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

Protocol Number:	SBP-9330-101
Altasciences Project Number:	CNO-P5-319
Investigational Product:	SBP-9330
Phase of Development:	1
Sponsor:	Camino Pharma, LLC 9920 Pacific Heights Blvd, Suite 150 San Diego, CA 92121 USA
Sponsor's Contact Person:	Gonul Velicelebi, PhD Chief Executive Officer

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation and all applicable federal and local regulations.

Protocol Version		Date
1.0	**FINAL**	**April 22, 2021**
2.0	**AMENDMENT 1**	**June 1, 2021**
3.0	**AMENDMENT 2**	**December 10, 2021**
4.0	**AMENDMENT 3**	**September 14, 2022**

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STUDY SYNOPSIS

Name of Sponsor:	Camino Pharma, LLC
Name of Product:	SBP-9330
Title of Study:	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
Study Development Phase:	1
Objectives:	**Primary Objective:** • To assess the safety and tolerability of single and multiple ascending oral doses of SBP-9330 in healthy nonsmokers and healthy smokers **Secondary Objectives:** • To determine single and multiple oral dose pharmacokinetics (PK) of SBP-9330 in healthy nonsmokers and healthy smokers • To explore the effect of food on the single oral dose PK of SBP-9330 in healthy nonsmokers **Exploratory Objectives:** • To explore the effect of SBP-9330 on smoking-related assessments
Endpoints:	**Primary Endpoints – Safety and Tolerability:** • Incidence and severity of adverse events (AEs) for subjects administered SBP-9330 compared to placebo • Changes in vital signs, physical examination findings, electrocardiogram (ECG) findings, Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire results, and clinical laboratory results for subjects administered SBP-9330 compared to placebo **Secondary Endpoints - Pharmacokinetics:** • Pharmacokinetic (PK) parameters, where appropriate, will be determined for SBP-9330 from individual concentration-time profiles in plasma. • Main PK parameters will be determined to assess the effect of food after a single oral dose of 600 mg SBP-9330. **Exploratory Endpoints – Smoking Assessments:** • Expired carbon monoxide (ECO) level • Plasma cotinine level • Number of cigarettes smoked (smoking log) • Minnesota Nicotine Withdrawal Scale (MNWS) responses

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

- Questionnaire on Smoking Urges – Brief version (QSU-Brief) responses

</td></tr>
<tr><td>Test Product, Dose, and Mode of Administration (proposed):</td><td>SBP-9330 75-mg, 150-mg and 300-mg capsules

Manufacturer: PACE Laboratory (previously Velesco Pharmaceutical Services, Inc.)

Small batches of 75-mg dose strength capsules will also be prepared by the Altasciences pharmacy using a Sponsor-supplied procedure.

Mode of administration: Oral</td></tr>
<tr><td>Placebo, Dose, and Mode of Administration:</td><td>Placebo (visually matching SBP-9330 75-mg, 150-mg and 300-mg capsules)

Manufacturer: PACE Laboratory (previously Velesco Pharmaceutical Services, Inc.)

Mode of administration: Oral</td></tr>
<tr><td>Study Design:</td><td>This is a single-center, first-in-human, randomized, double-blind, placebo-controlled, SAD/MAD 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

<u>Part A - SAD Phase with Nested Food-Effect Cohort</u>

Healthy adult nonsmoker subjects will be randomized to receive a single oral dose of either SBP-9330 or placebo in each of 5 planned SAD cohorts. Each cohort will consist of 8 subjects in 3:1 (SBP-9330:placebo) ratio to have a total of 6 subjects receiving SBP-9330 and 2 subjects receiving placebo.

The proposed SAD design and planned escalation are as follows:

<table>
<tr><th>Cohort</th><th>N (active:placebo)</th><th>Dose</th><th>Drug administration</th></tr>
<tr><td>A1</td><td>6:2
(1:1 [sentinel group] and 5:1 [remaining subjects])</td><td>150 mg</td><td>Single oral SBP-9330 or placebo administration</td></tr>
<tr><td>A2</td><td>6:2
(1:1 [sentinel group] and 5:1 [remaining subjects])</td><td>300 mg</td><td>Single oral SBP-9330 or placebo administration</td></tr>
<tr><td>A3</td><td>6:2
(1:1 [sentinel group] and 5:1 [remaining subjects] for Period 1 only)</td><td>600 mg</td><td>Single oral SBP-9330 or placebo administration under fasted and fed conditions in 2-period food-effect cohort with 7- to 14-day washout</td></tr>
<tr><td>A4</td><td>6:2
(1:1 [sentinel group] and 5:1 [remaining subjects])</td><td>1200 mg</td><td>Single oral SBP-9330 or placebo administration</td></tr>
<tr><td>A5</td><td>6:2
(1:1 [sentinel group] and 5:1 [remaining subjects])</td><td>2400 mg</td><td>Single oral SBP-9330 or placebo administration</td></tr>
</table>
</td></tr>
</table>

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, subjects 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 6 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 available plasma PK analysis of the previous dose, including delayed significant AEs in earlier cohorts, are acceptable to the Investigator, Sponsor and Data and Safety Monitoring Board (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.

Part B - MAD Phase

Healthy adult nonsmoker subjects will be randomized to receive either SBP-9330 or placebo orally in each of the 3 planned MAD cohorts. Each cohort will consist of 10 subjects 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 plasma PK data from previous cohorts.

The proposed MAD design and planned escalation are as follows:

Cohort	N (active:placebo)	Dose	Drug administrations
B1	8:2	adaptive	Once daily oral administrations for 14 consecutive days
B2	8:2	adaptive	Once daily oral administrations for 14 consecutive days
B3	8:2	adaptive	Once daily oral administrations for 14 consecutive days
Additional B4	8:2	adaptive	Once daily oral administrations for 14 consecutive days

Each subject will receive once daily oral administration of the assigned treatment 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 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 decreased at the discretion of the Sponsor depending on the emerging safety and PK data from the proceeding 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 administered in the SAD phase.

All subjects who complete the study and those terminating early will be required to complete the End of study/Follow-up procedures.

Part C – Smoker Phase

Healthy adult smokers will be randomized to receive either SBP-9330 or placebo orally in each of the 2 planned smoker cohorts. Each cohort will consist of 10 subjects randomly assigned in a 4:1 (SBP-9330:placebo) ratio, for a total of 8 subjects receiving SBP-9330 and 2 subjects receiving placebo.

The proposed Smoker phase design and planned escalation are as follows:

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
Additional C3	8:2	adaptive	Once daily oral administrations for 14 consecutive days

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

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

All relevant safety and 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. 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. There are 2 planned cohorts and an additional cohort may be added depending on the emerging PK

	and safety data in the previous cohorts. A Smoker cohort daily dose level cannot be higher than the highest dose level administered in the MAD phase. All subjects who complete the study and those terminating early will be required to complete the End of Study/Follow-up procedures.
Study Population:	Healthy adult male and female subjects aged 18 to 55 years, inclusive.
Planned Number of Subjects:	Part A – SAD Phase with nested Food-Effect Cohort: 40 subjects (5 cohorts of 8 subjects each). Part B – MAD Phase: 30 subjects (3 cohorts of 10 subjects each). An additional MAD cohort (10 subjects) may be added in Part B, depending on the emerging PK and safety data in the previous cohorts. Part C – Smoker Phase: 20 subjects (2 cohorts of 10 subjects each). An additional Smoker cohort (10 subjects) may be added in Part C depending on the emerging PK and safety data in the previous cohorts. Subjects cannot be enrolled in more than 1 cohort or study part.
Study Drug Administration:	**Part A - SAD Phase with Nested Food-Effect Cohort** For Cohorts A1, A2, A4, and A5: The assigned dose of SBP-9330 or placebo will be administered orally with approximately 240 mL of water in the morning, following a minimum 10-hour overnight fast. An additional volume of water of up to 150 mL may be provided in 50 mL increments to ensure that the whole dose is administered. For Cohort A3 only: In Period 1, the assigned dose of SBP-9330 or placebo will be administered orally with approximately 240 mL of water in the morning, following a minimum 10-hour overnight fast. During Period 2, the assigned dose of SBP-9330 or placebo will be administered orally with approximately 240 mL of water in the morning, following a minimum 10-hour overnight fast and 30 minutes after the start of a high-fat, high-calorie breakfast. An additional volume of water of up to 150 mL may be provided in 50 mL increments to ensure that the whole dose is administered. **Parts B and C - MAD Phase and Smoker Phase** The assigned dose of SBP-9330 or placebo will be administered orally with approximately 240 mL of water in the morning, once daily for 14 consecutive days, and each dose will follow a minimum 10-hour overnight fast. An additional volume of water of up to 150 mL may be provided in 50 mL increments to ensure that the whole dose is administered.
Duration of Treatment and Subject Confinement:	**Part A - SAD Phase with Nested Food-Effect Cohort** Duration of clinical trial (per subject): Screening: Day -28 to Day -1 (up to 28 days) Cohorts A1, A2, A4, and A5: • Subjects will be confined to the clinical research unit (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). • 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) 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. • 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 52 days (including Screening) **Parts B and C - MAD Phase and Smoker Phase** Duration of clinical trial (per subject): Screening: Day -28 to Day -1 (up to 28 days) 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). The total study duration will be up to 50 days (including Screening).
Safety Meetings for Dose Escalation and Adjustments:	A DSMB will be established to assure that the safety of study subjects is protected while the scientific goals of the study are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as recommending the appropriate termination of study when risks have been uncovered or when it appears that the clinical trial cannot be concluded successfully. The DSMB is responsible for reviewing and evaluating safety and available plasma PK data collected after each cohort and making a recommendation for dose escalation and adjustments. The DSMB, at a minimum, will review safety data up to discharge and available plasma PK data of all the subjects in the respective cohort in a blinded manner to decide whether to escalate doses between cohorts. The DSMB will be provided the randomization code to aide in the review for Part C. The minimum number of subjects required to decide on dose escalation is 6 subjects (i.e., at least 4 on active treatment) for Part A (SAD Phase) and 8 subjects (i.e., at least 6 on active treatment) for Parts B (MAD Phase) and C (Smoker Phase). The DSMB will also advise as to when MAD dosing may commence and whether any stopping criteria were met. These assessments will generally be made without breaking the randomization code. If judged necessary by the

	DSMB, an individual or the complete cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation. The DSMB may advise adjusting the dose based on the treatment-emergent safety and available PK data.
Inclusion Criteria	1. Provision of written informed consent prior to the initiation of any protocol-specific procedures 2. Stated willingness to comply with all study procedures and availability for the duration of the study 3. Healthy male or female subject ≥ 18 and ≤ 55 years of age 4. Body mass index (BMI) ≥ 18.5 kg/m^2 and ≤ 32.0 kg/m^2 5. Body weight ≥ 50.0 kg at Screening 6. A female subject must meet at least one of the following criteria: a. Is of childbearing potential and agrees to use an acceptable contraceptive method. Acceptable contraceptive methods include: • Total abstinence, in accordance with the lifestyle of the subject, from at least 30 days prior to the first study drug administration through to at least 90 days after the last dose of the study drug • One of the following contraceptive methods, used in combination with a barrier method (e.g., a diaphragm, a cervical cap, or a condom), from at least 30 days prior to the first study drug administration through to at least 90 days after the last dose of the study drug: ▪ Intrauterine device (with or without hormones) ▪ Spermicide Or b. Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or is in a postmenopausal state (i.e., at least 1 year without menses prior to the first study drug administration without an alternative medical condition and confirmed with a serum follicle-stimulating hormone [FSH] > 40 IU/L at Screening) 7. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from the first admission to the CRU until 90 days after the last study drug administration. Adequate contraception for the male subject (and/or his female partner) includes the following: • Use of spermicide, hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom • Double-barrier method Total abstinence, in accordance with the lifestyle of the subject, from at least 30 days prior to the first study drug administration until 90 days after the last study drug administration, is also acceptable

