collection time of a post-dose PK sample is unknown, but a valid concentration value has been measured, the sample will be set to missing in the PK analysis and will be presented in the listings as excluded from descriptive statistics. Unknown pre-dose collection times will be handled on a case-by-case basis.

7.2 Measurements Below the Lower Limit of Quantitation

Concentration values below the lower limit of quantitation (LLOQ) associated with pre-dose and post-dose collection times will be replaced with zero for the non-compartmental analyses (NCA); additional rules for samples that are below the LLOQ, if applicable.

Concentration values below the LLOQ will be replaced with zero for mean PK profile representations as well as for descriptive statistic calculations.

7.3 Actual Time

The NCA analysis will be based on the actual sampling times, except for predose samples, which will always be reported as zero, regardless of time deviations, provided that they were collected prior to dosing.

The individual concentration/time profiles will be presented using actual sampling times whereas the mean concentration/time profiles and tables presenting summary statistics of concentration time data will be presented using nominal sampling times.

Actual times will be listed in the report.

7.4 Non-Compartmental Analysis

The following configuration for the NCA analysis (with Phoenix® WinNonlin® version 8, or higher) will be used:

- Data: Serial sampled data
- Model/Dose options Type: Plasma (200 -202) / Extravascular
- AUC Calculation Method: Linear Up Log Down
- Lambda Z (λ_z) calculation: Best fit method for λ_z Linear-Log regression

Reasons for excluding PK parameters will include the following:

- AUC: AUC parameters will not be estimated if less than 3 consecutive measurable concentrations are observed.
- PK parameters requiring λ_z estimation (e.g., $AUC_{0-\infty}$ and T_{half}) will be set to Not Reported (NR) in the Tables and Listings if they meet one of the following:
  - $R^2 < 0.8$
  - Extrapolated area > 20%

- 3 time points used for terminal phase estimation include C_{max}

The PK parameters for SBP-9330 in plasma are presented in Table 7.

Table 7: Pharmacokinetic Parameters of SBP-9330 in Plasma

PK Parameter	Definition
Part A: SAD Phase	
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
AUC_{0-24}	Area under the concentration time curve from time 0 (dose administration) to 24 hours
AUC_{0-T}	Area under the concentration time curve from time 0 (dose administration) to the time of last quantifiable concentration (T_{last})
$AUC_{0-\infty}$	Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0-T} + C_{last}/\lambda_Z$, where C_{last} is the measured concentration at time T_{last}
T_{half}	Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$
CL/F	Apparent total clearance, calculated as $Dose/AUC_{0-\infty}$
V_z/F	Apparent volume of distribution, calculated as $Dose/\lambda_Z * AUC_{0-\infty}$
C_{max}/D	Dose-normalized C_{max}
AUC_{0-T}/D	Dose-normalized AUC_{0-T}
$AUC_{0-\infty}/D$	Dose-normalized $AUC_{0-\infty}$
Parts B and C: MAD nonsmoker and smoker Phases, Day 1:	
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration
AUC_{0-24}	Area under the concentration time curve from time 0 (dose administration) to 24 hours
AUC_{0-T}	Area under the concentration time curve from time 0 (dose administration) to the time of last quantifiable concentration (T_{last})
C_{max}/D	Dose-normalized C_{max}
AUC_{0-24}/D	Dose-normalized AUC_{0-24}
AUC_{0-T}/D	Dose-normalized AUC_{0-T}
Parts B and C: MAD nonsmoker and smokerPhases, Day 14:	
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration; if it occurs at more than one time point, T_{max} is defined as the first time point with this value
C_τ	Concentration at the end of the dosing interval. Observed concentration, otherwise the predicted concentration value will be calculated as per Phoenix® WinNonlin®'s built-in rules for interpolation/extrapolation, and subject to the criteria for PK parameters requiring λ_z estimation.
AUC_τ	Area under the concentration time curve over the dosing interval at steady state,

