Protocol Number: CDI-988-P1-001

A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of Oral CDI-988 in Healthy Adult Participants

Investigational Drug: CDI-988

Sponsor:
Cocrystal Pharma Australia Pty Ltd.

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Version 6.0, dated 03 April 2025

1. PROTOCOL SYNOPSIS

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Title: A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of Oral CDI-988 in Healthy Adult Participants

Objectives

Part 1: Single-Ascending Dose

The primary objective of Part 1 is to assess the safety and tolerability of increasing doses of CDI-988 when given as a single oral dose to cohorts of healthy participants. Secondary objectives are to assess the pharmacokinetics (PK) of CDI-988 following a single oral dose and to explore the effect of food on a single oral dose PK in healthy participants.

Part 2: Multiple-Ascending Dose

The primary objective of Part 2 is to assess the safety and tolerability of multiple-ascending doses of CDI-988 when administered orally to cohorts of healthy participants. A secondary objective is to assess the PK of CDI-988 when given as multiple oral doses to cohorts of healthy participants.

Study Design

This is a randomized, double-blind, placebo-controlled phase 1 study of the SARS-CoV-2 replication and protease inhibitor CDI-988 given orally to healthy participants.

Part 1: In Cohorts 1A–1D and 1F, participants will be randomly assigned within each cohort to receive a single dose of CDI-988 or placebo. Doses will escalate in sequential dose cohorts. It is planned that 5 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo in each cohort). In addition, 6 healthy participants will be enrolled and dosed with CDI-988 in an open-label, “standard non-high fat meal” food-effect cohort (Cohort 1E).

Cohorts 1A–1D and 1F will include the initial dosing of a sentinel group (1 CDI-988 and 1 placebo) at least 24 hours before dosing the remaining 6 subjects in the cohort (5 CDI-988 and 1 placebo). The remainder of the cohort will only be dosed if, in the opinion of the investigator and sponsor’s medical representative, there is no significant safety concern identified in the sentinel subjects within the first 24 hours after administration of the dose (CDI-988 or placebo).

The following regimens are planned:

- Cohort 1A (N=8): 100 mg CDI-988 or placebo.
- Cohort 1B (N=8): 200 mg CDI-988 or placebo.

- Cohort 1C (N=8): 400 mg CDI-988 or placebo on Days 1 and 9 (high-fat food-effect cohort).
- Cohort 1D (N=8): 600 mg CDI-988 or placebo.
- Cohort 1E (N=6): 100 mg CDI-988 on Days 1 and 9 (standard non-high fat food-effect cohort).
- Cohort 1F (N=8): 1200 mg or placebo on Days 1 and 9 (standard non-high fat food effect cohort).

Cohorts 1C, 1E, and 1F will be two-period sequential food-effect cohorts in which participants will receive a single dose of study drug under fasted conditions on Day 1 and a single dose of study drug under fed conditions on Day 9.

Part 2:

Part 2 of the study may be opened after satisfactory review of the safety and PK data from the cohorts in Part 1, as well as preclinical data to support the duration of multiple ascending dose cohorts. Cohort 2a may be started in parallel with the highest dose cohort in Part 1.

Participants will be randomly assigned to receive once-daily doses of CDI-988 or placebo for 10 days (Cohorts 2A-2C), once-daily doses of CDI-988 or placebo for 5 days (Cohort 2D), and twice-daily (q12h) doses of CDI-988 or placebo for 5 days (Cohorts 2E – 2F). It is planned that up to 6 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo). A minimum of 6 participants must be dosed in a given cohort to allow dose escalation to proceed.

The following regimens are planned:

- Cohort 2A (N=8): 200 mg CDI-988 or placebo once daily for 10 days.
- Cohort 2B (N=8): 400 mg CDI-988 or placebo once daily for 10 days.
- Cohort 2C (N=8): 800 mg CDI-988 or placebo once daily for 10 days
- Cohort 2D (N=8): 1200 mg CDI-988 or placebo once daily for 5 days
- Cohort 2E (N=8): Up to 1200 mg CDI-988 or placebo given twice daily (q12h) for 5 days (9 doses)
- Cohort 2F (N=8): Up to 1200 mg CDI-988 or placebo given twice daily (q12h) for 5 days (9 doses) with a standard meal

