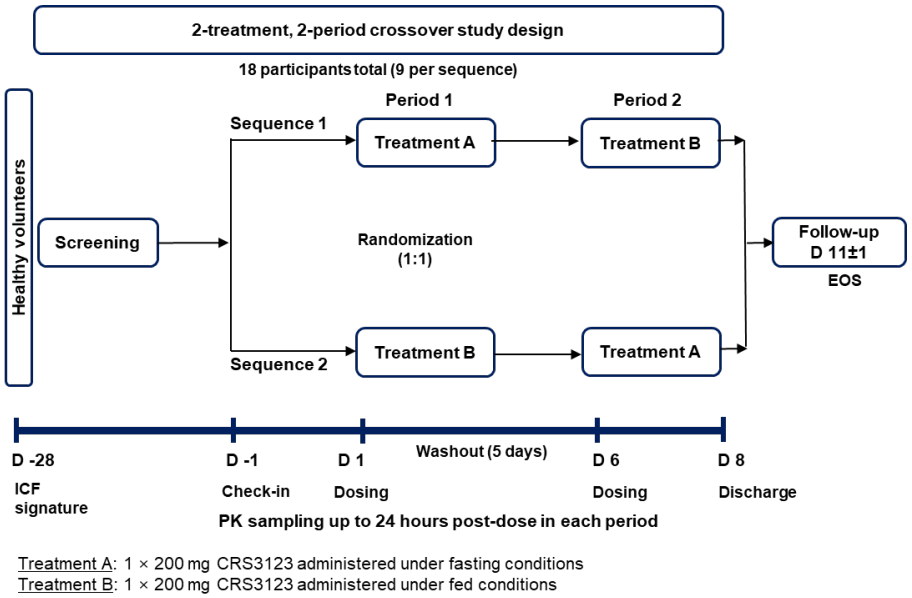
Synopsis of Protocol

Project Number:	Protocol Number: 242021 Sponsor Study Number: 24-3123-FE DMID Protocol Number: 25-0002
Title:	A Phase 1, Single-Center, Open-Label, Randomized, Single-Dose, 2-Period, Crossover Study to Evaluate the Potential Impact of High-fat Meal on the Pharmacokinetics of CRS3123 200 mg Capsule in Healthy Adult Participants
Investigational Product:	CRS3123 200 mg Capsule
Study Phase and Type:	Phase 1 – Food-Effect
Objectives:	Primary objective: • To evaluate the potential impact of high-fat meal on the systemic exposure and the plasma pharmacokinetics (PK) of CRS3123 when it is administered as a single oral capsule of 200 mg dose in healthy adult participants. Secondary objective: • To evaluate the safety and tolerability of a single oral CRS3123 capsule of 200 mg dose in healthy adult participants. • To evaluate the plasma PK of the metabolite CRS3123 GLU-3.
Endpoints:	Primary PK endpoints: • $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} Secondary endpoints: • PK endpoints: o For CRS3123: T_{max}, T_{lag}, $t_{½}$, K_{el}, Cl/F and V_z/F o For CRS3123 metabolite CRS3123 GLU-3: T_{max}, T_{lag}, $t_{½}$, K_{el} • Safety endpoints: Adverse events (AEs), vital signs measurements (blood pressure [BP], heart rate [HR], respiratory rate [RR], and oral temperature [OT]), 12-lead electrocardiogram (ECG) recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, and urinalysis.
Study Design:	This is a Phase 1, single-center, open-label, randomized, single-dose, 2-period, crossover study to evaluate the effect of high-fat meal on plasma PK of CRS3123 200 mg oral capsule in healthy adult participants.