	calculated from 0 to 24 hours (dosing interval)
AUC_{0-T}	Area under the concentration time curve from time 0 (dose administration) to the time of last quantifiable concentration (T_{last})
T_{half}	Terminal elimination half-life, calculated as $ln(2)/\lambda_Z$
$T_{half, eff}$	Effective half-life, calculated as $\tau * ln2 / ln(Rac_{(AUC)}/(Rac_{(AUC)}-1))$, where τ is 24 hours[1]
CL/F_{ss}	Apparent total clearance at steady state, calculated as $Dose/AUC_\tau$
Vz/F_{ss}	Apparent volume of distribution at steady state, calculated as $Dose/\lambda_Z * AUC_\tau$
C_{max}/D	Dose-normalized C_{max}
AUC_τ/D	Dose-normalized AUC_τ
AUC_{0-T}/D	Dose-normalized AUC_{0-T}
$Rac_{(Cmax)}$	Accumulation ratio evaluated by comparing Day 14 C_{max} to Day 1 C_{max}
$Rac_{(AUC)}$	Accumulation ratio evaluated by comparing Day 14 AUC_τ to Day 1 AUC_{0-24}
Parts B and C: MAD nonsmoker and smokerPhases, Various Days:	
C_{trough}	Observed concentration at the end of the dosing interval (predose concentrations on Days 2, 7, 11, 12, 13, and 14)
The following PK parameters will be used for PK calculation and presented in the PK listings only	
T_{last}	Time of last measurable observed concentration
C_{last}	Observed concentration corresponding to T_{last}
λ_Z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve
$\lambda_{Z\,Upper}$	Upper limit on time for values included in the calculation of λ_z
$\lambda_{Z\,Lower}$	Lower limit on time for values included in the calculation of λ_z
Number of Points	Number of data points in computing λ_Z
R^2	Goodness of fit for the terminal phase
Residual area	Extrapolated area (i.e., percentage of $AUC_{0-\infty}$ due to extrapolation from T_{last} to infinity: $[AUC_{0-\infty} - AUC_{0-T}]/ AUC_{0-\infty}*100$)

[1] Sources: Gidal et al., 2017 and Boxenbaum et al., 1995

7.5 Pharmacokinetic Statistical Methodology

All tables, figures and listings (TFLs), when appropriate, will be stratified by cohort and study day; for the food-effect cohort, additional stratification by meal condition will be performed.

7.5.1 Summary Statistics

Summary statistics of the individual concentration data and derived parameters will be calculated with Phoenix® WinNonlin® for the PK population. Summary statistics will be calculated for concentration at each individual time point and for all PK parameters.

Concentration data will be summarized by group using the following statistics: number of observations (N), arithmetic mean (mean), standard deviation (SD), minimum (min), median, maximum (max), and coefficient of variation (CV%). PK parameters will be summarized using these same statistics, as well as geometric mean and geometric mean CV%.

7.5.2 Statistical Analysis

Dose Proportionality

For all study parts, appropriate dose–normalized PK parameters (C_{max} and appropriate AUCs) will be assessed graphically for dose-proportionality (with Phoenix® WinNonlin®).

Natural log-transformed PK parameters (C_{max} and appropriate AUCs) will be assessed statistically for proportionality using SAS. Proportionality analysis will be done using a power model. The power model is defined as:

$$\ln(\text{PK parameter}) = \alpha + \beta \bullet \ln(\text{Dose}) + \varepsilon$$

where α is the intercept, β is the slope and ε is the error term. A linear model with ln-transformed dose as a continuous effect will be fitted. A point estimate and a 90% confidence interval will be derived for the slope (β).

Dose proportionality may be assessed within different dose ranges if deemed appropriate with at least three doses.

Food-Effect Assessment

A statistical comparison will be performed in subjects enrolled in Cohort A3 to evaluate the effect of food on the PK of SBP-9330 with the natural logarithmic transformation of C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$.

C_{max}, AUC_{0-T}, and $AUC_{0-\infty}$ will be statistically analyzed using an Analysis of Variance (ANOVA) model. The fixed factors included in this model will be the Fed or Fasting condition, the period at which it was given (Day 1 or Day 8 [or Day 15]), as well as the sequence in which the treatment is under Fed or Fasting condition. A random factor is also added for the subject effect (nested within sequence).

The 90% confidence interval for the exponential of the difference in least-squares (LS) means between the Fed and Fasting conditions will be calculated (Fed to Fasting ratio of geometric LS means).

The formula to estimate the intra-subject coefficient of variation will be: $\sqrt{e^{MSE} - 1}$, where MSE is the Mean Square Error obtained from the ANOVA model of the ln-transformed parameters.

The parameter T_{max} will be evaluated descriptively.

Steady State

C_{trough} will be displayed graphically and summarized descriptively by day to assess for steady state.

7.5.3 Smoking Assessment (Part C only)

The following data will be assessed for the Safety population of Part C and will be listed and summarized using descriptive statistics:

- Expired carbon monoxide (ECO) level
- Plasma cotinine level
- Number of cigarettes smoked (smoking log)
- Minnesota Nicotine Withdrawal Scale (MNWS) responses
- Questionnaire on Smoking Urges – Brief version (QSU-Brief) responses
-

Actual values and change from baseline will be presented in a listing and will be summarized by Symptoms (if applicable) and visit.

8 SAFETY ANALYSIS

Unless otherwise specified, all available data will be listed and summary tables for safety assessments will be presented for the safety population as detailed in Table 8.