	8. **Parts A and B only**: Never or non smoker (a non smoker is defined as someone who completely stopped using nicotine products for at least 2 years prior to the first study drug administration 9. Have no clinically significant medical or mental health conditions captured in the medical history or evidence of clinically significant findings on the physical examination and/or ECG, as determined by an Investigator 10. No clinically significant abnormalities in blood pressure, heart rate, body temperature and respiratory rate and no evidence of orthostatic hypotension or postural tachycardia at Screening as defined below: a) 100 mmHg ≤ systolic blood pressure (BP) ≤ 140 mmHg in supine position. b) 60 mmHg ≤ diastolic BP ≤ 90 mmHg in supine position. c) 60 beats per minute (bpm) ≤ heart rate ≤ 100 bpm in supine position. d) 35.5 °C ≤ body temperature ≤ 37.5 °C. e) 10 breaths per minute ≤ respiratory rate ≤ 22 breaths per minute. f) ≥ 20 mmHg decrease in systolic BP from supine to standing. g) ≥ 10 mmHg decrease in diastolic BP from supine to standing. h) ≥ 30 bpm increase in heart rate from supine to standing. **Part C Only:** 11. Are current tobacco cigarette smokers who smoke an average of 10 or more cigarettes per day in the 30 days prior to Screening 12. Expired breath CO level ≥10 parts per million (ppm) at Screening and prior to the first study drug administration 13. Positive test result for cotinine at Screening and prior to the first study drug administration 14. Are not motivated to try to quit smoking from Screening through 30 days from the first study drug administration
Exclusion Criteria:	1. Female who is lactating 2. Female who is pregnant according to the pregnancy test at Screening or prior to the first study drug administration 3. Female who is planning to become pregnant during this study or within 90 days after the last study drug administration 4. Male with female partner who is pregnant, lactating, or planning to become pregnant during this study or within 90 days after the last study drug administration 5. Poor venous access as determined by an Investigator at Screening 6. History of significant hypersensitivity to SBP-9330 or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs 7. Presence of any medical condition that, in the opinion of an Investigator, poses an unacceptable risk to the subjects

	8. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect drug absorption 9. Evidence or history of clinically significant cardiovascular, pulmonary, hematologic, psychiatric (including mood and substance use disorders), neurological (including migraines, seizures, and epilepsy), endocrine, renal, hepatic, gastrointestinal, immunologic or dermatologic disease 10. History of malignancy within the past five years, except for successfully treated basal cell carcinoma of the skin 11. History of suicidal ideation or suicidal behavior as per the C-SSRS questionnaire administered at Screening 12. Evidence or history of significant psychiatric disease or any DSM-5 disorder as assessed by the Mini International Neuropsychiatric Interview (M.I.N.I.) administered at Screening 13. Routine or chronic use of more than three grams of acetaminophen daily 14. Strenuous activity, sunbathing, and contact sports within 48 hours prior to (first) admission to the CRU 15. Current alcohol consumption exceeding two standard drinks per day on average (1 standard drink=10 grams of alcohol) for male subjects and one standard drink per day on average for female subjects 16. History of alcohol or drug (other than caffeine) use disorder within 12 months prior to Screening 17. Any clinically significant illness in the 28 days prior to the first study drug administration 18. QTcF interval (QT interval corrected for heart rate according to Fridericia) > 450 ms for males and > 470 ms for females at Screening or on Day –1 19. **Parts A and B only**: Positive test result for alcohol and/or drugs of abuse at Screening or prior to the first drug administration 20. Positive test results for HIV-1/HIV-2 antibodies, hepatitis B surface antigen or hepatitis C antibody 21. Consumption of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) or over-the-counter medications and nutrients known to modulate cytochrome P450 (CYP450) enzymes activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) or St. John's Wort within 14 days prior to the first study drug administration 22. Consumption of other prescription and over-the-counter medication not specifically excluded by Exclusion Criterion 21 including health supplements and herbal remedies within 7 days prior to the first study drug administration (an exception is made for paracetamol [acetaminophen], which is allowed up to admission to the clinic). 23. Any other clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of an Investigator, increase the subject's

	risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data 24. Intake of an investigational product in the 30 days or 5 half-lives (whichever is longer) prior to Screening 25. Inclusion in a previous cohort of this clinical study 26. Employee of the contract research organization (CRO) or the Sponsor. 27. Blood donation (excluding plasma donation) of approximately 500 mL within 56 days prior to Screening 28. Plasma donation within 7 days prior to Screening **Part C Only:** 29. History of generalized rash reaction to any drugs 30. Positive test result (except cotinine) for alcohol and/or drugs of abuse at Screening or prior to the first study drug administration 31. Use of smoking cessation aids (NRT, bupropion, or varenicline) within 30 days prior to the first study drug administration 32. Unable to abstain from smoking tobacco cigarettes for at least 1 hour before and 2 hours after study drug administration 33. Unable to abstain from using nicotine-containing products other than tobacco cigarettes (e.g., pipes, cigars, e-cigarettes or vapes, nicotine topical patches, nicotine gum, or nicotine lozenges) during the study
Bioanalysis:	SBP-9330 plasma concentrations will be measured by a validated bioanalytical method. Part C only: Cotinine plasma concentrations will also be measured by a validated bioanalytical method.
Safety Analysis	Safety data including adverse events, changes in vital signs, physical examination findings, ECG findings, C-SSRS) questionnaire results, and clinical laboratory results will be summarized by treatment and dose level.
Pharmacokinetic Analysis:	Plasma samples for determination of SBP-9330 concentration will be collected at various time points throughout the study. PK analyses will be performed by non-compartmental analysis, and will be further detailed in the SAP. The following PK parameters in plasma will be calculated for SBP-9330 in each study part: **Part A: SAD Phase with nested Food-Effect cohort** Day 1: C_{max}, T_{max}, AUC_{0-24}, AUC_{0-T}, $AUC_{0-\infty}$, T_{half}, CL/F, and V_z/F Day 8 (Cohort A3, Food-Effect only): C_{max}, T_{max}, AUC_{024}, AUC_{0-T}, $AUC_{0-\infty}$, T_{half}, CL/F, and V_z/F **Parts B and C: MAD Phase and Smoker Phase** 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}, $R_{AC}(C_{max})$, $R_{AC}(AUC)$
Smoking Assessments (Part C only):	Expired CO values, cotinine levels, number of cigarettes smoked, MNWS responses, and QSU-Brief responses will be summarized by treatment and dose level.
Statistical Analysis:	Descriptive statistics will be calculated for plasma SBP-9330 concentrations at each individual time point (or time interval, for urine) and for all PK parameters; individual and mean concentration-time profiles will also be presented. For all study phases, the appropriate PK parameters (C_{max}, AUCs) will be assessed statistically for dose proportionality. Proportionality analysis will be done using a power model. Dose proportionality may be assessed within different dose ranges, if deemed appropriate, with at least three doses. For SAD Phase Cohort A3, a statistical comparison will be performed to evaluate the effect of food on the PK of SBP-9330 with the natural logarithmic transformation of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. 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 parameter T_{max} will be evaluated descriptively. For the MAD and Smoker cohorts, C_{trough} will be displayed graphically and summarized descriptively to assess for steady state. Smoking data will be summarized by treatment and dose level using descriptive statistics. The statistical analysis of safety, PK, and smoking data will be further detailed in the SAP.

Table 1 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; P K= 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	See APPENDIX 6 for 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 2 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	See APPENDIX 6 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).
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 3 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		
FTCD	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**
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 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.

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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.

1.1. Study Rationale

1.1.1. Overview of Disease

Cigarette smoking remains the leading preventable cause of morbidity and mortality in the United States with the death toll from smoking and second-hand smoke exposure estimated at 480,000 adults per year[1]. While smoking rates have been declining in adults without mental health conditions for decades, several new combustible, noncombustible, and electronic products have emerged, leading to a growing cohort of dually- and newly-addicted nicotine users. Although there are approximately 47 million tobacco users in the US[1] and one billion worldwide, only three categories of medications – nicotine replacement therapies, the atypical antidepressant bupropion, and the nicotinic acetylcholine receptor partial agonist varenicline, have been approved by the U.S. Food and Drug Administration (FDA) to combat this pandemic. The long-term success rates of these FDA approved products are low, with 7-day point prevalence abstinence rates at 6 months of less than 25%[2,3]. Thus, there is considerable need for more effective therapeutics with different mechanisms of action which may be used as a single agent or in combination with other treatments.

1.1.2. Therapeutic Rationale

Substance use disorder is a chronic condition marked by relapse to drug use even after prolonged abstinence, escalation of drug intake, tolerance to drug effects, craving, and continued use despite adverse consequences to health, financial status, and relationships[4,5]. Cigarette smoking, attributable primarily to the addictive properties of nicotine[6,7], is one of the largest preventable causes of disease and death in the USA. According to the Centers for Disease Control and Prevention, cigarette smoking results in >400,000 premature deaths in the US each year, ~1 in every 5 deaths[1]. Additionally, e-cigarettes (e-cigs) have emerged as another highly effective nicotine delivery vehicle and represent the primary reason for increased nicotine addiction among young people. Cigarette smoking accounts for ~30% of all cancers, including 90% of lung cancer cases. While e-cigs do not exact the heavy carcinogenic toll that cigarettes do, they can actually be as addictive due to the greatly increased nicotine content of the vaping pods.

There is a great incentive to quit smoking as it markedly reduces the risk of developing smoking-related diseases and early death. Smokers can and do stop smoking – today in the US, there are more former smokers than current smokers. However, smoking cessation is very difficult and often takes multiple attempts. In the US, nearly 50-70% of adult smokers and approximately 45% of high school-age smokers report that they tried to quit smoking in the past 12 months. In addition to behavioral therapies, there are FDA-approved medications to help those trying to quit smoking. Specifically, these include the atypical antidepressant bupropion (Zyban), the nicotinic acetylcholine receptor partial agonist varenicline (Chantix®), and nicotine replacement therapies (NRTs: nicotine patch, gum, lozenge, inhaler and nasal spray). The abstinence rates of these

FDA-approved products remain low, less than 25% overall[2,3]. Thus, there is a considerable need for more effective therapeutics with novel mechanisms of action.

Extensive data suggest that glutamate, the primary excitatory neurotransmitter in the brain, critically modulates the actions of drugs of abuse[8,9]. For example, increases in excitatory glutamatergic transmission are likely to contribute to the positive reinforcing properties of addictive drugs[10]. Systemic psychostimulant administration, including nicotine[11] and cocaine, increases glutamate levels in the ventral tegmental area and nucleus accumbens (NAc). These structures reside in the extended amygdala, a brain circuit that mediates the rewarding effects of all major drugs of abuse[12]. Following prolonged abstinence, cues previously associated with drug taking trigger glutamate release from prefrontal cortex and amygdala afferents to the NAc core, leading to reinstatement of drug use[13].

Glutamate exerts its actions through two families of receptors, the ionotropic glutamate (iGlu) and metabotropic glutamate (mGlu) receptors. The iGlu receptors are multimeric ligand-gated ion channels that open in response to glutamate and mediate fast excitatory synaptic responses at glutamatergic synapses. The mGlu receptors are G protein-coupled receptors that modulate synaptic glutamatergic activity and constitute excellent targets for drug development[14,15]. There are eight mGlu subtypes, classified into three groups based on sequence homology, pharmacology, and signal transduction mechanism. The group II mGlus (metabotropic glutamate receptor subtype 2 [$mGlu_2$] and metabotropic glutamate receptor subtype 3 [$mGlu_3$]) are $G_{\alpha i/o}$-coupled, negatively regulate the activity of adenylyl cyclase[16], are presynaptically localized at glutamatergic synapses where they inhibit glutamate release, and play a key role in maintaining glutamate homeostasis[17]. The group II mGlu receptors are abundantly expressed in brain regions implicated in different aspects of drug abuse and dependence, including the cortex, hippocampus, striatum, and amygdala[18]. Chronic psychostimulant administration alters group II mGlu function[8], as well as their regulation by cysteine/glutamate exchange in the NAc, inducing profound changes in glutamatergic neurotransmission that are critically involved in the perpetuation of drug dependence[19]. Notably, chronic nicotine exposure downregulates $mGlu_{2/3}$ function in the mesolimbic system[20], indicating direct involvement of these receptors in the development of nicotine addiction. Further support for the specific role of $mGlu_2$ in the development of addiction to several drugs of abuse comes from studies in $mGlu_2$ knockout mice, which have increased alcohol consumption and preference[21]. In addition, studies in rats harboring a mutation in the $mGlu_2$ gene (GRM2 Cys407*), resulting in $mGlu_2$-null rats, display increased alcohol preference and consumption[22]. Furthermore, multiple lines of evidence indicate that increasing $mGlu_2$ activity using agonists or PAMs decreases self-administration of nicotine, as well as cue-induced reinstatement of psychostimulant seeking [reviewed in [19,23]]. Importantly, $mGlu_2$ agonists and PAMs show almost identical efficacy toward the abuse-related effects of several different types of psychostimulants in preclinical animal models, suggesting that $mGlu_2$ PAMs would be effective medications for treating nicotine addiction[23].

Only one $mGlu_2$ PAM (AZD8529) has been tested in the clinic for nicotine cessation, but its severe dose-limiting toxicity prevented dosing at predicted efficacious dose levels, and proof-of-mechanism was not achieved. SBP-9330 is structurally distinct from AZD8529 and has a different and improved safety profile compared to AZD8529. Thus, we expect to be able to dose humans at or above predicted efficacious doses and test the true potential of this mechanism for treating nicotine addiction.

A detailed description of the chemistry, preclinical pharmacology, nonclinical toxicology and pharmacokinetics (PK) of SBP-9330 is provided in the Investigator's Brochure.