	 Participants will receive a single oral CRS3123 capsule of 200 mg dose on Day 1 (Period 1) and Day 6 (Period 2), under fasting (Treatment A) or fed (Treatment B) conditions, followed by 24 hours of PK assessments and continuous safety assessments through the full duration of the study with a follow-up phone call on Day 11 (± 1 Day). The study will include a screening visit from Day -28 to Day -2. Eligible participants will be admitted to the clinical research unit (CRU) on Day -1 and will be confined until completion of the assessments on Day 8 (Period 2). The study will enroll healthy adult participants. A participant with a clinical abnormality on physical examination or laboratory parameter outside the normal reference range, but no more than Grade 1 (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [2007]) may be included only if deemed by the Investigator and the Investigator documents that the finding is not clinically significant, unlikely to introduce additional risk factors, will not interfere with the study procedures or the interpretation of the primary study objectives. Approximately 18 participants will be randomized on Day 1 (Period 1) in a 1:1 ratio (9 per sequence) to one of the 2 sequences: either Treatment A (fasting) in Period 1 followed by Treatment B (fed) in Period 2 (Sequence 1), or Treatment B (fed) in Period 1 followed by Treatment A (fasting) in Period 2 (Sequence 2). There will be a washout period of at least 5 days between dosing in Period 1 and Period 2. There will be a follow-up phone call on Day 11 (± 1 Day) to review current and new AEs.
Study Population:	Approximately, 18 non-smoker, healthy, non-pregnant and non-lactating adults will be enrolled in the study to have at least 16 evaluable participants. Every effort will be made to have an equal number of males (as assigned at birth) and females (as assigned at birth) enrolled into the study.
Inclusion Criteria:	Participants must meet all of the following criteria to be included in the study: 1. Non-pregnant and non-lactating adults, non-smoker (no use of tobacco or nicotine products within 3 months prior to screening), ≥ 18 and ≤ 64 years of age, with body mass index (BMI) > 18.5 and < 30.0 kg/m^2 and body weight ≥ 50.0 kg for males (as assigned at birth) and ≥ 45.0 kg for females (as assigned at birth), at the time of signing the informed consent.

	2. Healthy as defined by: a. the absence of clinically significant physical or laboratory findings (above Grade 1) and surgery within 4 weeks prior to dosing. b. the absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, hematological, immunological, psychiatric, gastrointestinal (GI), renal, hepatic, and metabolic disease. 3. Healthy females (as assigned at birth) of non-childbearing potential must be: a. postmenopausal (spontaneous amenorrhea for at least 12 months prior to dosing) with confirmation by documented follicle stimulating hormone (FSH) levels ≥ 40 mIU/mL; or b. surgically sterile (bilateral oophorectomy, hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion, bilateral salpingectomy, hysterectomy or tubal ligation) at least 3 months prior to dosing. 4. Sexually active females (as assigned at birth) of childbearing potential and non-sterile males (as assigned at birth) must be willing to use an acceptable contraceptive method throughout the study as detailed in section 8.1. 5. Able to understand the study procedures and provide signed informed consent to participate in the study.
Exclusion Criteria:	Participants to whom any of the following applies will be excluded from the study: 1. Any clinically significant abnormal finding at physical examination at screening that may interfere with the interpretation of safety and PK objectives of the study. 2. Abnormal laboratory test results (above Grade 1) that may interfere with the interpretation of safety and PK objectives of the study. 3. Positive serology test results for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or human immunodeficiency virus (HIV) antigen and antibody. 4. History of current or chronic liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 5. Positive pregnancy test at screening or admission to the clinical research unit. 6. Positive urine drug screen, urine cotinine test, or alcohol test at screening or admission to the clinical research unit. 7. Known allergic reactions to CRS3123 or other related drugs, or to any excipient in the formulation. 8. Use of medications within the timeframes specified in section 8.2. 9. Previous exposure to CRS3123 within 12 months prior to the first dose. 10. Participants with HR < 50 or > 100 beats per minute (bpm), systolic blood pressure (SBP) < 90 or > 140 mmHg, diastolic blood pressure (DBP) < 50 or > 90 mmHg, on vital sign assessment at screening or admission to the clinical research unit. 11. A baseline ECG at screening with corrected QT interval (QTc) using Fridericia's formula (QTcF) > 450 msec. 12. Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization). Any clinically significant (above Grade 1) conduction