Table 8: Data presentations for safety assessments

Data	Variables	Presentation
Adverse events	Adverse event (AE) description, onset and resolution date and time, time from product use, severity, relationship to study drug, action taken, and outcome	Listing (by subject, Cohort and treatment): L16.2.7.1 Summary tables, including number and percentage of subjects experiencing: • Reported AEs, • Treatment-emergent adverse events (TEAEs), • Drug-related TEAEs (i.e. those with a relationship classified as Definite, Probable, Possible and Unlikely), • TEAEs by relationship to study treatment (i.e., Definite, Probable, Possible, Unlikely and Not related), • TEAEs by severity, • Serious TEAEs, • Study drug-related serious TEAEs, • TEAEs leading to withdrawal, and • TEAEs with an outcome of death. Note: includes coded terms (system organ class [SOC] and preferred term [PT]) T14.3.1.1.1 – T14.3.1.4.4, T14.3.2.1 and T14.3.2.2
Concomitant medications	All medications taken during the study (as defined in the protocol and including prior medications that are continued), dose, units, frequency, formulation, route, indication/ reason taken, and date and time	Listing Note: includes coded terms (anatomic therapeutic chemical [ATC] level 1 and preferred name) L16.2.7.2
Extent of exposure	Category of drug, treatment, total dose, dose unit, formulation, frequency, administration date and time, route of administration, Was the treatment administered as specified in the protocol? and dosing comments	Listings: L16.2.5.1 L16.2.5.2 L16.2.5.3
Clinical laboratory	Laboratory results (refer to section	Listings:

Data	Variables	Presentation
evaluations	9.2 for parameters)	• All laboratory values by visit L16.2.8.1.1 – L16.2.8.1.7 • All out-of-range laboratory values • All clinically significant laboratory values T14.3.4.1.1 – T14.3.4.1.2 Summary tables • Summary of continuous tests • Summary of categorical tests T14.3.4.2.1 – T14.3.4.5.4
Vital signs	Blood pressure, pulse, respiratory rate and body temperature	Listings: • All vital signs values L16.2.8.3.1 – 16.2.8.3.2 • All out-of-range vital signs values • All clinically significant vital signs values T14.3.5.1.1 – T14.3.5.2.4Summary tables: • Summary of vital signs by visit T14.3.5.3.1 – T14.3.5.4.4
Physical examination	Physical examination findings	Listings: • All Physical examination findings • L16.2.8.2All clinically significant Physical Examination findings T14.3.6.1
Electrocardiograms (ECGs)	ECG interpretations and findings	Listings: • all 12-Lead ECGs findings L16.2.8.4Summary tables: • summary of ECG assessments by visit • all out-of-range ECG values • all clinically significant ECG values T14.3.7.1.1 – T14.3.7.1.2 T14.3.7.2.1 – T14.3.7.2.4
C-SSRS	Columbia Suicide Severity Rating Scale	Listing: L16.2.9.1

Note: Sub-bullets denote individual listings or tables to be generated.

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or

disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Treatment emergent adverse events (TEAEs) are AEs not present prior to the exposure to study treatment or AEs already present that worsen in intensity or frequency following exposure to study treatment. All AEs reported following exposure to study treatment are considered TEAEs.

All TEAEs will be assigned to a treatment using the following rules:

- A TEAEs will be assigned to the last treatment taken by the subject where the date and time of the last treatment dosing is on or before of the start date and time of the event. Such assignment will be performed irrespective of any washout period between the start and stop dates of the TEAE.
- Any TEAE started during the follow-up period will be assigned to the last treatment that the subject has taken.
- In case that the time of onset or time of resolution is unknown, worst case scenario will be considered. For the onset, 00h01 will be the time considered. For the resolution time, if the time is unknown, 23h59 will be the time considered.

Frequency tables summarizing all TEAEs and all study drug-related TEAEs (including SOC and PT) will be presented by Part A- SAD (Cohorts A1, A2, A4, A5, Pooled Placebo and Overall), Part A food-effect cohort (SBP-9330, Placebo and Overall), Part B – MAD (Cohorts B1, B2, B3, B4, Pooled Placebo and Overall) and Part C – Smoker (Cohorts C1, C2, C3, Pooled Placebo and Overall) as described in Table 8.

All averse events will be presented in a listing as well, by study part, cohort, subject and treatment.

8.2 Clinical Laboratory Evaluations

Laboratory data will be presented using units as reported by the clinical laboratory.

The following clinical laboratory tests listed will be performed as scheduled in Appendix A.