SBP-9330 is being evaluated as an aid to smoking cessation. To this end, the present study is being conducted to evaluate the safety and tolerability of single and multiple doses of SBP-9330 in healthy nonsmokers and healthy smokers. The study will also evaluate the PK profile of SBP-9330 in both populations. In addition, the feasibility of incorporating smoking-related assessments will be explored in healthy smokers. SBP-9330 has not been administered to humans prior to this study.

1.2. Background

1.2.1. Mechanism of Action

Positive allosteric modulators (PAMs) of $mGlu_2$ represent a new class of drugs being developed as aids to smoking cessation. Medications that activate $mGlu_2$ receptors can be effective via a dual mechanism: a) by reversing the acute effects of nicotine, thus, decreasing drug reinforcement, and b) by restoring glutamatergic function to normal levels, thus preventing relapse to drug use.

1.2.2. Preclinical Experience

Detailed information concerning the preclinical studies conducted with SBP-9330 can be found in the Investigator's Brochure. A summary is included below:

SBP-9330 is a potent and selective $mGlu_2$ PAM that shows acute and chronic efficacy in two well-established rat models of nicotine dependence: the nicotine intravenous self-administration (IVSA) model and the cue-induced reinstatement of nicotine seeking model. It has excellent drug-like properties, including oral bioavailability, metabolic stability, safety profile and is well-tolerated in pivotal (GLP) 14-day repeat dose toxicology studies in rats and dogs, with a no-adverse effect level (NOAEL) of 600 mg/kg/day and 200 mg/kg/day, respectively.

Primary *in vitro* pharmacology data show that SBP-9330 is a $mGlu_2$ receptor PAM with a potency of 23 nM on human and 45 nM on rat $mGlu_2$ receptors. SBP-9330 is selective for $mGlu_2$, with approximately 100-fold lower potency at $mGlu_3$ as well as other mGlu receptor subtypes. SBP-9330 was tested for off-target activity against a panel of 72 human central nervous system (CNS) targets including G protein-coupled receptors, ion channels and transporters. The only finding was 70% inhibition of cholecystokinin 2 receptor (CCK2) at 10 µM SBP-9330. This level of weak binding did not suggest any obvious safety concerns.

The primary *in vivo* pharmacology data showed that SBP-9330 had acute and chronic efficacy in rat models of both nicotine dependence and relapse without affecting natural reward. In the acute nicotine IVSA model, SBP-9330 at doses of 40 mg/kg and 60 mg/kg (p.o.) reduced nicotine IVSA by approximately 25 and 45%, respectively. These results are comparable to the published effects of varenicline, which showed a 50%–70% reduction in nicotine IVSA at single doses of 2.5–3 mg/kg (highest doses tested)[24-28]. Unlike SBP-9330, however, varenicline reduced food intake in rats at the highest dose[28].

SBP-9330 is highly bound to plasma protein from multiple species. In addition, SBP-9330 is also highly bound to rat brain tissue. The metabolite identification showed an identical pattern of

putative metabolites in all 5 species including human as well as rat and dog used in toxicology studies.

In vivo, SBP-9330 was dosed to fasted Wistar rats and beagle dogs. SBP-9330 showed excellent oral bioavailability.

The toxicology program for SBP-9330 was designed to support the proposed clinical study in healthy nonsmokers and in healthy smokers. The rat and dog were chosen as the appropriate species for toxicity studies based on (a) the similarity of the respective *in vitro* metabolic profiles to human, and (b) pharmacologic relevance of the rat as the *in vivo* efficacy model. The pivotal toxicity studies used the same Good Manufacture Practice (GMP) manufactured batch of SBP-9330 sodium salt with the identical impurity profile intended for the planned clinical study.

Completed toxicity studies include a series of repeat-dose and genetic toxicity studies. In addition, safety pharmacology studies evaluating the impact of administration of SBP-9330 on the cardiovascular, respiratory and central nervous systems were also completed. In addition, an exploratory 12-week testicular toxicity study was carried out in male Wistar rats to assess the potential of SBP-9330 to cause reproductive effects in males and a combination 14-day rat SBP-9330-nicotine safety study was conducted to assess whether there is an interaction between SBP-9330 and nicotine. The genotoxicity of SBP-9330 was evaluated in *in vitro* bacterial reverse mutation and mammalian micronucleus assays (see Table 4).

Table 4 Toxicity Data of SBP-9330 in Non-GLP Studies

Non-GLP Studies	
4-Day Tolerability Study in male Rat	Well-tolerated up to 1000 mg/kg
14-Day Dose-Range Finding Tox in Rat	Well-tolerated up to 600 mg/kg
12-Week Testicular Toxicology in male Rat	Well-tolerated up to 300 mg/kg
7-Day Tolerability Study in Dog	Well-tolerated at 1000 mg/kg
14-Day Dose-Range Finding Tox in Dog	Well-tolerated up to 600 mg/kg
hERG (Manual Patch Clamp)	IC_{50} = 47 µM
Bacterial Mutagenesis (Ames II)	No Activity
IND-enabling GLP Studies	
14-Day Definitive Toxicology in Rat	NOAEL = 600 mg/kg
14-Day Definitive Toxicology in Dog	NOAEL = 200 mg/kg
CNS Safety Pharmacology in Rat (Irwin)	Safe at 600 mg/kg
Cardiovascular & Respiratory Safety Pharmacology in Dog	Safe at 600 mg/kg
Bacterial Mutagenesis (5 strain Ames)	Not mutagenic
Micronucleus in TK6 cells	Not genotoxic
hERG (Manual Patch Clamp)	IC_{50} = 51 µM
14-Day SBP-9330 and Nicotine Combination Toxicology in Rats	NOAEL = 600 mg/kg SBP-9330 in combination with 0.3 mg/kg nicotine

Abbreviations: CNS = central nervous system; hERG = human ether-à-go-go-related gene; GLP = good laboratory practice; NOAEL = no-observed-adverse-effect level

The high doses for the pivotal (GLP) repeat-dose rat and dog toxicity studies were chosen based on the maximum tolerated dose defined in the dose range-finding studies. At the highest dose in the pivotal (GLP) repeat-dose studies, toxicity was characterized by poor tolerability without specific organ toxicity. In the 14-day pivotal (GLP) toxicity study in rats, doses up to 600 mg/kg/day were well tolerated. Treatment-related findings were limited to minor clinical pathology alterations in glucose, albumin, total protein, A/G ratio, triglycerides and cholesterol (total and HDL), and liver, adrenal gland and spleen weight increases without histopathologic correlates. Based on these findings, the NOAEL of SBP-9330 in rats was determined to be 600 mg/kg/day. At 600 mg/kg/day, the systemic exposure (AUC) values on study day 14 were 635,000 and 2,240,000 hr.ng/mL for males and females, respectively.

In the SBP-9330-nicotine combination study, Wistar rats were administered different combinations of SBP-9330 vehicle or SBP-9330 at 60, 120, 300, and 600 mg/kg/day, followed by a subcutaneous injection of nicotine vehicle or nicotine at 0.3 mg/kg/day. No interactions between SBP-9330 and nicotine were observed in the toxicity or exposure of either SBP-9330 or nicotine. The toxicity of SBP-9330 in this combination study was similar to that observed in the 14-day definitive rat toxicity study with SBP-9330. The findings in this combination study included non-adverse increases in the mean liver to body weight ratios, minimal diffuse hepatocellular hypertrophy, increases in albumin, albumin to globulin ratios, cholesterol,

creatinine, glucose and HDL and decreased LDL following treatment. The clinical chemistry findings were within historical control values and were completely reversible following the 4-week recovery period; the liver weight changes were also reversible and the liver findings were considered non-adverse adaptive changes without correlative changes in markers of liver injury (ALT, AST, GGT). SBP-9330 dosed orally at 600 mg/kg/day with a nicotine injection on Day 14 showed C_{max} and AUC_{last} for the males at 63,500 ng/mL and 904,000 hr*ng/mL, respectively, and for the females at 198,000 ng/mL and 2,210,000 hr*ng/mL, respectively. Nicotine administered subcutaneously at 0.3 mg/kg/day with SBP-9330 (Group 7) on Day 14 showed C_{max} and AUC_{last} for the males at 68.1 ng/mL and 94.3 hr*ng/mL, respectively, and for the females at 73.9 ng/mL and 109 hr*ng/mL, respectively.

In the 14-day pivotal (GLP) toxicity study in dogs, doses of > 600 mg/kg/day were not tolerated. At > 600 mg/kg/day, treatment-related findings included salivation, vomiting, diarrhea, lethargy, and body weight loss. At this dose, the alterations in clinical pathology, relative organ weight changes and the histopathologic observation limited to lymphoid depletion in the thymus were considered secondary in nature to a general stress-related response due to the poor tolerability at > 600 mg/kg/day. At 200 mg/kg/day, SBP-9330 was generally well tolerated with treatment-related findings limited to occasional episodes of salivation and vomiting. Based on these findings, the NOAEL in dogs was determined to be 200 mg/kg/day. At 200 mg/kg/day, the systemic exposure (AUC) on study day 14 was 382,000 and 430,000 hr.ng/mL for males and females, respectively.

In the *in vitro* genetic toxicity assays, SBP-9330 was negative for mutagenic and genotoxic potential up to the highest testable concentration under the test conditions of the assays. Moreover, SBP-9330 at doses up to 300 mg/kg/day for 12 weeks in male Wistar rats was well-tolerated with no evidence of testicular toxicity based on an evaluation of sperm parameters and histopathological evaluation of the testis/secondary sex organs.

Lastly, SBP-9330 showed low potency to functionally inhibit the cardiac ion channel ether-a-go-go (hERG) with an IC_{50} of 51 µM. SBP-9330 had no adverse effects on the nervous system of conscious rats or on cardiovascular and respiratory functions in conscious dogs.

In conclusion, SBP-9330 has a low order of toxicity. SBP-9330 is neither mutagenic nor genotoxic. In repeat-dose toxicity studies in rats and dogs, toxicity was defined by the lack of oral tolerability with no evidence of systemic target organ toxicity while achieving high systemic exposure. The NOAEL following 14 daily doses was determined to be 600 mg/kg/day and 200 mg/kg/day in rats and dogs, respectively. The safety profile of SBP-9330 achieved in the toxicity studies supports the proposed clinical studies as outlined.

1.2.3. Clinical Experience

SBP-9330 has not been evaluated in any clinical setting.

1.3. Rationale for Study Design and Dose Selection

This study is a first-in-human study designed to explore the safety, tolerability, and pharmacokinetic profile of SBP-9330 in healthy human subjects over a range of doses anticipated to have biologic effect in humans based on the drug's preclinical pharmacology. Healthy male and female adult volunteers (nonsmokers and smokers) will be enrolled.

The proposed starting dose in the single ascending dose (SAD) study was derived from the NOAEL determined in the pivotal (GLP) 14-day repeat-dose toxicology studies in rats and dogs, corresponding to a human equivalent dose (HED) of 96 mg/kg and 108 mg/kg, respectively. The maximum recommended starting dose (MRSD) of SBP-9330 was calculated to be approximately 600 mg/day (Table 5) in accordance with European Medicines Agency (EMA) guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1, July 2017) and U.S. FDA guidance for industry for estimating the maximum safe starting dose initial clinical trials for therapeutics in adult healthy volunteers (CDER, July 2005).

Table 5 Calculations of the Maximum Recommended Starting Dose of SBP-9330 in First in Human Clinical Trials in Adult Healthy Volunteers

Species	NOAEL (mg/kg)	HED (mg/kg)[1]	MRSD (mg/day)[2]
Rat	600	96	576
Dog	200	108	648

Abbreviations: NOAEL = no observed adverse effect level; HED = human equivalent dose; MRSD = maximum safe human starting dose
[1]animal NOAEL in mg/kg × 0.16 (rat), 0.54 (dog)
[2]HED × 60 kg human subject ÷ Safety Factor of 10

The nonclinical safety data of SBP-9330 support a safe human starting dose of 576 mg/day, which is approximately 4-fold higher than the proposed starting dose of 150 mg in this study (Phase 1 Study SBP-9330-101). This starting dose will provide a 40-fold safety margin and is also expected to result in an exposure lower than the anticipated therapeutic exposure.

1.4. Benefit/Risk Assessment

Although SBP-9330 has not been administered to humans previously, the potential risks to human subjects associated with SBP-9330 are detailed in the Summary of Data and Guidance for the Investigator within the Investigator's Brochure.

Considering the 40-fold safety factor based on the 2-week NOAEL values of rat and dog and the projected starting human therapeutic dose range of SBP-9330 of 300-600 mg/day, the proposed starting dose of 150 mg/day is not expected to induce any potential risk or benefit to subjects participating in this study.

In addition to specific safety stopping criteria (Section 3.5), dose-escalation PK stopping criteria will be implemented such that systemic exposures in subjects do not exceed 1/10th of the $AUC_{0\text{-}24hr}$ and C_{max} levels associated with the identified NOAEL of the GLP 14-day rat study.