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Participant Eligibility Criteria

Inclusion Criteria:

1. Healthy males or non-pregnant, non-lactating females aged 18 to 55 years.

2. Body weight of at least 45 kg.
3. Body mass index ≥18.0 and ≤32.0 kg/m^2. If outside this range, eligible if not considered clinically significant.
4. Good state of health (mentally and physically) in the opinion of the investigator as indicated by a comprehensive clinical assessment (detailed medical history and a complete physical examination), electrocardiogram (ECG), and laboratory investigations (hematology, clinical chemistry, coagulation, and urinalysis).
5. Willing and able to refrain from alcohol and caffeine from 48 hours before the first dose through the last dose of study drug.
6. Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test on Day -1.
7. Female participants are eligible to participate if they are not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
    - Not of childbearing potential, defined as surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy - verbal confirmation through medical history review acceptable), or postmenopausal (no menses for 12 months and confirmed by serum follicle-stimulating hormone (FSH) concentration ≥40 mIU/mL).
    - Of childbearing potential and agrees to practice true abstinence or agrees to use a highly effective method of contraception consistently from 30 days before Day 1 until at least 30 days after dosing. The reliability of sexual abstinence is to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Highly effective contraception includes hormonal contraception (oral, injected, implanted, or transdermal) plus use of a condom, placement of an intrauterine device or intrauterine system plus use of a condom, tubal ligation plus use of a condom, or a vasectomized male partner (performed at least 6 months prior) who has been documented to no longer produce sperm – verbal confirmation through medical history review is acceptable – plus use of a condom. Contraception requirements do not apply for participants in an exclusively same-sex relationship. Female participants should not donate eggs until at least 30 days after their last dose.
8. Male participants must agree to practice true abstinence; be surgically sterilized (performed at least 6 months prior and documented azoospermia 90 days post-procedure to no longer produce sperm) and wear a condom; wear a condom if their partner has had a tubal ligation, or agree to use a condom plus effective contraception (i.e., established use of hormonal contraception - started at least 30 days before Day 1; or placement or an intrauterine device or intrauterine system) for their female partner, if of childbearing potential, from screening and for at least 90 days after dosing and refrain from donating sperm during this period. Contraception requirements do not apply for participants in an

exclusively same-sex relationship.

9. Must provide written informed consent before any study procedure is performed

Exclusion Criteria:

1. Participants who have received any investigational drug in a clinical research study within the previous 30 days before screening or 5 half-lives, whichever is longer.
2. Participants who have received a coronavirus disease 2019 (COVID-19) vaccine within 7 days prior to randomization.
3. Participants who are study site or sponsor employees, or immediate family members of a study site or sponsor employee.
4. History of any drug or alcohol abuse in the past 12 months defined as >21 units of alcohol per week for males and >14 units of alcohol per week for females. Where 1 unit = 360 mL of beer, 150 mL wine, or 45 mL of spirits.
5. History of asthma or reactive airway disease. Fully resolved childhood asthma with no history of hospitalizations and no recurrence in adulthood is permitted.
6. Current regular smokers. Social smokers who have had 5 or less tobacco- or nicotine-containing products (including tobacco, e-cigarettes, and marijuana) in the 30 days before first study drug administration are permitted if willing to abstain from smoking during the confinement period.
7. Females of childbearing potential who are pregnant or lactating or planning to become pregnant during the study (female participants of childbearing potential must have a negative pregnancy test at screening and Day -1). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy - verbal confirmation through medical history review acceptable) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum follicle-stimulating hormone (FSH) concentration ≥40 mIU/L).
8. Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the investigator at screening.
9. Clinically significant abnormal biochemistry, hematology, coagulation, or urinalysis as judged by the investigator. A repeat test may be taken at the investigator's discretion.
10. Positive alcohol breath test or urine test for drugs of abuse at Screening or Day -1.
11. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance of <59 mL/min/1.73m^2 using the CKD-EPI equation.
12. Abnormal liver function tests as indicated by alanine aminotransferase (ALT) >1.5x upper limit of normal (ULN), aspartate aminotransferase (AST) >1.5x ULN or total bilirubin >1.5x ULN. Note: may be repeated once at the discretion of the investigator. Participants with Gilbert's syndrome may be enrolled at the discretion of the investigator.