	abnormality (including but not specific to left or right complete bundle branch block, atrioventricular block [second degree or higher], Wolf Parkinson White syndrome), sinus pauses > 3 seconds, non-sustained or sustained ventricular tachycardia (≥ 3 consecutive ventricular ectopic beats) or any significant arrhythmia which, in the opinion of the Investigator will interfere with the safety of the individual participant. 13. Participant has any surgical or medical condition (active or chronic) or GI tract condition (e.g., surgical resection of significant proportions of the stomach or bowel, gastric bypass, gastric banding, irritable bowel syndrome, inflammatory bowel disease, or any other condition that may interfere with normal gastric emptying or transit time) that may interfere with drug absorption, distribution, metabolism, or excretion of the study drug, or any other condition that may place the participant at risk, in the opinion of the Investigator. 14. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days or 5× $t_{½}$ (whichever is longer) prior to the first dose, administration of a biological product in the context of a clinical research study within 90 days or 5× $t_{½}$ (whichever is longer) prior to the first dose or concomitant participation in an investigational study involving no drug or device administration. 15. Participants with serum creatinine level > 1.5 mg/dL. 16. History of drug abuse within 1 year prior to screening or recreational use of soft drugs (such as marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening. 17. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%). 18. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to first dosing. 19. Participant is unable to comply with all the study procedures in the opinion of the Investigator. 20. Any reason the participant should not participate in the study in the opinion of the Investigator.
Study Treatments:	In each period (Day 1 and Day 6), participants will receive one of the following treatments, according to the randomization scheme: Treatment A: A single 200 mg dose of CRS3123 administered orally as 1 × 200 mg capsule (Crestone, Inc., USA) under fasting conditions. Treatment B: A single 200 mg dose of CRS3123 administered orally as 1 × 200 mg capsule (Crestone, Inc., USA) under fed conditions. For Treatment A: No food will be allowed from at least 10 hours before dosing until at least 4 hours after dosing. For Treatment B: After a supervised fast of at least 10 hours, participants will be served a high-fat and high-calorie breakfast. Study drug administration will occur approximately 30 minutes (± 1 minute) after the start of the breakfast.

	For both treatments, study drug will be administered to each participant with approximately 240 mL of water. Except for fluids provided with the high-calorie and high-fat breakfast (Treatment B) and water given with study drug, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose. Except for the high-calorie and high-fat meal, meals will be standardized and similar in composition between periods.
Study Procedures:	Blood samples for PK analysis will be collected and safety procedures will be performed at pre-defined times throughout the study as specified in Table 1. Schedule of Assessments. Participants will be monitored throughout the study by the clinical staff for AEs and concomitant medication use.
Statistical Analyses:	PK analysis: Using general linear model (GLM) procedures in statistical analysis system (SAS), analysis of variance (ANOVA) will be performed on untransformed T_{max}, K_{el}, and $t_{½}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the alpha level of 0.05. Factors incorporated in the model will include: sequence, subject (sequence), period, and treatment. Intra and inter-subject percentage coefficient of variation (CV%) will be estimated. The ratio of geometric means (B/A) and 90% confidence intervals (CIs) for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. The clinical relevance of any difference in T_{max} and T_{lag} will also be described. For T_{max}, a non-parametric analysis of the same comparisons will be performed using a Wilcoxon signed rank test. The median T_{max} for each treatment and the median of pairwise differences between the fasted and fed treatments will be presented along with the approximate 90% CI. No food-effect will be concluded if the 90% CIs for the ratio of geometric means (B/A) based on least-squares means from the ANOVA of the ln-transformed CRS3123 AUC_{0-t}, AUC_{0-inf}, and C_{max} are within 80.00% to 125.00%. Safety and tolerability analysis: Safety and tolerability of CRS3123 will be evaluated through the assessment of AEs (i.e., severity and relationship to the study drug), vital signs, 12-lead ECGs, clinical laboratory tests, and physical examinations. Treatment-emergent adverse events (TEAEs) will be tabulated by treatment. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1 system organ class and preferred term. Changes from baseline values in vital signs, ECG, clinical laboratory parameters and physical examination will be evaluated. Safety and tolerability data will be reported using descriptive statistics. All AEs (including abnormal laboratory findings) will be graded using the Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007). A Statistical Analysis Plan (SAP) will be prepared after completion of the final protocol.