Routine clinical assessments including hematology, chemistry, and urinalysis will be performed as a means of monitoring subject safety. Potential safety considerations were limited to minor clinical pathology alterations in glucose, albumin, total protein, triglycerides and cholesterol (total and HDL) based on nonclinical safety assessments. As such, subjects will be monitored for adverse effects related to these parameters.

Overall, the safety monitoring practices employed by this protocol (i.e., physical examination, 12-lead electrocardiogram (ECG), vital signs (including orthostatic blood pressures and pulse

rate), clinical laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire, and AEs) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of the study drug. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical tests received at Screening and during the study.

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
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
Secondary	
To determine single and multiple oral dose pharmacokinetics (PK) of SBP-9330 in healthy nonsmokers and healthy smokers	<u>Single Ascending Dose (SAD) Phase</u> The main PK endpoints for the SAD phase are the following PK parameters: • C_{max}, T_{max}, AUC_{0-24}, AUC_{0-T}, $AUC_{0-\infty}$, T_{half}, CL/F, and V_z/F <u>Multiple Ascending Dose (MAD) Phase</u> The main PK endpoints for the multiple ascending dose (MAD) phase are the following PK parameters: • C_{max}, T_{max}, C_{trough}, C_τ, AUC_{0-24} or AUC_τ, AUC_{0T}, effective T_{half}, CL/F_{ss}, V_z/F_{ss}, $R_{AC}(C_{max})$, and $R_{AC}(AUC)$ For all study phases, additional PK parameters (as noted in Section 8.4) may be estimated as appropriate to support the main PK endpoints.
To explore the effect of food on the single oral dose PK of SBP-9330 in healthy nonsmokers	The main PK endpoints to assess the effect of food after a single oral dose of 600 mg SBP-9330 to healthy nonsmokers are the following: • C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$; T_{max} will also be evaluated Additional PK parameters may be estimated as appropriate to support the main PK endpoints (Section 8.4).
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

OBJECTIVES	ENDPOINTS
	• Questionnaire on Smoking Urges – Brief version (QSU-Brief) responses

3. STUDY DESIGN

3.1. Adaptive Features and Risk Management of Study Design

The rationale for the following adaptive features is based on taking an iterative, hypothesis-forming approach in this clinical trial. The following categories will be adapted as shown in Table 6.

Table 6 Adaptive Features and Boundaries

Adaptive study design category	Adaptive Features	Boundaries
Dose level for the SAD cohorts	SAD dose levels may be adjusted based on safety and available PK data reported in the previous cohort(s).	Doses are intended to escalate; however, they may be adjusted to an intermediate (lower) or equivalent dose, based on safety and available PK data reported in the previous cohort(s). Escalation from one dose level to the next dose level will not be more than 3-fold the previous dose.
Dose level for the MAD cohorts	Doses for the MAD cohorts will be adapted in accordance with safety and available PK data collected in previous cohorts during the SAD or MAD phase.	The first MAD dose must be lower or equal to a dose administered in a SAD cohort for which safety and PK data are available. Doses are intended to escalate; however, they may be adjusted to an intermediate (lower) or equivalent dose, based on safety and available PK data reported in the previous cohort(s). Escalation from one dose level to the next dose level will not be more than three-fold the previous dose. A MAD daily dose level cannot be higher than the highest dose level tested in SAD.
Dose level for the Smoker cohorts	Smoker cohort dose levels will be adapted in accordance with safety and available PK data collected in previous cohorts during the SAD or MAD phase.	The first Smoker dose must be lower or equal to a dose administered in a MAD cohort for which safety and PK data are available. Doses are intended to escalate; however, they may be adjusted to an intermediate (lower) or equivalent dose, based on safety and available PK data reported in the previous cohort(s). Escalation from one dose level to the next dose level will not be more than three-fold the previous dose. A Smoker cohort daily dose level cannot be higher than the highest dose level tested in the MAD phase.
Dosing frequency for the MAD and Smoker cohorts	The dosing frequency may be modified from once daily to twice daily.	The modification from once daily to twice daily administration will not change the total daily dose outlined in this protocol.
The quantity of cohorts in each phase (SAD or MAD)	The quantity of cohorts may be decreased.	The maximum number of cohorts for the SAD and MAD phase are 5 and 4, respectively. The number of cohorts in each phase may be decreased at the discretion of the Sponsor

Adaptive study design category	Adaptive Features	Boundaries
		depending on the emerging safety and PK data from the previous cohorts.
The quantity of cohorts during the Smoker phase	A 3rd cohort may be added.	The Smoker phase will have a maximum of 3 cohorts. There are 2 planned cohorts and an additional cohort may be added depending on the emerging PK and safety data in the previous cohorts.
Overlap between SAD and MAD phases	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 start and the doses to be administered will be determined by the Sponsor after consultation with the DSMB based on emerging safety and PK data. A MAD dose level cannot be higher than the last dose level administered in the SAD phase.
Blood collection during the MAD phase	The PK blood sampling timepoints during the MAD phase may be modified.	Depending on data obtained during the SAD phase, the PK sampling timepoints during the MAD phase may be modified in order to optimize characterization of PK parameters of interest.
Food-Effect cohort	The food-effect cohort may be done in a cohort with a dose level other than 600 mg.	Depending on data obtained in the previous cohorts, the food-effect may be evaluated at a dose level other than 600 mg to optimize characterization of PK parameters of interest.

Abbreviations: DSMB = Data and Safety Monitoring Board; MAD = multiple ascending dose; PK = pharmacokinetic; SAD = single ascending dose

The decision-making process for the above adaptive study categories will be as follows, unless otherwise stated:

- Interim review of safety and emerging PK data for SBP-9330 from completed or ongoing SAD, MAD, or Smoker cohorts in a blinded fashion by the Data and Safety Monitoring Board (DSMB). For Part C (Smoker Phase), the DSMB will be provided the randomization code to aide in the review of safety and PK data.
- Outcome on the adaptive study category will be documented by the DSMB.

Based on the above, progression to the next dose cohort may be performed without delay (i.e., without prior approval from the Institutional Review Board (IRB) or regulatory authorities), unless the adaptive features are outside of the pre-specified boundaries. If it is anticipated to progress with adaptive features outside of the pre-specified boundaries, prior approval must be granted by the IRB and regulatory authorities.

3.2. Data and Safety Monitoring Board (DSMB)

A DSMB will be established to assure that the safety of the study subjects is protected while the scientific goals of the study are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies when risks have been uncovered or when it appears that the clinical trial cannot be

concluded successfully. The DSMB is responsible for reviewing and evaluating safety and available plasma PK data collected after each cohort.

The DSMB will be comprised of voting members who are independent of the Sponsor and CRU and will, at a minimum, include physicians experienced in drug safety. The composition and operations of the DSMB will be detailed in a separate document that will serve as the Data and Safety Monitoring Plan (DSMP).

The DSMB will review safety data up to discharge and available plasma PK data of all the subjects in the respective cohort in a blinded manner to provide recommendations to the Sponsor and PI whether to escalate doses between cohorts. The minimum number of subjects required to decide on dose escalation is six subjects (i.e., at least four on active treatment) for Part A (SAD) and eight subjects (i.e., at least six on active treatment) for Parts B (MAD) and C (Smoker).

The DSMB will also advise as to when MAD dosing may commence and whether any stopping criteria were met. For Part A and Part B, these assessments will generally be made without breaking the blinded randomization code. For Part C, the DSMB will be provided the randomization code to aide in the review. If judged necessary by the DSMB, an individual or the complete cohort may be unblinded during evaluation of the study data. Before unblinding, a decision should be made about the action to be taken based on the revealed treatment allocation. The DSMB may adjust the dose based on the treatment-emergent safety and available PK data.

3.3. Overall Study Design

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
- Parc C: Smoker phase

Each cohort will receive SBP-9330 in an ascending dose order or until stopping rules as outlined in Section 4.3.2 are met.

Part A – SAD phase with nested food-effect cohort will include approximately 40 subjects (5 cohorts of 8 subjects), 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.

The End of Trial will correspond to the last patient last visit of the study.

3.3.1. 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 7.

Table 7 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 placebo)	Single oral dose administration of SBP-9330 or placebo under fasting 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 (8 × 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)

The schedule of activities of the SAD Phase of the study is described in Table 1.

3.3.2. 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 8.

Table 8 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).

The schedule of activities of the MAD Phase of the study is described in Table 2.

3.3.3. 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.

The proposed Smoker phase design and planned escalation are presented in Table 9.

Table 9 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).

The schedule of activities of the Smoker Phase (Part C) of the study is described in Table 3.

3.4. Study Treatments

The following investigational products (IPs) will be administered according to the outlined dose levels in Sections 3.3.1 and 3.3.2.

- 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

3.5. Dose Escalation and Stopping Rules

Escalation to the next higher dose will only proceed if none of the stopping criteria below 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. Dose escalation will be stopped if it is determined that the limits of safety and/or tolerability or the PK stopping criteria (Section 3.5.2) have been reached. This decision will be made by the Sponsor and the Principal Investigator based on DSMB recommendation. If dose escalation is stopped due to any findings, additional cohorts may receive the same or lower doses of the investigational compound. However, in the event that the findings are likely related to C_{max}, dose escalation may continue by dividing the dose ensuring that the C_{max} is the same or lower.

3.5.1. Individual Subject Stopping Rules

Participation in the clinical study may be discontinued by the Principal Investigator or by the Sponsor for any of the following reasons, but not limited to:

- Any subject experiencing a confirmed drug-related moderate or severe AE or serious AE (SAE) will not receive the next scheduled dose of IP until a safety review of the AE is performed by an Investigator and Sponsor Medical Monitor. The decision to continue dosing must be agreed upon by both an Investigator and Sponsor Medical Monitor.
- Any subject experiencing seizures, intractable headaches, or suicidal ideations.
- Liver chemistry elevations that meet any of the following parameters:
  - ALT or AST > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN without elevated alkaline phosphatase.
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
  - ALT or AST > 8 × ULN, which is confirmed.
- Meets either of the following ECG criteria:
  - QTcF >500 ms
  - QTcF change from baseline >60 ms
  - Subject non-compliance (including any violation of protocol requirements which may affect the study outcome)

3.5.2. Cohort Stopping Rules

If any of the following safety concerns are observed, dosing of all subjects at the given dose level or higher will be suspended/halted and all available data will be evaluated by the DSMB.

Dose continuation (remaining subjects within a cohort or remaining dosing for a subject) or escalation should not proceed for any of, but not limited to, the following reasons:

- If one SBP-9330-related SAE occurs in a cohort
- Severe AE at least possibly related to SBP-9330 in two or more subjects in the same cohort*
- Other findings that, at the discretion of the DSMB or Sponsor, indicate further dosing should be stopped

* Prior to suspending the cohort, if severe AEs are reported in two or more subjects at a given dose level, consideration should be given to the treatment assignment (SBP-9330 or placebo). After causality assessment, the Investigator (or designee) should open the individual randomization code to verify the treatment received. Dosing at the given dose level may continue if only one subject received SBP-9330 and the other(s) received the placebo.

Subjects experiencing severe AEs will be followed up with serial measurements of the related clinical parameter(s), as per medical judgment, until resolution, stabilization, or until the subject is lost to follow-up.

Dose escalation will be discussed during the DSMB meeting and may be stopped depending on Principal Investigator's or Sponsor's decision, based on but not limited to the following:

- New clinically significant abnormalities in physical examination, 12-lead ECG, or vital signs in two or more subjects
- Overall pattern of clinical changes or symptoms that may have appeared minor in terms of an individual AE or subject, but which collectively present a safety concern
- Clinically significant changes in organ-specific laboratory parameters (e.g., liver function enzymes in one or more subjects)
- Pattern of laboratory changes (e.g., a consistent increase or decrease in two or more subjects or within or across dosing cohorts) that might indicate an overall safety concern

In addition to the safety stopping criteria listed above, dose-escalation PK stopping criteria will be implemented such that systemic exposures in subjects do not exceed $1/10^{th}$ of the $AUC_{0\text{-}24hr}$ and C_{max} levels associated with the identified NOAEL of the GLP 14-day rat study. The $1/10^{th}$ stopping values for C_{max} and $AUC_{0\text{-}24hr}$ are 25.4 µg/mL and 224 µg* hr/mL, respectively. Dose escalation in the SAD, MAD, or Smoker components of the study will be stopped before these exposures are achieved.

3.5.3. Trial Stopping Rules

The trial can be prematurely terminated by the DSMB or Sponsor for any of the following reasons:

- Occurrence of two SBP-9330-related SAEs in a cohort

- Occurrence of one death attributable to the study treatment

4. SUBJECT POPULATION

Subjects meeting all the inclusion criteria and none of the exclusion criteria at Screening may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the CRU, prior to the first study drug administration.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

An effort will be made to include similar proportions of males and females in the study.