13. Positive test result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening.
14. Evidence or history of clinically relevant allergic (except for untreated, asymptomatic, seasonal allergies at time of dosing), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, renal, psychiatric, or neurological disease.
15. Acute illness (gastrointestinal, infection [e.g., influenza] or known inflammatory process) at screening or Day -1.
16. Abnormal screening ECG, including QT intervals corrected with Fridericia's formula >450 msec for males or >470 msec for females, or participant has any cardiac rhythm other than sinus rhythm that is interpreted by the investigator to be clinically significant.
17. Known personal or family history of congenital long QT syndrome or known family history of sudden death.
18. Resting bradycardia (pulse heart rate [HR] <40 bpm) or a resting tachycardia (HR >100 bpm) at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
19. Hypertension, defined as a resting systolic blood pressure >140 mm Hg or a resting diastolic blood pressure >90 mm Hg at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
20. Hypotension, defined as a resting systolic blood pressure <90 mm Hg or a resting diastolic blood pressure <40 mm Hg at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
21. Has donated blood within 30 days or plasma within 7 days prior to screening or had a loss of whole blood of more than 500 mL within the 30 days prior to screening, or receipt of a blood transfusion within one year prior to screening.
22. Taking, or having taken, any prescribed medication in the 14 days before dosing or over-the-counter drug, including herbal remedies, within 7 days before dosing. Exceptions are vitamins, minerals, paracetamol, hormone replacement therapy, and hormonal contraception. Additional exceptions may apply on a case-by-case basis if considered not to interfere with the objectives of the study, as agreed by the principal investigator and sponsor's medical monitor.
23. Failure to satisfy the investigator of fitness to participate for any other reason.

Investigational Drug

CDI-988

Study Drug Doses and Route of Administration

CDI-988 or placebo given orally. Study drug will be dosed as an oral suspension. Part 1 will include single-ascending doses of 100 mg, 200 mg, 400 mg, 600 mg and 1200 mg CDI-988. The food-effect cohorts (1C, 1E, and 1F) will receive a second dose on Day 9. Part 2 will include multiple doses of CDI-988 (200 mg, 400 mg, and 800 mg) once daily for 10 days, multiple doses of CDI-988 (1200 mg) once daily for 5 days, and multiple doses of CDI-988 (up to 1200 mg) twice daily for 5 days.

Safety Assessments

- Clinical chemistry, hematology, coagulation, and urinalysis.
- Vital signs (blood pressure, heart rate, body temperature, respiratory rate).
- Electrocardiogram.
- Physical examination.
- Adverse events.

Pharmacokinetic Assessment

Plasma CDI-988 concentration

Criteria for Dose Escalation

- A Safety Monitoring Committee comprising 3 members will review safety and available PK data prior to dose escalation to the next dose cohort in Parts 1 and 2.
- For dose escalation to proceed, safety data must be available from a minimum of 7 participants who completed the planned safety assessments at least 48 hours after dosing to ensure that at least 5 participants received active study drug.
- The following data are required for interim study decisions: adverse events, vital signs, safety laboratory values, and ECGs.
- Dose escalation will not occur with any of the following:
    - A serious adverse reaction (i.e., a serious adverse event considered at least possibly related to the active drug) in one subject.
    - A grade 3 or higher nonserious adverse reactions (i.e., severe nonserious adverse event considered related to the active drug administration) in two participants in the same cohort, independent of whether they occurred within the same system organ class.

Sample Size, Power, and Number of Sites

- No formal sample size calculation was done. Based on experience from similar studies, the target number of participants to be enrolled is appropriate for the assessment of safety and tolerability.

- In Part 1, 46 healthy participants will be enrolled: 5 randomized cohorts of 8 participants and 1 open-label cohort of 6 participants. In Part 2, 48 healthy participants will be enrolled into 6 cohorts, each with 8 participants.
- In both Parts 1 and 2, up to 2 replacement participants may be enrolled per cohort. Participants withdrawn due to an adverse event related to CDI-988 will be considered evaluable and will not be replaced.
- Planned number of sites: Up to 2 (Australia).