Clinical Laboratory Test Panel	Description
Clinical Chemistry:	Alanine aminotransferase, albumin, alkaline phosphatase, bilirubin total, chloride, creatinine, glucose, potassium, carbon dioxide, calcium, uric acid, albumin, total bilirubin, lactate dehydrogenase, creatinine kinase, aspartate transaminase, amylase, lipase, and sodium
Lipid profile:	Total cholesterol, cholesterol high-density lipoprotein, cholesterol low-density lipoprotein and triglycerides

Coagulation:	Prothrombin time (PT)/INR and partial thromboplastin time (PTT) levels
Endocrinology[1]:	Follicle-stimulating hormone (for female subjects)
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume, and platelet count
Serology[1]:	HIV-1/HIV-2 antibodies, hepatitis B surface antigen and hepatitis C virus antibody
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Amphetamines, alcohol, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, opiates and phencyclidine
Pregnancy test:	Serum pregnancy test at Screening only and urine pregnancy test for all other scheduled days

Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

For hematology, chemistry and urinalysis, actual values and change from baseline will be presented in the listings and will be summarized by study part, laboratory test and visit. Values outside the normal range will be flagged in the listing. The results' relationship to the reference range will be summarized by their status (Normal, Abnormal – Low, Abnormal – High) using frequencies and percentages. Frequency tables and percentages based on the number of subjects per visit will be used to summarize tests with categorical results.

Subject listings of abnormal on-study laboratory values will be provided. Similarly, clinically significant on-study laboratory data will be presented in a second listing.

8.3 Vital Signs

Vital signs will be measured as outlined in Appendix A.
Vital signs to be measured are listed below.

- Orthostatic systolic and diastolic BP and pulse rate
- Body temperature

- Respiratory rate

Blood pressure and pulse rate will be measured after the subject has been in the supine position for at least 5 minutes, repeat measurements will be taken after the subject has been standing in the upright position for at least 2 to 3 minutes (respiratory rate and temperature will be measured with blood pressure and pulse rate in the supine position only).

When vital signs are scheduled at the same time as PK blood draws, the blood draws will be obtained at the scheduled time point and the vital signs will be obtained prior to the blood draw, as close as possible to the scheduled time point.

On-study time points for vital sign measurements are presented in Table 9 (SAD Phase) and Table 10 (MAD Phase).

Table 9: Vital Sign Recording Schedule – SAD Phase

Vital Sign Recording - Scheduled Time Points[1]
Upon admission (check-in)
Prior to dosing (within 60 minutes of dosing)
0.75, 1.25, 1.75, 3.75, 8, 11.75, and 23.25 hours post-dose (±15 minutes)
Prior to discharge
End of Study/Follow-up Visit

[1]For the food-effect cohort, the vital signs assessments will be performed for each dosing

Table 10: Vital Sign Recording Schedule – MAD and Smoker Phase

Vital Sign Recording - Scheduled Time Points
Upon admission (check-in)
Prior to dosing (within 60 minutes of dosing)
1.75 hours post-dose (±15 minutes) on each dosing day
3.5 hours post-dose (±15 minutes) on each dosing day[1]
Prior to discharge
End of Study/Follow-up Visit

1. Time point applicable to Smoker Phase only.

The normal range values for vital signs are as follows:

- 100 mmHg ≤ systolic blood pressure (BP) ≤ 140 mmHg in supine position.
- 60 mmHg ≤ diastolic BP ≤ 90 mmHg in supine position.
- 60 beats per minute (bpm) ≤ heart rate ≤ 100 bpm in supine position.
- 35.5 °C ≤ body temperature ≤ 37.5 °C.
- 10 breaths per minute ≤ respiratory rate ≤ 22 breaths per minute.

- ≥ 20 mmHg decrease in systolic BP from supine to standing.
- ≥ 10 mmHg decrease in diastolic BP from supine to standing.
- ≥ 30 bpm increase in heart rate from supine to standing.

Actual values and change from baseline will be presented in a listing and will be summarized by study part, vital signs parameter, visit and time points. Values outside the reference range will be flagged in the listing.

Subject listing of abnormal on-study vital signs values (Out-of-Range) will be provided. Similarly, clinically significant on-study vital signs values will be presented in a second listing.

8.4 Physical Examination Findings

A physical examination will be performed by a medically qualified and licensed individual as outlined in Appendix A.

The physical examination will include a general review of the following body systems (at minimum): general appearance, head, eye, ear, nose, throat, neck/thyroid, cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal/extremities, and skin. An abbreviated physical examination may be performed at the Investigator's discretion upon admission or discharge from the clinical site.

All physical examination records will be presented in a listing, by study part, cohort, subject, visit and category. Similarly, clinically significant physical examinations will be presented in a second listing.

8.5 12-Lead ECG Findings

Triplicate 12-lead ECG (each performed approximately 1 minute apart) will be performed as outlined in Appendix A.
On-study ECG measurements are specified in Table 11 (SAD Phase) and Table 12 (MAD Phase).