4.1. Inclusion Criteria

1. Provision of written informed consent prior to the initiation of any protocol-specific procedures
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Healthy male or female subject ≥ 18 and ≤ 55 years of age
4. Body mass index (BMI) ≥ 18.5 kg/m^2 and ≤ 32.0 kg/m^2
5. Body weight ≥ 50.0 kg at Screening
6. A female subject must meet at least one of the following criteria:

   a) Is of childbearing potential and agrees to use an acceptable contraceptive method. Acceptable contraceptive methods include:
   - Total abstinence, in accordance with the lifestyle of the subject, from at least 30 days prior to the first study drug administration through to at least 90 days after the last dose of the study drug
   - One of the following contraceptive methods, used in combination with a barrier method (e.g., a diaphragm, a cervical cap, or a condom), from at least 30 days prior to the first study drug administration through to at least 90 days after the last dose of the study drug:
     - Intrauterine device (with or without hormones)
     - Spermicide

   Or

   b) Is of non-childbearing potential, defined as surgically sterile (i.e., has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or is in a postmenopausal state (i.e., at least 1 year without menses prior to the first study drug administration without an alternative medical condition and confirmed with a serum follicle-stimulating hormone [FSH] > 40 IU/L at Screening)
7. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from the first admission to the CRU until 90 days after the last study drug administration. Adequate contraception for the male subject (and/or his female partner) includes the following:

- Use of spermicide, hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom
- Double-barrier method

Total abstinence, in accordance with the lifestyle of the subject, from at least 30 days prior to the first study drug administration until 90 days after the last study drug administration, is also acceptable

8. **Parts A and B only:** Never- or nonsmoker (a nonsmoker is defined as someone who completely stopped using nicotine products for at least 2 years prior to the first study drug administration)
9. Have no clinically significant medical or mental health conditions captured in the medical history or evidence of clinically significant findings on the physical examination and/or ECG, as determined by an Investigator
10. No clinically significant abnormalities in blood pressure, heart rate, body temperature and respiratory rate and no evidence of orthostatic hypotension or postural tachycardia at Screening as defined below:
    a) 100 mmHg ≤ systolic blood pressure (BP) ≤ 140 mmHg in supine position.
    b) 60 mmHg ≤ diastolic BP ≤ 90 mmHg in supine position.
    c) 60 beats per minute (bpm) ≤ heart rate ≤ 100 bpm in supine position.
    d) 35.5 °C ≤ body temperature ≤ 37.5 °C.
    e) 10 breaths per minute ≤ respiratory rate ≤ 22 breaths per minute.
    f) ≥ 20 mmHg decrease in systolic BP from supine to standing.
    g) ≥ 10 mmHg decrease in diastolic BP from supine to standing.
    h) ≥ 30 bpm increase in heart rate from supine to standing.

Part C Only:

11. Are current tobacco cigarette smokers who smoke an average of 10 or more cigarettes per day in the 30 days prior to Screening
12. Expired breath CO level ≥10 parts per million (ppm) at Screening and prior to the first study drug administration
13. Positive test result for cotinine at Screening and prior to the first study drug administration
14. Are not motivated to try to quit smoking from Screening and through 30 days from the first study drug administration

4.2. Exclusion Criteria

1. Female who is lactating
2. Female who is pregnant according to the pregnancy test at Screening or prior to the first study drug administration

3. Female who is planning to become pregnant during this study or within 90 days after the last study drug administration
4. Male with female partner who is pregnant, lactating, or planning to become pregnant during this study or within 90 days after the last study drug administration
5. Poor venous access as determined by an Investigator at Screening
6. History of significant hypersensitivity to SBP-9330 or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
7. Presence of any medical condition that, in the opinion of an Investigator, poses an unacceptable risk to the subjects
8. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect drug absorption
9. Evidence or history of clinically significant cardiovascular, pulmonary, hematologic, psychiatric (including mood and substance use disorders), neurological (including migraines, seizures, and epilepsy), endocrine, renal, hepatic, gastrointestinal, immunologic or dermatologic disease
10. History of malignancy within the past five years, except for successfully treated basal cell carcinoma of the skin
11. History of suicidal ideation or suicidal behaviour as per the C-SSRS questionnaire administered at Screening
12. Evidence or history of significant psychiatric disease or any DSM-5 disorder as assessed by the Mini International Neuropsychiatric Interview (M.I.N.I.) administered at Screening
13. Routine or chronic use of more than three grams of acetaminophen daily
14. Strenuous activity, sunbathing, and contact sports within 48 hours prior to (first) admission to the CRU
15. Current alcohol consumption exceeding two standard drinks per day on average (1 standard drink=10 grams of alcohol) for male subjects and one standard drink per day on average for female subjects
16. History of alcohol or drug (other than caffeine) use disorder within 12 months prior to Screening
17. Any clinically significant illness in the 28 days prior to the first study drug administration
18. QTcF interval (QT interval corrected for heart rate according to Fridericia) > 450 ms for males and > 470 ms for females at Screening or on Day –1
19. **Parts A and B only**: Positive test result for alcohol and/or drugs of abuse at Screening or prior to the first drug administration
20. Positive test results for HIV-1/HIV-2 antibodies, hepatitis B surface antigen (HBsAg) or hepatitis C antibody (HCVAb)

21. Consumption of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) or over-the-counter (OTC) medications and nutrients known to modulate cytochrome P450 (CYP450) enzymes activity (e.g., grapefruit or grapefruit juice, pomelo juice, star fruit, or Seville [blood] orange products) or St. John's Wort within 14 days prior to the first study drug administration
22. Consumption of other prescription and over-the-counter medication not specifically excluded by Exclusion Criterion 21 including health supplements and herbal remedies within 7 days prior to the first study drug administration (an exception is made for paracetamol [acetaminophen], which is allowed up to admission to the clinic).
23. Any other clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of an Investigator, increase the subject's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data
24. Intake of an investigational product in the 30 days or 5 half-lives (whichever is longer) prior to Screening
25. Inclusion in a previous cohort of this clinical study
26. Employee of the contract research organization (CRO) or the Sponsor.
27. Blood donation (excluding plasma donation) of approximately 500 mL within 56 days prior to Screening
28. Plasma donation within 7 days prior to Screening

Part C Only:

29. History of generalized rash reaction to any drugs
30. Positive test result (except cotinine) for alcohol and/or drugs of abuse at Screening or prior to the first study drug administration
31. Use of smoking cessation aids (NRT, bupropion, or varenicline) within 30 days prior to the first study drug administration
32. Unable to abstain from smoking tobacco cigarettes for at least 1 hour before and 2 hours after study drug administration
33. Unable to abstain from using nicotine-containing products other than tobacco cigarettes (e.g., pipes, cigars, e-cigarettes or vapes, nicotine topical patches, nicotine gum, or nicotine lozenges) during the study

4.3. Withdrawal Criteria

4.3.1. Before First Treatment Administration

Before the first treatment administration, continuing to meet the study inclusion/exclusion criteria will govern which subjects are randomized to treatment. Subjects withdrawn before first treatment administration will not be followed up and will not undergo EOS/Follow-up assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

4.3.2. After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an Investigator or Sponsor. An Investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject or if their behavior is deleterious to the study environment.

If such withdrawal occurs, or if the subject fails to return for visits, an Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

An Investigator may remove a subject from the study on the recommendation of the PK facility and/or Sponsor due to an unanticipated event that could result in an inadequately characterized PK profile, such as a missed blood draw, an AE, meal deviation or concomitant medication intake.

Attempts should be made to have such subjects complete the EOS/Follow-up assessments. The EOS/Follow-up assessments should be performed as soon as possible after the last study treatment administration.

The blind may be broken only in emergency situations, where knowledge of the treatment that the subject received is necessary for safety management (Section 5.2.4).

Details of reasons for removal of subjects will be recorded, reported to the Sponsor and documented in the clinical study report.

For subjects lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), an investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

4.4. Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming food or beverages containing grapefruit and/or pomelo for 14 days prior to the first study drug administration and during the study.
- Subjects will be prohibited from consuming alcohol for 48 hours prior to each admission to the CRU until discharge. Throughout the study, in case of any doubt about alcohol consumption, a test for alcohol may be performed if requested by an Investigator
- Subjects will be prohibited from consuming food or beverages containing xanthines (i.e., tea, coffee, cola drinks, energy drinks or chocolate) for 48 hours prior to each admission to the CRU until last discharge.
- Subjects will eat only the food provided by the CRU during confinement.
- Female subjects of childbearing potential will have to take appropriate measures to prevent pregnancy from at least 30 days prior to the first study drug administration,

during the study and for at least 90 days after the last dose of the study drug, as described in Section 4.1. It is the participant's responsibility to notify the CRU if a pregnancy occurs from the end of their study participation until 90 days after the last dose of the study drug.

- Male subjects will be expected to use an acceptable contraceptive regimen and not to donate sperm from the first admission to the CRU, during the study, and until at least 90 days after the last study drug administration, as described in Section 4.1. Reporting for pregnancy in female partners is detailed in Section 7.5.
- For the Smoker cohorts, subjects will abstain from smoking tobacco cigarettes for at least 1 hour before and 2 hours after study drug administration. Subjects will also abstain from using nicotine-containing products other than tobacco cigarettes (e.g., pipes, cigars, e-cigarettes or vapes, nicotine topical patches, nicotine gum, or nicotine lozenges) or other tobacco products (cigars, cigarillos, pipes) during the study.

4.5. Concomitant Treatment

Except for medication which may be required to treat AEs, no other treatment or medication other than the study drugs will be allowed from the first dosing until all study activities and evaluations have been completed.

Systemic contraceptives and hormone replacement therapy are permitted for female subjects as per Section 4.1.

Subjects will be instructed to notify the CRU about any new medications taken after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject case report form (CRF). The drug name and dose taken will be noted. An investigator or delegate and/or the Sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

Subjects receiving the COVID-19 vaccine should be fully vaccinated at least 14 days prior to receiving Investigational Product.

5. STUDY TREATMENTS

5.1. Investigational Products

All IPs will be provided by the Sponsor. The lot number and the measured content of the dosage form, if available, will be included in the final report.

5.1.1. SBP-9330

SBP-9330 75 mg, 150 mg, and 300 mg capsules are manufactured by PACE Laboratory (previously Velesco Pharmaceutical Services, Inc.) for oral administration. Small batches of 75 mg dose strength capsules will also be prepared by the Altasciences pharmacy using a Sponsor-supplied procedure. Each white gelatin capsule contains SBP-9330 sodium equivalent to 75 mg, 150 mg or 300 mg SBP-9330.

5.1.2. Placebo

Placebo capsules matched to Sponsor's SBP-9330 75, 150 and 300 mg capsules will be supplied by the Sponsor. The placebo formulation will be comprised of the same white gelatin capsule, filled with Avicel microcrystalline cellulose, without SBP-9330 (active ingredient).

5.2. Investigational Product Management

5.2.1. Packaging, Labeling and Dispensing

The Sponsor will be responsible for ensuring that the IP is manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

The IPs will be labeled according to the requirements of local law and legislation. The IPs will be dispensed by the CRU's pharmacy.

5.2.2. Storage and Handling

All study drugs will be shipped from the Sponsor or Sponsor resources to the CRU's pharmacy.

The study medication must be carefully maintained at 25°C; excursions permitted to 15-30°C.

The CRU's pharmacy will maintain an inventory record of the IPs received, stored (in a secure restricted area), and dispensed. IPs will be provided to study subjects only.

5.2.3. Method of Assigning Subjects to Treatment Groups

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.

5.2.4. Blinding

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 DSMB will be provided the randomization code to aide in the review for Part C. 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.

5.2.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be maintained. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

The labeling, storage conditions, quantity of reserve samples for the IP, and retention period of the reserve samples shall comply with the current FDA rules and regulations. Drug accountability will be performed at the completion of the trial.

5.3. Administration of Study Drug

Study drug will be administered in the morning at approximately the same time each day. The date and time of each dose will be recorded. For each subject, all scheduled post-dose activities and assessments will be performed relative to the time of study drug administration.

Each oral dose of the assigned formulation will be administered to subjects with approximately 240 mL of water at ambient temperature. An additional volume of water of up to 150 mL may be provided in 50 mL increments to ensure that the whole dose is administered.

5.3.1. Part A – SAD phase with Nested Food-Effect Cohort

For Cohorts A1, A2, A4, and A5, dosing will occur following a minimum 10-hour overnight fast. Fasting will continue for at least 4 hours following drug administration, after which a standardized lunch will be served.