Statistical Analysis

Safety will be assessed based on the actual treatment received for all participants who have received study drug. Data will be summarized using descriptive statistics (number of participants, arithmetic mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency and percentages for categorical variables. In addition, for pharmacokinetic data, the geometric mean and geometric coefficient of variation will be calculated. Where confidence intervals are presented, they will be two-sided 95% confidence intervals.

Sponsor: Cocrystal Pharma Australia Pty Ltd.

2. SCHEDULE OF EVENTS

2.1. Part 1: Single-Ascending Dose Schedule of Events

	Screening	Clinical Unit						EOS Visit [1]
	Day -28 to -2	Day -1	Day 1			Day 2	Day 3	Day 8
Assessments			Pre-dose	Dosing	Post-dose			(+1 d)
Unit Check-in		X						
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical history	X	X	X					
Prior medication history	X	X						
Vein assessment	X							
Height	X							
Weight	X	X						
Pregnancy screen [2]	X	X						X
FSH [3]	X							
Serology [4]	X							
Drugs of abuse screen [5]	X	X						
Alcohol breath test	X	X						
Physical examination [6]	X	X			X (abbrev)		X (abbrev)	X (abbrev)
Clinical safety labs [7]	X	X			X	X		X
Lipid panel (fasted)		X				X		X
Vital signs [8]	X	X	X		X	X	X	X
12-lead ECG [9]	X	X	X		X	X	X	X
Randomization [10]			X					
Study Drug				X				
Adverse event reporting [11]				X	X	X	X	X
Concomitant medications			X			X	X	X
PK samples [12]			X		X	X	X	
Discharge from Unit							X	

Footnotes

1 End of study (EOS) visit for all cohorts except for the food-effect cohorts, Cohorts 1C, 1E, and 1F. See Section 2.2 and Section 2.3 for Schedules of Events for days 8-16 for Cohorts 1C, 1E, and 1F.

2 Females of childbearing potential will be tested for pregnancy by detecting the presence of β-HCG (serum test at Screening and urine test at other time points).

3 Only for women of postmenopausal status.

4 Serology screening will include tests for hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.

5 Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).

6 Physical examination will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. The physical exam will take place after the ECG and vital signs (4-hr ECG on Day 1).

7 Standard clinical safety labs may be collected fasted or non-fasted. Post-dose samples will be collected 6 hours ±1 hour after dosing.

8 Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured once prior to dosing (within 2 hours) and 2 and 4 hours ±15 minutes post-dosing on Day 1 and before blood draw on Days 2, 3 and 8.

9 Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG once during screening, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, and once on Days 2, 3, and 8. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.

10 Randomization not required for Cohort 1E (open-label food-effect cohort)

11 Adverse event reporting will be continuous through end of study on Day 8.

12 PK samples to be collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, and 48 h after dosing. Sampling windows are within 1 hour pre-dose, ±5 minutes for samples through 4 h post-dose and ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hour and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

2.2. Part 1 Cohort 1C Schedule of Events – Period 2

	Clinical Unit						EOS Visit [1]
	Day 8	Day 9			Day 10	Day 11	Day 16
Assessments		**Pre-dose**	**Dosing**	**Post-dose**			**(+/-1 d)**
Unit Check-in	X						
Inclusion/exclusion criteria	X	X					
Weight	X						
Pregnancy screen [2]	X						X
Drugs of abuse screen [3]	X						
Alcohol breath test	X						
Physical examination [4]	X			X (abbrev)		X (abbrev)	X (abbrev)
Clinical safety labs [5]	X			X	X		X
Lipid panel (fasted)	X				X		X
Vital signs [6]	X	X		X	X	X	X
12-lead ECG [7]	X	X		X	X	X	X
High-fat breakfast [8]		X					
Study Drug			X				
Adverse event reporting [9]	X	X	X	X	X	X	X
Concomitant medications	X	X			X	X	X
PK samples [10]		X		X	X	X	
Discharge from Unit						X	

Footnotes

Note: The washout window between Period 1 and Period 2 may be optionally extended for up to 3 days, with other Period 2 visits adjusted accordingly. Thus, dosing for Period 2 may occur between Day 9 and Day 12.