Table 11: ECG Recording Schedule – SAD Phase

ECG Recording - Scheduled Time Points[1]
Upon admission (check-in)
Prior to dosing (within 60 minutes of dosing)
1, 3, 6, and 12 hours post-dose (±15 minutes)
Prior to discharge
End of Study/Follow-up Visit

[1]For the food-effect cohort, the vital signs assessments will be performed for each dosing

Table 12: ECG Recording Schedule – MAD and Smoker Phase

ECG Recording - Scheduled Time Point
Upon admission (check-in)
Prior to dosing (within 60 minutes of dosing) on Day 1 only
3 hours post-dose (±15 minutes) on each dosing day
Prior to discharge
End of Study/Follow-up Visit

Mean values will be used for triplicate ECG results in summary tables. Actual values and change from baseline will be presented in a listing and will be summarized by study part, 12-Lead ECG parameter, visit and time point. Values outside the reference range will be flagged in a listing.

The 12-Lead ECG parameters and overall assessments (Normal, NCS, or Abnormal – CS) will be presented in a listing.

Subject listings of abnormal on-study ECG assessments (Abnormal – NCS or Abnormal – CS)

will be provided. Similarly, clinically significant on-study 12-Lead ECG assessments (Abnormal – CS) will be presented in a second listing.

8.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behavior in adolescents and adults. This will include events in the last 2 years prior to Screening.

To monitor for the emergence of suicidal ideation and behavior, subjects will undergo C-SSRS evaluations at the time points indicated in Appendix A.

On-study C-SSRS should be completed upon admission, upon discharge (each admission and discharge for Cohort A3 [Food-Effect Cohort]) and the EOS/Follow-up visit.

If a subject becomes suicidal during the study as per the results of the C-SSRS questionnaire, an Investigator should provide the appropriate treatment to the subject.

Listing will be presented for C-SSRS data.

9 DATA HANDLING AND PRESENTATION

All safety and statistical outputs will be generated using SAS software, version 9.4. Pharmacokinetic outputs will be generated using WinNonlin version 8.0.

All programs used to generate statistical analyses will be validated according to standard operating procedures (SOPs) of Altasciences.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and/or prior to breaking the blind. Any analyses performed subsequent to database lock and/or breaking the blind that are not described within the present plan will be considered post hoc and exploratory. Post hoc analyses will be labeled as such in the corresponding statistical output and identified in the clinical study report (CSR).

9.1 Safety Analysis Presentation

Adverse events and medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 24.0 as defined in the study data management plan (DMP).

Prior and concomitant medications will be coded with the World Health Organization Drug Dictionary- Enhanced (WHO-DDE) March 2021 as defined in the study DMP.

In general, all safety summary tables will be presented for the safety population. Summaries will be presented for each study part as below:

- Part A- SAD (Cohorts A1, A2, A3 fasted, A4, A5, Pooled Placebo and Overall)
- Part A food-effect cohort (SBP-9330, Placebo and Overall)
- Part B – MAD (Cohorts B1, B2, B3, B4, Pooled Placebo and Overall)
- Part C - Smoker (Cohorts C1, C2, C3, Pooled Placebo and Overall)

In general, the data listings will include all enrolled subjects up to the point of study completion or discontinuation; exceptions will be listings pertaining to a subset of subjects only (e.g., subjects with protocol deviations) or a subset of records/events (e.g., abnormal laboratory values).

Categorical variables will be summarized using the PROC FREQ procedure. Continuous variables will be summarized using the PROC UNIVARIATE procedure. For natural log (ln)-transformed endpoints, geometric mean, geometric standard deviation (SD), and coefficient of variation (CV%) will also be presented.

The following general comments also apply to all statistical analyses and data presentations:

- Duration variables will be calculated using the general formula: (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.

- When assessments are repeated for a given time point or performed at unscheduled times, only the result which is the closest to the dosing time will be included in summary tables.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data.
- Means, medians, and quartiles will be displayed to 1 additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.
- Percentages will be displayed to 1 decimal place. Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'.
- P-values will be displayed to 3 decimal places. P-values that are less than 0.001 will be displayed as '<0.001'.

The numbers of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case-by-case basis. In general:

- Minima and maxima will be displayed to the commonly used unit of precision for the parameter.
- Means, medians, quartiles, and confidence limits will be displayed to 1 additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.

9.2 Pharmacokinetic Analysis Presentation

In general, all PK summary tables will be presented for the PK population.

Individual raw PK concentrations will be displayed with the same precision as received from the bioanalytical laboratory.

Precision for individual PK parameters will be displayed as follows:

- Concentration-related PK parameters (e.g., C_{max}, AUCs) will be displayed to 3 significant figures,
- Clearance and volume of distribution will be displayed with 3 significant figures,
- Parameters associated with time (e.g. T_{max} and T_{half}) will be displayed with 2 decimal places,
- Percentages will be displayed with 2 decimal places,
- R^2 and λ_z will be displayed with 4 decimal places.