For Cohort A3 only, during Period 1, dosing will occur following a minimum 10-hour overnight fast. Fasting will continue for at least 4 hours following drug administration, after which a standardized lunch will be served. During Period 2, dosing will occur following a minimum 10-hour overnight fast and 30 minutes after the start of a high-fat, high-calorie breakfast. An example meal would consist of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test meal may be made provided that the meal delivers a similar number of calories from protein, carbohydrate, and fat and has comparable meal volume and texture. Subjects must eat the total content of this meal in 30 minutes or less. A standardized lunch will be served at least 4 hours after dosing.

Water will be provided as needed until at least 1 hour pre-dose. Water will be allowed beginning at least 1 hour after the administration of the drug.

5.3.2. Parts B and C – MAD and Smoker Phase

From Days 1 to 14, dosing will occur following a minimum 10-hour overnight fast.

On Days 1 and 14 only, fasting will continue for at least 4 hours following drug administration, after which a standardized lunch will be served. Water will be provided as needed until at least 1 hour pre-dose. Water will be allowed beginning at least 1 hour after the administration of the drug.

Meals and water will be provided at least 1-hour postdose on Days 2 to 13.

5.3.3. Treatment Compliance

The study drug will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's standard operating procedures (SOPs).

5.4. Meals and Fluids

Food and fluid intake other than water will be controlled for each confinement period and for all subjects. Meals and fluids will be provided at appropriate times during the confinement periods unless otherwise specified in this protocol.

5.5. Other Protocol Restrictions

5.5.1. Part A – SAD phase with Nested Food-Effect Cohort

Subjects will remain seated or kept in minimal ambulatory movement for the first 4 hours following drug administration. However, should AEs occur at any time, subjects may be placed in an appropriate position. Subjects will not engage in strenuous activity at any time during the confinement periods.

5.5.2. Parts B and C– MAD and Smoker Phase

On Day 1, subjects will remain seated or kept in minimal ambulatory movement for the first 4 hours following drug administration. On Days 2 to 14, subjects will remain seated or kept in minimal ambulatory movement for the first hour following drug administration. However, should AEs occur at any time, subjects may be placed in an appropriate position. Subjects will not engage in strenuous activity at any time during the confinement periods.

6. STUDY PROCEDURES

Unless otherwise stated in the protocol, the SOPs of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. Procedure windows, including PK sample collection windows, will follow the CRU's SOPs.

An overview of the study activities for each participant is detailed in Table 1 (SAD Phase), Table 2 (MAD Phase), or Table 3 (Smoker Phase).

When safety, PK blood draws, and/or smoking assessments coincide, procedures should be carried out in the following order: (1) ECGs, (2) vital signs, (3) PK blood sampling (nominal), (4) smoking assessments.

Any deviation from protocol procedures should be noted in the source documentation and compiled for reporting in the Clinical Study Report.

6.1. Safety Assessments

Safety assessments will include physical examination, vital signs, 12-lead ECG, clinical laboratory tests, C-SSRS, and AE monitoring. At the discretion of an Investigator, additional safety assessments may be performed as needed to ensure subject safety.

Subjects will be admitted to the CRU, where they will be monitored to detect AEs during the study and followed appropriately to ensure resolution of AEs. An Investigator in charge will be present at the CRU for at least the first 4 hours following drug administration (on Day 1 only for the MAD Phase) and will remain available at all times throughout the study. An Advanced Cardiovascular Life Support (ACLS)-certified Safety Officer/Paramedic will be onsite 24/7, to assist Investigators with any observed AEs and the medical management of study participants. Adverse events, such as but not limited to syncope and seizures, will be managed according to standard of care. A crash cart will be available in the CRU.

6.1.1. Medical History

The medical history at Screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, sex, race, body weight, height, and BMI) and baseline characteristics. Alcohol and smoking habits will also be recorded.

Smoking history will also be collected at Screening for Part C.

6.1.2. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as outlined in Table 1 (SAD Phase), Table 2 (MAD Phase) or Table 3 (Smoker Phase).

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.

6.1.3. Vital Signs

Vital signs will be measured as outlined in Table 1 (SAD Phase), Table 2 (MAD Phase) or Table 3 (Smoker Phase).

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 10 (SAD Phase) and Table 11 (MAD and Smoker Phase).

Table 10 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 11 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.

6.1.4. 12-Lead Electrocardiogram

Triplicate 12-lead ECG (each performed approximately 1 minute apart) will be performed as outlined in Table 1 (SAD Phase), Table 2 (MAD Phase) or Table 3 (Smoker Phase).

On-study ECG measurements are specified in Table 12 (SAD Phase) and Table 13 (MAD and Smoker Phase).

Table 12 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 13 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

6.1.5. Laboratory Evaluations

Laboratory evaluations will be performed as outlined in Table 1 (SAD Phase), Table 2 (MAD Phase), or Table 3 (Smoker Phase).

The laboratory evaluations to be conducted for this study are presented in APPENDIX 6. Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

An Investigator in charge or delegate will assess each abnormal value to determine if it is clinically significant. Post-dose clinically significant laboratory values will be reported as AEs, if applicable, as judged by an Investigator or delegate.

Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on report requirement.

6.1.6. 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 Table 1 (SAD Phase), Table 2 (MAD Phase), or Table 3 (Smoker Phase).

The questionnaire must be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 7 for a sample C-SSRS (Baseline/Screening

Version) assessment and APPENDIX 8 for a sample post-dose C-SSRS (Since Last Visit Version) assessment. The 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.

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.

6.1.7. Mini International Neuropsychiatric Interview (M.I.N.I.)

The M.I.N.I. is a clinician-rated diagnostic assessment that will be administered at Screening and will be considered a source document[31]. The M.I.N.I will be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 9 for a sample M.I.N.I. assessment.

6.2. Blood Volume Collected

The total volume of blood withdrawn, including the volume required for screening, on-study and post-study tests, should be approximately:

- 166 mL for Part A – SAD Phase (Cohorts A1, A2, A4, and A5)
- 250 mL for Part A – SAD Phase (Cohorts A3 [Food-Effect Cohort])
- 330 mL for Part B – MAD Phase (all cohorts)
- 379 ml for Part C – Smoker Phase (all cohorts)

The total blood donation may be higher if repeat blood samples are required for safety assessments.

6.3. Pharmacokinetic Assessments

Blood samples will be collected (1 tube of 6 mL each) for PK assessments.

For the SAD Phase, blood sampling for PK of SBP-9330 in plasma will be performed 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%). The food-effect cohort will have identical PK draws in Periods 1 and 2.

For the MAD and Smoker Phase, blood sampling for PK of SBP-9330 in plasma will be done at the following timepoints:

- At pre-dose (within 60 minutes of dosing) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours post-dose (±10%) on Day 1
- At predose (within 60 minutes prior to morning drug administration) on Day 7, 11, 12, and 13
- At pre-dose (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%).

The complete blood sampling schedule is also presented Table 1 (SAD Phase), Table 2 (MAD Phase) or Table 3 (Smoker Phase).

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the vein of the subject.

The time of PK blood sample collection will be calculated relative to the time of treatment administration. The actual time of all PK blood draws will be recorded and reported for all subjects.

SBP-9330 concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method.

Bioanalysis procedures will be presented in the bioanalytical plan.

6.3.1. Pharmacokinetic Sample Processing, Storage and Shipping

Blood samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

6.3.2. Residual Biological Samples

Plasma samples remaining after the completion of protocol-defined analyses will be retained for potential future metabolite and/or biomarker analysis. No characterization of human genetic material (genes, DNA, RNA) will be performed.

6.4. Smoking Assessments for Part C only

6.4.1. Fagerström Test for Cigarette Dependence (FTCD)

The Fagerström Test for Cigarette Dependence (FTCD) is a standardized self-report questionnaire measuring nicotine dependence severity administered at Screening and will be considered a source document. The FTCD will be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 10 for a sample FTCD.

6.4.2. Smoking Time-Line Follow-back (TLFB)

The Smoking Time-Line Follow-back (TLFB) is a standardized method to obtain estimates of daily consumption of tobacco cigarettes using a calendar technique administered at Screening and on Day -1 and will be considered a source document. The Smoking TLFB will be administered by an Investigator or other individual that is suitably qualified by education or training.

6.4.3. Expired Carbon Monoxide (ECO) Level

Expired breath CO will be measured with a Bedfont Smokerlyzer™ at the following timepoints as outlined in Table 3:

- Screening
- Check-in (Day -1)
- At predose on Days 1 to 14

6.4.4. Blood Sampling for Cotinine

Blood samples will be collected (1 tube of 3 mL each) to measure plasma cotinine levels at predose on Days 1, Day 7, and Day 14 as outlined in Table 3.

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the vein of the subject.

Cotinine concentrations for smoking assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method.

Bioanalysis procedures will be presented in the bioanalytical plan.

6.4.5. Smoking Log

Subjects will be asked to provide sufficient quantity of their usual brand of cigarettes to smoke during their confinement. Subjects will ask for a cigarette from the clinical staff each time they want to smoke. A daily smoking log will be kept to document the number of cigarettes smoked by the subjects from Day -1 to Day 15 as outlined in Table 3.

6.4.6. Minnesota Nicotine Withdrawal Scale (MNWS)

The Minnesota Nicotine Withdrawal Scale (MNWS) is a self-report measure used to monitor symptoms of tobacco withdrawal. The MNWS will be administered by an Investigator or other individual that is suitably qualified by education or training on Day -1 and at 5 hours (±30 minutes) postdose on Days 1 to 14 as outlined in Table 3. The assessment on Day -1 should be completed at approximately the same time as the 5-hour postdose timepoint on dosing days. See APPENDIX 11 for a MNWS example.

6.4.7. Questionnaire on Smoking Urges – Brief version (QSU-Brief)

The Questionnaire on Smoking Urges – Brief version (QSU-Brief) is a self-report questionnaire used to measure cravings to smoke. The QSU-Brief will be administered by an Investigator or other individual that is suitably qualified by education or training on Day -1 and at 5 hours (±30 minutes) postdose on Days 1 to 14 as outlined in Table 3. The assessment on Day -1 should be completed at approximately the same time as the 5-hour postdose timepoint on dosing days. See APPENDIX 12 for a QSU-Brief example.

7. ADVERSE EVENTS DOCUMENTATION

7.1. Definitions

An AE is defined as any untoward medical occurrence in a 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 for example, a clinically significant abnormal clinical laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lower degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an investigator considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an investigator)

7.2. Severity Assessment

All AEs will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience transient slight discomfort

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. Causality Assessment

An Investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 14.

Table 14 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory rechallenge (the drug is readministered to determine if the same reaction occurs) procedure if necessary.
Probable	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
Not related	Any event that does not meet the above criteria; there is sufficient information that etiology of the event is in no relation to the study drug.

7.4. Adverse Event Monitoring

For the purposes of this study, the monitoring period for AEs extends from the pretrial evaluation until the Follow-up Visit. From Screening to the first dose of the study, AEs will be recorded as screening events or as part of the medical history, as applicable. AEs occurring after initiation of study drug will be indicated as TEAEs in the clinical study report.

Subjects will be questioned on their health status at the beginning of each study period and before each departure from the CRU. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

In the case of AEs deemed related to the Investigational Product, every effort will be made to determine the final outcome.

It is an investigator's responsibility to ensure that subjects experiencing AEs receive appropriate follow-up treatment where required, and that every action is well documented.

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or higher.

Concomitant medications will be coded using the World Health Organization drug dictionary (WHO-DDE March 2019 or later).

7.5. Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by an investigator or delegate (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Pregnancy that occurs within 4 weeks after the last drug administration in a female partner of a male study subject shall be reported to the Sponsor within 24 hours of the knowledge of its occurrence by the clinical site that such pregnancy occurred during the course of the study or right after. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the safety of the subject's female partner, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the CRU to the Sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

7.6. Serious Adverse Event Reporting

The CRU will notify any SAE to the Sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence. The NIDA Project Official (Tanya Ramey, MD PhD) and Project Scientist (Evan Herrmann, PhD) will be notified of the SAE within 72 hours of the SAE occurrence via email.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

The notification should be directed to the following Sponsor representative:

Vijay Hingorani, MD, PhD
Study Medical Monitor
Tel.: (858) 864-8124
Email: vhingorani@vh-inc.com

An SAE will be considered “unexpected” if the AE is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

All serious, unexpected, related AEs must be reported to the IRB. The event will be reported via fax or email within 15 calendar days of an investigator or staff becoming aware of the event.

The Sponsor will determine whether the SAE must be reported in an expedited manner to the applicable regulatory agencies. If so, the Sponsor will report the event to those agencies and to all participating investigators.

If reports of any new and unexpected AEs become available to the Sponsor during the clinical portion of this study (related or not to the present study), the Sponsor must advise the CRU, through its clinical investigator, of those events. If required by the Sponsor, the CRU may advise the applicable regulatory authorities.

7.6.1. Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy’s Law cases) and should always be considered important medical events.

Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal (3X ULN) concurrent with a total bilirubin ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 X ULN or not available, with no other cause for LFT abnormalities identified at the time should be considered to have potentially met Hy's Law. Such potential Hy's Law cases should be reported as SAEs.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

8.1.1. Safety Population

The Safety population will include all subjects who received at least 1 dose 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.