1. End of study visit.
2. Pregnancy will be determined by urine dipstick.
3. Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
4. Physical examination will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. The physical exam will take place after the ECG and vital signs (4-hr ECG on Day 9).
5. Standard clinical safety labs may be collected fasted or non-fasted. Post-dose samples will be collected 6 hours ±1 hour after dosing.
6. Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured on Day 8, on Day 9 prior to dosing (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, and on Days 10, 11, and 16.
7. Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG on Day 8, on Day 9 pre-dose (within 2 hours) and 2 and 4 hours after dosing ±15 minutes, and on Days 10, 11, and 16. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
8. High-fat breakfast started and finished within 30 minutes prior to dosing. Breakfast is considered completed if ≥75% is consumed.
9. Adverse event reporting will be continuous to end of study on Day 16.
10. PK samples to be collected before dosing (within 1 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, and 48 h after dosing. Sampling windows are within 1 hour pre-dose, ±5 minutes for samples through 4 h post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hours and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

2.3. Part 1 Cohort 1E and Cohort 1F Schedule of Events – Period 2

	Clinical Unit						EOS Visit [1]
	Day 8	Day 9			Day 10	Day 11	Day 16
Assessments		Pre-dose	Dosing	Post-dose			(+/-1 d)
Unit Check-in	X						
Inclusion/exclusion criteria [2]	X	X (abbrev)					
Weight	X						
Pregnancy screen [3]	X						X
Drugs of abuse screen [4]	X						
Alcohol breath test	X						
Physical examination [5]	X			X (abbrev)		X (abbrev)	X (abbrev)
Clinical safety labs [6]	X			X	X		X
Lipid panel (fasted)	X				X		X
Vital signs [7]	X	X		X	X	X	X
12-lead ECG [8]	X	X		X	X	X	X
Standard non-high fat breakfast [9]		X					
CDI-988			X				
Adverse event reporting [10]	X	X	X	X	X	X	X
Concomitant medications	X	X			X	X	X
PK samples [11]		X		X	X	X	
Discharge from Unit						X	

Footnotes

Note: The washout window between Period 1 and Period 2 may be optionally extended for up to 3 days, with other Period 2 visits adjusted accordingly. Thus, dosing for Period 2 may occur between Day 9 and Day 12.

1. End of study visit.
2. Full eligibility review on Day 8 and abbreviated review on Day 9.
3. Pregnancy will be determined by urine dipstick.
4. Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
5. Physical examination will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. The physical exam will take place after the ECG and vital signs (4-hr ECG on Day 9).
6. Standard clinical safety labs may be collected fasted or non-fasted. Post-dose samples will be collected 6 hours ±1 hour after dosing
7. Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured on Day 8, on Day 9 prior to dosing (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, and on Days 10, 11, and 16.
8. Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG on Day 8, on Day 9 pre-dose (within 2 hours) and 2 and 4 hours after dosing ±15 minutes, and on Days 10, 11, and 16. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
9. Standard non-high fat breakfast started and finished within 30 minutes prior to dosing. Breakfast is considered completed if ≥75% is consumed.
10. Adverse event reporting will be continuous to end of study on Day 16.
11. PK samples to be collected before dosing (within 1 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, and 48 h after dosing. Sampling windows are within 1 hour pre-dose, ±5 minutes for samples through 4 h post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hour and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

2.4. Part 2: Multiple-Ascending Dose Schedule of Events (Cohorts 2A – 2C)

	SCRN Day -28 to -2	Clinical Unit														EOS [1] visit Day 17
		Day -1	Day 1			Day 2-4			Day 5-9			Day 10			Day 12	
Assessments			Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose		(+ 1 d)
Check-in		X														
Informed consent	X															
Eligibility[2] criteria	X	X														
Demographic data	X															
Medical history	X	X	X													
Prior medication history	X	X														
Vein assessment	X															
Height	X															
Weight	X	X														
Pregnancy screen [3]	X	X														X
FSH [4]	X															
Serology [5]	X															
Drugs of abuse screen [6]	X	X														
Alcohol breath test	X	X														
Physical examination [7]	X	X			X(Ab)			X(Ab)						X(Ab)		X(Ab)
Clinical safety labs [8]	X	X			X	X (D3)								X		X
Lipid panel (fasted)		X										X				X
Vital signs [9]	X	X	X		X			X			X			X	X	X
12-lead ECG [10]	X	X	X		X			X						X		
Randomization			X													
Study Drug				X			X			X			X			
AE reporting [11]				X	X	X	X	X	X	X	X	X	X	X	X	X
Con. medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK samples [12]			X		X	X (D3)			X (D6 & 9)			X		X	X	
Discharge															X	