Summary statistics for concentration and PK parameters will be displayed with the same precision as the individual values, with the exception of number of observations (N) and CV% which will be presented with 0 and 1 decimal place, respectively.

9.3 Analysis Timepoints

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study medication.

9.4 Methods for Handling Missing Data

No imputations of values for missing data (i.e, blank, "Not Done", "Not Applicable", etc) will be performed and data presentations will reflect the data point as it appears in the case report form (CRF) or electronic data file.

10 INTERIM ANALYSES AND DATA SAFETY MONITORING

Preliminary blinded "top line" PK results will be generated after each cohort of the SAD and MAD phase for dose selection and safety assessment prior to the next dose escalation.

These preliminary blinded PK results will be performed on SBP-9330 data as outlined in Sections 7.1 through 7.4, with the exception that nominal times will be used in the analysis instead of actual times. Blinded concentration tables, mean and blinded individual plasma concentration-time profiles, blinded PK parameter tables of the key PK endpoints (e.g., C_{max}, T_{max}, and AUCs) will be generated, data permitting.

11 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

No changes from the protocol-specified analyses are planned.

12 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document and are common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics. Minor format changes will not require updates to the SAP, rather they may be documented in a Note to SAP.

APPENDIX A STUDY SCHEDULE(S)

Table 13: Schedule of Activities – Part A (SAD Phase with Nested Food-Effect Cohort)

		Assessment Period[1]					
Visit[2]	**Screening**	**Pretreatment**		**Treatment**			**Follow-up/ End of Study[3]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**8±1**
Confinement		X	X	X	X	X	
Ambulatory	X						X
Admission		X					
Discharge						X	
Informed Consent	X						
Eligibility Check	X	X	X				
Medical History	X	X					
Demographics	X						
Physical Examination	X	X[4]				X[4]	X
Body Weight and Height (Including BMI Calculation)	X	X[5]					
Serology (HBsAg, HCVAb, anti-HIV 1 and 2)	X						
Urine Drug and Alcohol Screen[6]	X	X					
FSH (postmenopausal females only)	X						
Pregnancy Test (Females Only)[7]	X	X					X
Clinical Laboratory Tests[6,8]	X	X	X			X	X
12-lead ECG[9,10]	X	X	X	X		X	X
Vital Signs[10,11]	X	X	X	X	X	X	X
C-SSRS Questionnaire[12]	X	X				X	X
M.I.N.I.	X						
Randomization		X					
Study Drug Administration				X			
Blood Sampling for PK[10,13]			X	X	X	X	
Previous and Concomitant Medication	X	X	X	X	X	X	X

		Assessment Period[1]					
Visit[2]	**Screening**	**Pretreatment**		**Treatment**			**Follow-up/ End of Study[3]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**8±1**
Adverse Event Monitoring		X	X	X	X	X	X

Abbreviations: BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCVAb=hepatitis C virus antibody; HIV= human immunodeficiency virus; M.I.N.I. = Mini International Neuropsychiatric Interview; PK= pharmacokinetic; SAD = single ascending dose;

1 Subjects will be in the clinic from Day -1 until 48 hours (Day 3) post-dose. Subjects will return for follow-up/EOS assessments on Day 8±1. Subjects for the fed period of the food-effect cohort (Cohort A3) should report to the clinic after the washout period (at least 7 to 14 days after fasting dose) and repeat the 8-day SAD schedule of assessments beginning on Day -1.

2 The timing, type, and number of safety and PK assessments may be updated depending on emerging safety and PK data.

3 Subjects who discontinue the study early should complete the EOS procedures. Subjects in SAD cohorts A1, A2, A4, and A5 should return to the clinic for follow-up at Day 8±1; subjects in the food-effect 2-period cohort (Cohort A3) should return to the clinic for follow-up at Day 8±1 in Period 2 (5 days after the last PK blood sample in fed part).

4 An abbreviated physical examination may be performed at the Investigator's discretion upon admission and discharge from the clinical site.

5 Weight only.

6 Refer to Appendix6 for more details.

7 Serum pregnancy test for all female subjects at Screening and urine pregnancy test, for female subjects of childbearing potential only, at all other timepoints.

8 Clinical laboratory tests (including clinical chemistry, lipid profile, coagulation, hematology, and urinalysis): at Screening; on Day -1 (admission) and at pre-dose, 48 hours post-dose; and at follow-up/EOS.

9 Triplicate 12-lead ECG: at Screening; Day -1 (admission), at pre-dose (within 60 minutes of dosing) and at 1, 3, 6, and 12 hours post-dose (±15 minutes); prior to discharge, and at follow-up/EOS.