8.1.2. 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 will be included in the PK population.

The PK population will be described in a Statistical Analysis Plan (SAP).

8.2. Demographic Data and Other Baseline Characteristics

Listings and descriptive summary statistics of demographic (age, sex, race, height, body weight and BMI) and baseline data will be presented.

Statistics for demographic and baseline data will be further detailed in the SAP.

8.3. Safety

8.3.1. Safety Endpoints

The primary safety endpoint includes the incidence of subjects who experienced an AE and severity of AEs following study drug administration. Changes in vital signs, physical examination findings, 12-lead ECG findings, C-SSRS questionnaire findings, and clinical laboratory abnormalities will also be assessed.

8.3.2. Safety Analysis

Reported AEs, results from clinical laboratory tests, vital signs measurements, ECGs, physical examinations, C-SSRS questionnaires and other safety parameters will be used to perform the safety statistical analysis.

8.3.3. Safety Statistical Methodology

Descriptive statistics will be used to summarize AEs and safety results.

8.4. Pharmacokinetics

The PK analysis will be carried out according to Altasciences SOPs. Pharmacokinetic data handling and analysis will also be detailed in the SAP.

8.4.1. 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.

8.4.2. 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, will be detailed in the SAP.

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

8.4.3. 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.

8.4.4. Baseline Reference Timepoint

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first drug administration.

8.4.5. 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 λz 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 15.

Table 15 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 $AUC_{0-\infty}$
Part B: MAD Phase, 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})

Part B and Part C: MAD and Smoker Phase, 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}
Part B and Part C: MAD and Smoker Phase, Various Days:	
C_{trough}	Observed concentration at the end of the dosing interval
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

8.4.6. Data Precision

Precision for individual values will be display as follows:

- Raw data will be displayed with the same precision as received from the bioanalytical laboratory,
- 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 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.

8.4.7. 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.

8.4.7.1. 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%.

Summary statistics will be displayed with the same precision as the individual values (Section 8.4.6), with the exception of N and CV% which will be presented with 0 and 1 decimal place, respectively.

8.4.7.2. 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.

8.5. 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

Smoking data will be summarized by treatment and dose level using descriptive statistics which will be detailed in the SAP.

8.6. Planned Interim Pharmacokinetic Analyses

Interim PK analysis may be performed after each cohort of the SAD, MAD, and Smoker phase for dose selection and safety assessment.

The SAP will describe the planned interim analyses in greater detail.

8.7. 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.

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10. APPENDIX 1: ETHICS

10.1. Institutional Review Board

This protocol and the ICF will be submitted to an IRB (or Independent Ethics Committee [IEC]) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

10.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the European regulation EU 536/2014, and the Tri-Council Policy Statement (Canada).

10.3. Subject Information and Consent

Before screening activities commence, each volunteer will be given a copy of the ICF to read, as well as a full explanation of the purpose of the study, the procedures to be carried out, and the potential AE(s). Once this essential information is provided to the volunteer and an Investigator in charge or delegate has the conviction the volunteer understands the implications of participating in the study, and if the volunteer chooses to continue the screening process, they will be requested to sign and date a properly executed ICF prior to enrollment. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify).

Subjects will be given a signed copy of the ICF. If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

10.4. Subject Confidentiality

Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the Sponsor. In compliance with Federal regulations/ICH GCP Guidelines, it is required an investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for verification of study-related procedures and data. An investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the subject's confidentiality.

11. APPENDIX 2: DATA COLLECTION, RETENTION, AND MONITORING

11.1. Case Report Forms

The data required by the protocol is obtained in 2 ways. Source Documents are used in the clinic as recording devices during procedures. The data is transcribed from source into an electronic data capture (EDC) software (Medrio) and stored in the secure database for each subject included in a clinical trial (i.e., who received an IP treatment). Screen Failure data may be transcribed into the database at the discretion of the Sponsor.

Data assembled outside the clinic source will be received from a specified external vendor via an electronic data file. The file received encrypted (or posted to a secure File Transfer Protocol) and is stored in a secure folder on a server. The electronic data file(s) are independent of the EDC data during the conduct of the study.

The Medrio EDC cleaned data will be reviewed, approved and electronically signed by the Principal Investigator or delegate. The Medrio EDC data will be output in a CRF format. The external data files will be output in SAS® datasets. All data will be included with the final report provided to the Sponsor.

11.2. Data Management and Processing

Data Management develops documentation to define activities performed during the data management conduct of the study trial. Medrio EDC system is the tool used to conduct all data cleaning activities, monitoring activities and review/approval activities for clinic collected data and procedure data. The external data files are reconciled (to compare the external vendor data and Medrio EDC sample collection data). Data Management activities are performed in accordance with the Data Management SOPs.

In addition to the cleaning activities, data entered in Medrio EDC will be checked for accuracy through quality control (QC) assessments. When the database data is declared to be complete and accurate, the database will be locked, and user access removed.

11.3. Quality Control and Quality Assurance

Designated personnel from the quality assurance unit(s) will be responsible for maintaining QA of the clinical, PK, statistical and bioanalytical facilities to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for GCP, applicable requirements as outlined in the FDA and OECD Principles of GLP, and the *Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples* (EMA/INS/GCP/532137/2010).

Designated personnel from each corresponding operation unit will be responsible to maintain and assure the QC of all data generated and documented in compliance with the protocol.

11.4. Record Retention

All essential documents and records will be maintained by the CRU in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA CFR 312.57 [C]).

11.5. Monitoring of the Study

The Sponsor or its representative may monitor the study at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The CRU will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11.6. Safety Oversight

A DSMB will be established and operated according to National Institute on Drug Abuse (NIDA) guidelines. The operation of the DSMB will be documented in the Data and Safety Monitoring Plan (DSMP) which will be subject to approval by NIDA. The purpose of the DSMB is to assure that the safety of study subjects is protected while the scientific goals of the study are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies when risks have been uncovered or when it appears that the clinical trial cannot be concluded successfully.

12. APPENDIX 3: ADMINISTRATIVE PROCEDURES

12.1. Liabilities

It is the Sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

12.2. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

12.3. COVID-19 Response Plan

Regulatory authorities have recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the IP or adhering to protocol-mandated visits and laboratory/diagnostic testing. To accommodate these challenges and mitigate safety risks associated with COVID-19, protocol modifications may be required which include (and are not limited to):

- Conducting the study in multiple (smaller) subject groups;
- Altering the timing of study procedures and subject confinement;
- Modification of standard inclusion or exclusion criteria;

The exact mitigations will be documented in the study Risk Assessment and Mitigation Plan.

Additional health checks including COVID-19 testing, body temperature monitoring, etc. may be performed during the trial, even if not planned within the protocol.

12.4. Statement of Investigator

The FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], will be signed by the Investigator, and will be kept on file.

12.5. Delegation of Investigator Duties

An investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

An investigator will maintain a list of sub-investigator(s) and other appropriately-qualified persons to whom he/she delegates significant trial-related duties.

Should an investigator delegate the supervision of the IP administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

12.6. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the CRU or an Investigator (or delegate) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

13. APPENDIX 4: PROTOCOL REVIEW AND APPROVALS

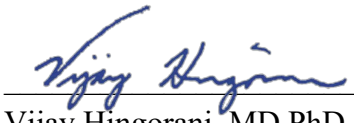
TITLE: A Randomized, Double-Blind, Placebo-Controlled, First-In-Human Study to Assess Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Doses of SBP-9330 (with a Nested Food-Effect Arm) after Oral Administration in Healthy Subjects

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with GCP and the applicable regulatory requirements.

Martin Kankam MD, PhD, MPH Principal Investigator	Date (yyyy/mm/dd)

TITLE: 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

On behalf of the Sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol.



2022/09/14

Vijay Hingorani, MD PhD
Study Medical Monitor
Camino Pharma, LLC

Date (yyyy/mm/dd)

14. APPENDIX 5: LIST OF ABBREVIATIONS

ACLS	Advanced Cardiovascular Life Support
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate transaminase
AUC	Area under curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
C-SSRS	Columbia-suicide severity rating scale
CNS	Central nervous system
CO	Carbon monoxide
COVID-19	Coronavirus disease 2019
CV%	Coefficient of Variation
CFR	Code of Federal Regulations
CRF	Case report form
CRU	Clinical research unit
CYP	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTCD	Fagerström Test for Cigarette Dependence
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacture Practice
h	Hour
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HED	Human equivalent dose

HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
iGlu	Ionotropic glutamate
IRB	Institutional Review Board
IU	International Unit
kg	Kilogram
L	Liter
LLOQ	Lower limit of quantitation
LS	Least-squares
ln	Neperian log transformation
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mGlu	metabotropic glutamate
$mGlu_2$	metabotropic glutamate receptor subtype 2
$mGlu_3$	metabotropic glutamate receptor subtype 3
min	Minute
MINI	Mini International Neuropsychiatric Interview
mL	Milliliters
mmHg	Millimeter of mercury
MNWS	Minnesota Nicotine Withdrawal Scale
MRSD	Maximum recommended starting dose
ms	millisecond
MTD	Maximum tolerated dose
NAc	Nucleus accumbens
NAOEL	No adverse effect level
NCA	Non-compartmental analysis
NDA	New Drug Application
ng	Nanograms
NRT	Nicotine Replacement Therapies
OECD	Organization for Economic Co-operation and Development

OTC	Over-the-counter
p.o.	Per os
PAM	Positive allosteric modulator
Pgp	P-glycoprotein
pH	The Logarithm, On The Base 10, of The Reciprocal of The Hydrogen Ion Concentration
PK	Pharmacokinetic
PT	Preferred Term
q.d.	Once daily
QA	Quality Assurance
QC	Quality Control
QSU-Brief	Questionnaire on Smoking Urges – Brief version
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Correction Formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TLFB	Time-Line Follow-back
ULN	Upper limit of normal
WHO-DDE	World Health Organization Drug Dictionary Enhanced

15. APPENDIX 6: CLINICAL LABORATORY EVALUATIONS

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

[1] Screening visit only.

16. APPENDIX 7: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

The Columbia-Suicide Severity Rating Scale Baseline/Screening Version will be provided to the clinical site and is not included here in its entirety.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

17. APPENDIX 8: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT VERSION

The Columbia-Suicide Severity Rating Scale Since Last Visit Version will be provided to the clinical site and is not included here in its entirety.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

18. APPENDIX 9: MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW (M.I.N.I)

The MINI version 7.0.2 will be provided to the clinical site and is not included here in its entirety.

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 7.0.2

For

DSM-5

19. APPENDIX 10: FAGERSTRÖM TEST FOR CIGARETTE DEPENDENCE (FTCD)

The FTCD will be provided to the clinical site and is not included here in its entirety.

FAGERSTRÖM TEST FOR CIGARETTE DEPENDENCE QUESTIONNAIRE

Instructions: Please answer each question below by checking (✓) your answer in the box (☐)

1. How soon after you wake up do you smoke your first cigarette?
   - ☐ Within 5 minutes
   - ☐ 6 - 30 minutes
   - ☐ 31 - 60 minutes
   - ☐ After 60 minutes

2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?
   - ☐ Yes
   - ☐ No

3. Which cigarette would you hate most to give up?
   - ☐ The first one in the morning
   - ☐ Any other

4. How many cigarettes per day do you smoke?
   - ☐ 31 or more
   - ☐ 21 - 30
   - ☐ 11 - 20
   - ☐ 10 or less

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   - ☐ Yes
   - ☐ No

6. Do you smoke if you are so ill that you are in bed most of the day?
   - ☐ Yes
   - ☐ No

The questionnaire was adapted from previously validated questionnaire (Fagerström, 2012).[v]

Subject Initials: _____

Once the subject has completed and initialed the questionnaire.

Staff Initials: _____ **Time completed:** ___ : ___

20. APPENDIX 11: MINNESOTA NICOTINE WITHDRAWAL SCALE (MNWS)

The MNWS will be provided to the clinical site and is not included here in its entirety.

Minnesota Nicotine Withdrawal Scale

Fill in the appropriate circle that corresponds

0 = None 1 = Slight 2 = Mild 3 = Moderate 4 = Severe

Symptoms	0	1	2	3	4
1. Desire/ cravings	☐	☐	☐	☐	☐
2. Anger/ irritability/ frustration	☐	☐	☐	☐	☐
3. Anxiety/ nervousness	☐	☐	☐	☐	☐
4. Difficulty concentrating	☐	☐	☐	☐	☐
5. Restlessness	☐	☐	☐	☐	☐
6. Insomnia/ sleep problems/ waking at night	☐	☐	☐	☐	☐
7. Increased appetite/ weight gain	☐	☐	☐	☐	☐
8. Depressed mood	☐	☐	☐	☐	☐
9. Constipation	☐	☐	☐	☐	☐
10. Coughing	☐	☐	☐	☐	☐
11. Decreased pleasure from events	☐	☐	☐	☐	☐
12. Dizziness	☐	☐	☐	☐	☐
13. Drowsy	☐	☐	☐	☐	☐
14. Impatient	☐	☐	☐	☐	☐
15. Impulsive	☐	☐	☐	☐	☐

Subject Initials: _____

Once the subject has completed and initialed the questionnaire.
Staff Initials: _____ **Time completed:** __ __ : __ __

21. APPENDIX 12: QUESTIONNAIRE ON SMOKING URGES – BRIEF VERSION (QSU-BRIEF)

The QSU-BRIEF will be provided to the clinical site and is not included here in its entirety.