Table 1. Schedule of Assessments

Study Stage	**Screening**	**Baseline**	**Period 1**					**Period 2**			**Follow-up[14]**
			Washout[1] (from Day 1 post-dose until Day 6 dosing)								
Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 ET/Discharge[13]**	**11 ± 1 Day/EOS**
Informed consent	X										
Inclusion/exclusion criteria	X										
Demographic data	X										
Medical and medication history	X										
Confinement		X	X	X	X	X	X	X	X		
Discharge										X	
Follow-up call											X
PSRT review[2]			←							→	
Study drug administration											
CRS3123[3]			X					X			
Pharmacokinetics											
Blood samples for PK analysis[4]			X	X				X	X		
Safety											
Physical examination[5]	X	X		X			X		X	X	
Body measurements (height, weight, BMI)	X	X[6]									
Vital signs[7]	X	X	X	X	X		X	X	X	X	
12-lead ECG[8]	X	X					X			X	
Serology tests[9]	X										
Clinical laboratory tests[10]	X	X		X			X		X	X	
FSH (for postmenopausal participants)[11]	X										
Pregnancy tests[12]	X	X								X	
Drug, cotinine, and alcohol screens	X	X									
Monitoring and recording of AEs and prior/concomitant medication use	←										→

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate, OT = oral temperature; PK = pharmacokinetic(s), PSRT = protocol safety review team; RR = respiratory rate.

1 The washout period between each dosing (Day 1 and Day 6) will be at least 5 days.

2 The PSRT will review safety listings from at least Day 3 and prior to dosing on Day 6 of Period 2 and make recommendations with regards to study progression.

3 CRS3123 will be administered under fasting or fed conditions on Day 1 and Day 6.

4 Blood samples for PK analysis (Period 1, Day 1 dosing and Period 2, Day 6 dosing): pre-dose (within 1 hour of dose, prior to the meal) and 0.5 hour (± 2 mins), 1 hour (± 5 mins), 1.5 hours (± 5 mins), 2 hours (± 5 mins), 2.5 hours (± 5 mins), 3 hours (± 5 mins), 4 hours (± 10 mins),), 5 hours (± 10 mins), 6 hours (± 10 mins), 7 hours (± 10 mins), 8 hours (± 10 mins), 10 hours (± 10 mins), 12 hours (± 10 mins), 16 hours (± 10 mins) and 24 hours (± 15 mins) post-dose. For more information, please refer to Table 4. PK blood sample collection will be performed closest to the nominal time. When vital signs measurement or/and ECG recording coincide with a blood collection, they will preferably be performed before the PK blood collection, whenever possible.

5 A complete physical examination will be performed at screening, and on Day -1 and prior to discharge from the clinical site on Day 8. A brief physical examination will be performed on Day 2 (36 hours post Day 1 dose), on Day 5 (baseline Day 6 dosing) and on Day 7 (36 hours post Day 6 dose). A targeted physical examination may be performed at any time at the discretion of the Investigator.

6 Body weight only.

7 Vital signs (BP, HR, RR, and OT): at screening, on Day -1, Day 1 pre-dose, 36 hours (Day 2), and 48 hours (Day 3) post-dose; on Day 5, Day 6 pre-dose, Day 7 (36 hours post Day 6 dose) and on Day 8 (48 hours post Day 6 dose). The time window for all vital signs will be ± 30 mins.

8 12-lead ECG: at screening, on Day -1, on Day 5 (baseline Day 6 dosing), and prior to discharge from the clinical site on Day 8. The time window for all 12-lead ECGs will be ± 30 mins.

9 Serology tests include HBsAg, HCV antibody, and HIV antigen and antibody.

10 Standard biochemistry, hematology, and urinalysis tests will be performed at screening, on Day -1, on Day 2 (24 hours post Day 1 dose), on Day 5 (baseline Day 6 dosing) on Day 7 (24 hours post Day 6 dose) and prior to discharge from the clinical site on Day 8.

11 FSH levels will be measured at screening to confirm the postmenopausal status.

12 A urine pregnancy test will be performed for all females (as assigned at birth) at screening and at ET/Discharge. A serum pregnancy test will be performed for all females (as assigned at birth) on Day -1.

13 In case of ET discharge procedures (all procedures specified under Period 2 Day 8 ET/Discharge under Table 1. Schedule of Assessments) will be performed as soon as possible.

14 Following dosing in the last study treatment period, subjects will receive a follow-up call from the site on Day 11 ± 1 for safety follow-up to review current and new AEs.