10 When safety and PK blood draws coincide, procedures should be carried out in the following order: (1) ECGs, (2) vital signs, (3) PK blood sampling (nominal).

11 Vital signs: Screening; Day -1 (admission); at pre-dose (within 60 minutes of dosing) and at 0.75, 1.25, 1.75, 3.75, 8, 11.75, and 23.25 hours post-dose (±15 minutes); prior to discharge; and at follow-up/EOS. Orthostatic measurements will be obtained at Screening, Day -1, pre-dose, and at 1.75 hours (±15 minutes) post dose. For orthostatic measurements blood pressure and pulse rate will be measured after the subject has been in the supine position for at least 5 minutes, repeat measurements will be taken after the subject has been standing in the upright position for at least 2 to 3 minutes (respiratory rate and temperature will be measured with blood pressure and pulse rate in the supine position only).

12 A baseline/screening version of the C-SSRS will be used at Screening and a "since-last-visit" version will be used at all subsequent visits where the C-SSRS is administered.

13 Blood sampling for PK of SBP-9330 in plasma: at pre-dose (within 60 minutes of dosing) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours post-dose (±10%).

Table 14: Schedule of Activities – Part B (MAD Phase)

		Assessment Period																	
Visit[1]	**Screening**	**Pretreatment**		**Treatment**															**Follow-up/ End of Study[2]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**21±1**
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ambulatory[2]	X																			X
Admission		X																		
Discharge																			X	
Informed Consent	X																			
Medical History	X	X																		
Demographics	X																			
Physical Examination	X	X[3]																	X[3]	X
Body Weight and Height (Including BMI Calculation)	X	X[4]																		
Serology (HBsAg, HCVAb, anti-HIV 1 and 2)	X																			
Urine Drug and Alcohol Screen[5]	X	X																		
FSH (postmenopausal females only)	X																			
Pregnancy Test (Females Only)[6]	X	X																	X	X
Clinical Laboratory Test[5,7]	X	X	X		X					X							X		X	X
12-lead ECG[8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital Signs[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Eligibility Check	X	X																		
Randomization		X																		
Study Drug Administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood Sampling for PK[9,11]			X	X	X					X				X	X	X	X	X	X	
C-SSRS Questionnaire[12]	X	X															X			X
M.I.N.I.	X																			
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

		Assessment Period																		
Visit[1]	**Screening**	**Pretreatment**		**Treatment**																**Follow-up/ End of Study[2]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**21±1**
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; MAD = multiple ascending dose; M.I.N.I. = Mini International Neuropsychiatric Interview; PK = pharmacokinetic

1 The timing, type, and number of safety, and PK assessments may be updated depending on emerging safety and PK data.

2 Subjects who discontinue the study early should complete the EOS procedures.

3 An abbreviated physical examination may be performed at the Investigator's discretion upon admission or discharge from the clinical site.

4 Weight only.

5 Refer to Appendix6 for more details.

6 Serum pregnancy test for all female subjects at Screening and urine pregnancy test, for female subjects of childbearing potential only, at all other timepoints.

7 Clinical laboratory tests (including clinical chemistry, lipid profile, coagulation, hematology, and urinalysis): at Screening; on Day -1 (admission); at pre-dose on Days 1, 3, 7, 14, and 16; and at follow-up/EOS.

8 Triplicate 12-lead ECG: at Screening; Day -1 (admission); at pre-dose (within 60 minutes) on Day 1 and at 3 hours post-dose on each dosing day (i.e., Days 1 to 14) (±15 minutes); prior to discharge; and at follow-up/EOS.

9 When safety and PK blood draws coincide, procedures should be carried out in the following order: (1) ECGs, (2) vital signs, (3) PK blood sampling (nominal).

10 Vital signs: at Screening; Day -1 (admission); at pre-dose (within 60 minutes) and 1.75 hours post-dose on each dosing day (i.e., Days 1 to 14) (±15 minutes); prior to discharge; and at follow-up/EOS. Orthostatic measurements will be obtained at Screening, Day -1, pre-dose, and at 1.75 hours (±15 minutes) post dose. For orthostatic measurements blood pressure and pulse rate will be measured after the subject has been in the supine position for at least 5 minutes, repeat measurements will be taken after the subject has been standing in the upright position for at least 2 to 3 minutes (respiratory rate and temperature will be measured with blood pressure and pulse rate in the supine position only).

11 Blood sampling for PK of SBP-9330 in plasma: at pre-dose (within 60 minutes of dosing); at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours post-dose (±10%) on Day 1; within 60 minutes prior to morning drug administration on Day 7, 11, 12, and 13; and within 60 minutes prior to drug administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours post-dose on Day 14 (±10%).