QUESTIONNAIRE OF SMOKING URGES – BRIEF (QSU-BRIEF)[1]

Time of Assessment: _____:_____

Directions: For each item, please indicate how you feel RIGHT NOW.
Scale: 1= Strongly Disagree to 7=Strongly Agree

		Strongly Disagree						Strongly Agree
1.	I have a desire to smoke right now.	1	2	3	4	5	6	7
2.	Nothing would be better than smoking a cigarette right now.	1	2	3	4	5	6	7
3.	If it were possible, I would probably smoke right now.	1	2	3	4	5	6	7
4.	I could control things better right now if I could smoke.	1	2	3	4	5	6	7
5.	All I want right now is a cigarette.	1	2	3	4	5	6	7
6.	I have an urge for a cigarette.	1	2	3	4	5	6	7
7.	A cigarette would taste good now.	1	2	3	4	5	6	7
8.	I would do almost anything for a cigarette now.	1	2	3	4	5	6	7
9.	Smoking would make me less depressed.	1	2	3	4	5	6	7
10.	I am going to smoke as soon as possible.	1	2	3	4	5	6	7

[1] Based on Cox, Tiffany and Christen (2001).

Subject Initials: _____ **Date:** _____ **Staff Initials:** _____

Total Score: _____

Scorer Initials: _____

22. APPENDIX 13: SUMMARY OF CHANGES AMENDMENT 1

The changes below were made to Protocol SBP-9330-101 Version 1.0 (FINAL / 22 April 2021)

Major Changes

- Exclusion criterion number 22 was revised based on FDA feedback and to enhance clarity.

Detailed Changes

- Section 4.2 Exclusion criteria (page 38). Exclusion criterion number 22 was revised as follows:

  22. Consumption of other ~~OTC~~ ***prescription and over-the-counter*** medication ***not specifically excluded by Exclusion Criterion 21*** including ~~(~~health supplements and herbal remedies~~)~~ within 7 days prior to the first study drug administration (an exception is made for paracetamol [acetaminophen], which is allowed up to admission to the clinic).

- Table 2 (page 19) footnote 7 was revised as follows:

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, 7, 14, and ~~17~~***16***; and at follow-up/EOS.

- Table 7 (page 31) was revised as follows:

A5	6:2 (1:1 [sentinel group] and 5:1 [remaining subjects])	2400 mg (~~6~~***8*** × 300-mg SBP-9330 capsule or matched placebo)	Single oral dose administration of SBP-9330 or placebo under fasting conditions on Day 1.

- Added Appendix 13: Summary of Changes Amendment 1
- In addition, the following minor changes were made:
  - Cover page and throughout the document: Added Amendment 1 (Version 2.0 / 1 June 2021)
  - Protocol synopsis has been updated to be consistent with Amendment 1 changes
  - Minor typographical errors, formatting updates and changes for clarification and consistency have also been made throughout the protocol.

23. APPENDIX 14: SUMMARY OF CHANGES AMENDMENT 2

The changes below were made to Protocol SBP-9330-101 Version 2.0 (Amendment 1 / 1 June 2021)

Major Changes

- A Clinical Laboratory Test timepoint was added to Part B (MAD) Day 3.
- The protocol was updated to allow for the use of 75mg dose strength capsules to allow for intermediate dose levels during dose escalation.

Detailed Changes

- Table 2 Schedule of Activities – Part B (MAD Phase) was modified to add a Day 3 Clinical Laboratory Test assessment:

		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**
Clinical Laboratory Test[5,7]	X	X	X			***X***				X							X		X	X

Footnote 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.

- Section 3.2 Data and Safety Monitoring Board (DSMB), Paragraph 2 was modified as follows:

The DSMB will be comprised of voting members who are independent of the Sponsor and CRU and will, at a minimum, include ~~a~~ physician**s** experienced in drug safety~~, a clinical pharmacologist, and a biostatistician~~. The composition and operations of the DSMB will be detailed in a separate document that will serve as the Data and Safety Monitoring Plan (DSMP).

- Section 3.3.1 Part A – SAD Phase with Nested Food-Effect Cohort was modified as follows:

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).***

- Section 3.4 Study Treatments was modified to include 75-mg formulation.

The following investigational products (IPs) will be administered according to the outlined dose levels in Sections 3.3.1 and 3.3.2.

- 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

- Section 4.1 Inclusion Criteria (inclusion criterion7) was modified as follows:

7. Male subjects, if not surgically sterilized, must agree to use adequate contraception and not donate sperm from the first admission to the CRU until 90 days after the last study drug administration. Adequate contraception for the male subject (and/or his female partner) includes the following:

- Use of spermicide, hormonal contraceptives or an intrauterine device combined with at least one of the following forms of contraception: a diaphragm, a cervical cap, or a condom
- Double-barrier method ~~(e.g., condom with diaphragm or cervical cap)~~

- Section 4.5 Concomitant Treatment was modified to include the following statement:

Subjects receiving the COVID-19 vaccine should be fully vaccinated at least 14 days prior to receiving Investigational Product.

- Section 5.1.1 SBP-9330 was modified as follows:

SBP-9330 150 mg and 300 mg capsules are manufactured by PACE Laboratory (previously Velesco Pharmaceutical Services, Inc.) for oral administration. ***Small batches of 75 mg dose strength capsules will be prepared by the Altasciences pharmacy using a sponsor-supplied procedure.*** Each white gelatin capsule contains SBP-9330 sodium equivalent to ***75 mg***, 150 mg or 300 mg SBP-9330.

- Section 5.1.2 Placebo was modified as follows:

Placebo capsules matched to Sponsor's SBP-9330 ***75,*** 150 and 300 mg capsules will be supplied by the Sponsor. The placebo formulation will be comprised of the same white gelatin capsule, filled with Avicel microcrystalline cellulose, without SBP-9330 (active ingredient).

- Section 6.2 Blood Volume Collected was modified as follows:

  - ~~292~~ ***330*** mL for Part B – MAD Phase (all cohorts)

- Section 7.6 Serious Adverse Event Reporting was modified as follows:

The CRU will notify any SAE to the Sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence. The NIDA Project Official (***Tanya Ramey, MD PhD*** ~~Evan Herrmann, PhD~~) and Project Scientist (***Evan Herrmann, PhD*** ~~Tanya Ramey, MD PhD~~) will be notified of the SAE within 72 hours of the SAE occurrence via email.

- Added Appendix 14: Summary of Changes Amendment 2
- In addition, the following minor changes were made:
    - Cover page and throughout the document: Added Amendment 2 (Version 3.0 / 10 December 2021)
    - Protocol synopsis was updated to be consistent with Amendment 2 changes
    - Correction of typographical errors, formatting updates, and changes for clarification and consistency have been made throughout the protocol.

24. APPENDIX 15: SUMMARY OF CHANGES AMENDMENT 3

The changes below were made to Protocol SBP-9330-101 Version 3.0 (Amendment 2 / 10 December 2021).

Major Changes

- A Smoker Phase (Part C) was added to the study to evaluate the safety, PK, and to explore the effects on smoking-related assessments of SBP-9330 in smokers, which is the target population for treatment with SBP-9330.

Detailed Changes

- Updated all relevant sections of the protocol to include Part C: Smoker Phase information including the study rationale, background information, study design, blood volume, and screening, safety, smoking, and PK assessments. The summary of the Part C: Smoker Phase is presented below.

  Healthy adult smokers will be randomized to receive either SBP-9330 or placebo orally in each of the 2 planned smoker cohorts. Each cohort will consist of 10 subjects randomly assigned in 4:1 (SBP-9330:placebo) ratio, for a total of 8 subjects receiving SBP-9330 and 2 subjects receiving placebo.

  The proposed Smoker phase design and planned escalation are as follows:

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
Additional C3	8:2	adaptive	Once daily oral administrations for 14 consecutive days

  Each subject will receive once daily oral administration of the assigned treatment 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 the highest MAD dose for which complete safety and PK data are available.

  All relevant safety and 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. 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. There are 2 planned cohorts and an additional cohort may be added depending on the emerging PK and safety data in the

previous cohorts. A Smoker cohort daily dose level cannot be higher than the highest dose level tested in the MAD phase.

All subjects who complete the study and those terminating early will be required to complete the End of study/Follow-up procedures.

- The primary and secondary objectives in the Synopsis and Section 2. Study Objectives and Endpoints were updated to specify that the study population includes healthy nonsmokers and/or healthy smokers.

- The following exploratory endpoints were added for Part C in the Synopsis and Section 2. Study Objectives and Endpoints:

    - 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

- Updated the Synopsis and Section 4.1 Inclusion Criteria to include criteria (#11 to #14) specific to Part C only.

  11. Are current tobacco cigarette smokers who smoke an average of 10 or more cigarettes per day in the 30 days prior to Screening

  12. Expired breath CO level ≥10 parts per million (ppm) at Screening and prior to the first study drug administration

  13. Positive test result for cotinine at Screening and prior to the first study drug administration

  14. Are not motivated to try to quit smoking from Screening through 30 days from the first study drug administration

- Updated the Synopsis and Section 4.2 Exclusion Criteria to include criteria (#29 to #33) specific to Part C only.

  29. History of generalized rash reaction to any drugs

  30. Positive test result (except cotinine) for alcohol and/or drugs of abuse at Screening or prior to the first study drug administration

  31. Use of smoking cessation aids (NRT, bupropion, or varenicline) within 30 days prior to the first study drug administration

  32. Unable to abstain from smoking tobacco cigarettes for at least 1 hour before and 2 hours after study drug administration

33. Unable to abstain from using nicotine-containing products other than tobacco cigatettes (e.g., pipes, cigars, e-cigarettes or vapes, nicotine topical patches, nicotine gum, or nicotine lozenges) during the study

- Updated the Synopsis and added Section 8.5 Smoking Assessment (Part C only) to present analysis of smoking data.

- Added Table 3. Schedule of Activities – Part C (Smoker Phase)

- Updated Table 5. Adaptive Features and Boundaries to include possibility of adapting the dose level and other adaptive features for the Smoker cohorts.

- Added the following restriction to Section 4.4. Lifestyle and/or Dietary Requirements

  For the Smoker cohorts, subjects will abstain from smoking tobacco cigarettes for at least 1 hour before and 2 hours after study drug administration. Subjects will also abstain from using nicotine-containing products other than tobacco cigarettes (e.g., pipes, cigars, e-cigarettes or vapes, nicotine topical patches, nicotine gum, or nicotine lozenges) or other tobacco products (cigars, cigarillos, pipes) during the study.

- Added to Section 6.1.3 vital signs normal ranges.
- Added the following sections and appendix:

  - Section 6.4. Smoking Assessments for Part C only
  - Section 6.4.1. Fagerström Test for Cigarette Dependence (FTCD) and Appendix 10
  - Section 6.4.2. Smoking Time-Line Follow-back (TLFB)
  - Section 6.4.3. Expired Carbon Monoxide (CO) Level
  - Section 6.4.4. Blood Sampling for Cotinine
  - Section 6.4.5. Smoking Log
  - Section 6.4.6. Minnesota Nicotine Withdrawal Scale (MNWS) and Appendix 11
  - Section 6.4.7. Questionnaire on Smoking Urges – Brief version (QSU-Brief) and Appendix 12

- Updated the Synopsis and Section 8.5 Smoking Assessments (Part C only) to indicate that expired CO values, cotinine levels, number of cigarettes smoked, MNWS responses, and QSU-Brief responses will be summarized using descriptive statistics.

- Added Appendix 15: Summary of Changes Amendment 3

- Updated the Sponsor address from 12707 High Bluff Drive, Suite 200 San Diego, CA 92130 USA to 9920 Pacific Heights Blvd, Suite 150 San Diego, CA 92121 USA

- Updated the manufacturer for the Test Product and Placebo from Velesco Pharmaceutical Services, Inc. to PACE Laboratory (previously Velesco Pharmaceutical Services, Inc.)

- In addition, the following minor changes were made:
    - Cover page and throughout the document: Added Amendment 3 (Version 4.0 / 14 September 2022)
    - Correction of typographical errors, formatting updates, and changes for clarification and consistency have been made throughout the protocol.