Footnotes

1 End of study visit.
2 Eligibility does not need to be re-reviewed between doses.
3 Females of childbearing potential will be tested for pregnancy by detecting the presence of β-HCG (serum test at Screening and urine test at other time points).
4 Only for women of postmenopausal status.
5 Serology screening will include tests for tests hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.
6 Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
7 Physical examination will be performed at screening and Day -1 and will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam (Ab) will be performed at other timepoints and will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. The physical exam will take place after the ECG and vital signs (4-hr ECG on Day 1).
8 Standard clinical safety labs may be collected fasted or nonfasted. Post-dose samples will be collected 8 hours ±1 hour after dosing.
9 Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured at screening, on Day -1, on Day 1 prior to dosing (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, on Days 2-12 and Day 17.
10 Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG once during screening, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, and after blood draw on Days 2-4 post-dose, and once post-dosing on Day 10. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
11 Adverse event reporting will be continuous to end of study on Day 17.
12 Dense PK sampling done on Days 1 and 10, with pre-dose trough sampling (within 1 hour pre-dose) on Days 3, 6, and 9. On Day 1, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, and 24 hours postdose (pre-dose on Day 2). On Day 10, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, 24 hours post-dose (pre-dose on Day 11), 36 hours (Day 11), and 48 hours (Day 12). Sampling windows for Days 1 and 10 are ±5 minutes for samples through 4 hours post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hours and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

2.5. Part 2: Multiple-Ascending Dose Schedule of Events (Cohort 2D)

	SCRN Day -28 to -2	Clinical Unit											EOS[1] visit
		Day -1	Day 1			Day 2-4			Day 5			Day 7	Day 12
Assessments			Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose		(+ 1 d)
Check-in		X											
Informed consent	X												
Eligibility[2] criteria	X	X											
Demographic data	X												
Medical history	X	X	X										
Prior medication history	X	X											
Vein assessment	X												
Height	X												
Weight	X	X											
Pregnancy screen[3]	X	X											X
FSH[4]	X												
Serology[5]	X												
Drugs of abuse screen[6]	X	X											
Alcohol breath test	X	X											
Physical examination[7]	X	X			X(Ab)			X(Ab)			X(Ab)		X(Ab)
Clinical safety labs[8]	X	X			X	X (D3)					X		X
Lipid panel (fasted)		X							X				X
Vital signs[9]	X	X	X		X			X			X	X	X
12-lead ECG[10]	X	X	X		X			X			X		X
Randomization[11]		X	X										
Study Drug				X			X			X			
AE reporting[12]				X	X	X	X	X	X	X	X	X	X
Con. medications			X	X	X	X	X	X	X	X	X	X	X
PK samples[13]			X		X	X (D3, D4)			X		X	X	
Discharge												X	

Footnotes

1 End of study visit.
2 Eligibility does not need to be re-reviewed between doses.
3 Females of childbearing potential will be tested for pregnancy by detecting the presence of β-HCG (serum test at Screening and urine test at other time points).
4 Only for women of postmenopausal status.
5 Serology screening will include tests for tests hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.
6 Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
7 Physical examination will be performed at screening and Day -1 and will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. An abbreviated exam (Ab) will be performed at other timepoints and will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. On Day 1 the abbreviated exam will be done at 4 hours post dose ±1 hour. On Days 2-5 the abbreviated exam will be done at 4 hours post dose ±1 hour. The Day 1 physical exam will take place after the ECG and vital signs (4-hr ECG on Day 1). Operational discretion can be used to define the order of assessments at all other visits.
8 Standard clinical safety labs may be collected fasted or nonfasted. Post-dose samples on Day 1 and Day 5 will be collected 8 hours ±1 hour after dosing. A predose sample will be collected on Day 3 within 2 hours prior to dosing.
9 Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured at screening, on Day -1, on Day 1 prior to dosing (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, on Days 2-5 at 2 and 4 hours ±15 minutes after dosing, on Day 7 prior to discharge and on Day 12.
10 Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG at screening, on Day -1, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±15 minutes after dosing, on Days 2-5 at 2 and 4 hours ±15 minutes after dosing, and on Day 12. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
11 Randomization can be performed either on Day -1 or pre-dose on Day 1
12 Adverse event reporting will be continuous to end of study on Day 12.
13 Dense PK sampling done on Days 1 and 5, with pre-dose trough sampling (within 1 hour pre-dose) on Days 3 and 4. On Day 1, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, and 24 hours postdose (pre-dose on Day 2). On Day 5, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, 24 hours post-dose (Day 6), 36 hours (Day 6), and 48 hours (Day 7). Sampling windows for Days 1 and 5 are ±5 minutes for samples through 4 hours post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hours and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw. All pre-dose PK samples should be collected prior to the meal.