12 A baseline/screening version of the C-SSRS will be used at Screening and a "since-last-visit" version will be used at all subsequent visits where the C-SSRS is administered.

Table 15: Schedule of Activities – Part C (Smoker Phase)

		Assessment Period																		
Visit[1]	**Screening**	**Pretreatment**		**Treatment**																**Followup/ End of Study[2]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**21±1**
Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Ambulatory[2]	X																			X
Admission		X																		
Discharge																			X	
Informed Consent	X																			
Medical and Smoking History	X	X																		
Demographics	X																			
Physical Examination	X	X[3]																	X[3]	X
Body Weight and Height (Including BMI Calculation)	X	X[4]																		
Serology (HBsAg, HCVAb, antiHIV 1 and 2)	X																			
Urine Drug and Alcohol Screen[5]	X	X																		
FSH (postmenopausal females only)	X																			
Pregnancy Test (Females Only)[6]	X	X																	X	X
Clinical Laboratory Test[5,7]	X	X	X			X				X							X		X	X
12-lead ECG[8,9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital Signs[9,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Eligibility Check	X	X																		
Randomization		X																		
Study Drug Administration				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood Sampling for PK[9,11]			X	X	X					X				X	X	X	X	X	X	
Expired CO Level[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Blood Sampling for Cotinine[13]			X							X							X			
Smoking Log		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

		Assessment Period																		
Visit[1]	**Screening**	**Pretreatment**		**Treatment**																**Followup/ End of Study[2]**
Study Day	**-28 to -2**	**-1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**21±1**
FTCD	X																			
Smoking TLFB	X	X																		
MNWS		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
QSU-Brief		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
C-SSRS Questionnaire[14]	X	X															X			X
M.I.N.I.	X																			
Previous and Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; CO = carbon monoxide; ECG = electrocardiogram; EOS = end of study; FSH = follicle-stimulating hormone; FTCD = Fagerström Test for Cigarette Dependence; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus; MAD = multiple ascending dose; M.I.N.I. = Mini International Neuropsychiatric Interview; MNWS = Modified Minnesota Nicotine Withdrawal Scale; PK = pharmacokinetic; QSU-Brief = Questionnaire on Smoking Urges – Brief version; TLFB = Smoking Time-Line Follow-back

1. The timing, type, and number of safety, and PK assessments may be updated depending on emerging safety and PK data.
2. Subjects who discontinue the study early should complete the EOS procedures.
3. An abbreviated physical examination may be performed at the Investigator's discretion upon admission or discharge from the clinical site.
4. Weight only.

5. See APPENDIX 6 from protocol for details.
6. Serum pregnancy test for all female subjects at Screening and urine pregnancy test, for female subjects of childbearing potential only, at all other timepoints.
7. Clinical laboratory tests (including clinical chemistry, lipid profile, coagulation, hematology, and urinalysis): at Screening; on Day -1 (admission); at pre-dose on Days 1, 3, 7, 14, and 16; and at follow-up/EOS.
8. Triplicate 12-lead ECG: at Screening; Day -1 (admission); at pre-dose (within 60 minutes) on Day 1 and at 3 hours post-dose on each dosing day (i.e., Days 1 to 14) (±15 minutes); prior to discharge; and at follow-up/EOS.
9. When safety and PK blood draws coincide, procedures should be carried out in the following order: (1) ECGs, (2) vital signs, (3) PK blood sampling (nominal), (4) smoking assessments.
10. Vital signs: at Screening; Day -1 (admission); at pre-dose (within 60 minutes) and 1.75 hours post-dose on each dosing day (i.e., Days 1 to 14) (±15 minutes); prior to discharge; and at follow-up/EOS. Orthostatic measurements will be obtained at Screening, Day -1, pre-dose, 1.75 hours (±15 minutes), and 3.5 hours (±15 minutes) post dose. For orthostatic measurements blood pressure and pulse rate will be measured after the subject has been in the supine position for at least 5 minutes, repeat measurements will be taken after the subject has been standing in the upright position for at least 2 to 3 minutes (respiratory rate and temperature will be measured with blood pressure and pulse rate in the supine position only).
11. Blood sampling for PK of SBP-9330 in plasma: at pre-dose (within 60 minutes of dosing); at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours post-dose (±10%) on Day 1; within 60 minutes prior to morning drug administration on Day 7, 11, 12, and 13; and within 60 minutes prior to drug administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours post-dose on Day 14 (±10%).
12. Expired breath CO will be measured with a Bedfont Smokerlyzer™.
13. Cotinine samples should be collected within 60-minutes prior to dosing on dosing days.
14. A baseline/screening version of the C-SSRS will be used at Screening and a "since-last-visit" version will be used at all subsequent visits where the C-SSRS is administered.