2.6. Part 2: Multiple-Ascending Dose Schedule of Events (Cohort 2E)

	SCRN Day -28 to -2	Clinical Unit											EOS[1] visit
		Day -1	Day 1			Day 2-4			Day 5			Day 7	Day 12
Assessments			**Pre-dose**	**Dosing**	**Post-First Dose**	**Pre-dose**	**Dosing**	**Post-First Dose**	**Pre-dose**	**Dosing**	**Post-Dose**		**(+ 1 d)**
Check-in		X											
Informed consent	X												
Eligibility[2] criteria	X	X											
Demographic data	X												
Medical history	X	X	X										
Prior medication history	X	X											
Vein assessment	X												
Height	X												
Weight	X	X											
Pregnancy screen[3]	X	X											X
FSH[4]	X												
Serology[5]	X												
Drugs of abuse screen[6]	X	X											
Alcohol breath test	X	X											
Physical examination[7]	X	X			X(Ab)			X(Ab)			X(Ab)		X(Ab)
Clinical safety labs[8]	X	X			X	X (D3)					X		X
Lipid panel (fasted)		X							X				X
Vital signs[9]	X	X	X		X			X			X	X	X
12-lead ECG[10]	X	X	X		X			X			X		X
Randomization[11]		X	X										
Study Drug[12]				X			X			X			
AE reporting[13]				X	X	X	X	X	X	X	X	X	X
Con. medications			X	X	X	X	X	X	X	X	X	X	X
PK samples[14]			X		X	X			X		X	X	
Discharge												X	

Footnotes

1 End of study visit.
2 Eligibility does not need to be re-reviewed between doses.
3 Females of childbearing potential will be tested for pregnancy by detecting the presence of β-HCG (serum test at Screening and urine test at other time points).
4 Only for women of postmenopausal status.
5 Serology screening will include tests for tests hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.
6 Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
7 Physical examination will be performed at screening and Day -1 and will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam (Ab) will be performed at other timepoints and will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. On Day 1 the abbreviated exam will be done at 4 hours post first dose ±1 hour. On Days 2-5 the abbreviated exam will be done at 4 hours post first dose ±1 hour.The Day 1 physical exam will take place after the ECG and vital signs (4-hr ECG on Day 1). Operational discretion can be used to define the order of assessments at all other visits.
8 Standard clinical safety labs may be collected fasted or nonfasted. Samples on Day 1 and Day 5 will be collected 8 hours ±1 hour after the first dose of study drug. A predose sample will be collected on Day 3 within 2 hours prior to the first dose of study drug.
9 Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured at screening, on Day -1, on Day 1 prior to the first dose of study drug (within 2 hours) and 2 and 4 hours ±15 minutes after the first dose, on Days 2-5 at 2 and 4 hours ±15 minutes after the first dose, on Day 7 prior to discharge and on Day 12.
10 Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG at screening, on Day -1, on Day 1 prior to the first dose (within 2 hours) and 2 and 4 hours ±15 minutes after the first dose, on Days 2-5 at 2 and 4 hours ±15 minutes after the first dose, and on Day 12. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
11 Randomization can be performed either on Day -1 or pre-dose on Day 1
12 Study drug will be administered for 5 days (9 doses); q12h dosing on Days 1 through 4 and a single last dose given on Day 5. The q12h times (± 30 minutes) for study drug dosing are to be set on Day 1 and reverted back to each day. Participants will be required to fast for one hour prior and two hours after each dose of study drug.
13 Adverse event reporting will be continuous to end of study on Day 12.
14 Dense PK sampling done on Days 1 and 5, with pre-dose trough sampling (within 1 hour pre-dose) on Days 2, 3 and 4. On Day 1, samples taken prior to the first dose of study drug and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, and 12 hours after the first dose of study drug. The 12-hour PK sample should be collected prior to administering the second dose of study drug. On Day 5, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, 24 hours post-dose (Day 6), 36 hours (Day 6), and 48 hours (Day 7). Sampling windows for Days 1 and 5 are ±5 minutes for samples through 4 hours post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hours and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

2.7. Part 2: Multiple-Ascending Dose Schedule of Events (Cohort 2F)

	SCRN Day -28 to -2	Clinical Unit											EOS[1] visit
		Day -1	Day 1			Day 2-4			Day 5			Day 7	Day 12
Assessments			**Pre-dose**	**Dosing**	**Post-First Dose**	**Pre-dose**	**Dosing**	**Post-First Dose**	**Pre-dose**	**Dosing**	**Post-Dose**		**(+ 1 d)**
Check-in		X											
Informed consent	X												
Eligibility[2] criteria	X	X											
Demographic data	X												
Medical history	X	X	X										
Prior medication history	X	X											
Vein assessment	X												
Height	X												
Weight	X	X											
Pregnancy screen[3]	X	X											X
FSH[4]	X												
Serology[5]	X												
Drugs of abuse screen[6]	X	X											
Alcohol breath test	X	X											
Physical examination[7]	X	X			X(Ab)			X(Ab)			X(Ab)		X(Ab)
Clinical safety labs[8]	X	X			X	X (D3)					X		X
Lipid panel (fasted)		X							X				X
Vital signs[9]	X	X	X		X			X			X	X	X
12-lead ECG[10]	X	X	X		X			X			X		X
Randomization[11]		X	X										
Study Drug[12]				X			X			X			
AE reporting[13]				X	X	X	X	X	X	X	X	X	X
Con. medications			X	X	X	X	X	X	X	X	X	X	X
PK samples[14]			X		X	X			X		X	X	
Discharge												X	

Footnotes

1 End of study visit.
2 Eligibility does not need to be re-reviewed between doses.
3 Females of childbearing potential will be tested for pregnancy by detecting the presence of β-HCG (serum test at Screening and urine test at other time points).
4 Only for women of postmenopausal status.
5 Serology screening will include tests for tests hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus.
6 Includes amphetamines (AMP), methamphetamines (MET), methadone (MTD), barbiturates (BAR), benzodiazepines (BZO), cocaine (COC), opiates (OPI), methylenedioxymethamphetamine (MDMA), phencyclidine (PCP), and tetrahydrocannabinol (THC).
7 Physical examination will be performed at screening and Day -1 and will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Abbreviated exam (Ab) will be performed at other timepoints and will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system. On Day 1 the abbreviated exam will be done at 4 hours post first dose ±1 hour. On Days 2-5 the abbreviated exam will be done at 4 hours post first dose ±1 hour.The Day 1 physical exam will take place after the ECG and vital signs (4-hr ECG on Day 1). Operational discretion can be used to define the order of assessments at all other visits.
8 Standard clinical safety labs may be collected fasted or nonfasted. Samples on Day 1 and Day 5 will be collected 8 hours ±1 hour after the first dose of study drug. A predose sample will be collected on Day 3 within 2 hours prior to the first dose of study drug.
9 Vital signs include blood pressure, heart rate, respiratory rate, and body temperature and will be collected prior to blood draws following a minimum 5-minute rest in a seated position. Vital signs will be measured at screening, on Day -1, on Day 1 prior to the first dose of study drug (within 2 hours) and 2 and 4 hours ±15 minutes after the first dose, on Days 2-5 at 2 and 4 hours ±15 minutes after the first dose, on Day 7 prior to discharge and on Day 12.
10 Electrocardiogram will be taken in triplicate (at least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG at screening, on Day -1, on Day 1 prior to the first dose (within 2 hours) and 2 and 4 hours ±15 minutes after the first dose, on Days 2-5 at 2 and 4 hours ±15 minutes after the first dose, and on Day 12. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.
11 Randomization can be performed either on Day -1 or pre-dose on Day 1
12 Study drug will be administered for 5 days (9 doses); q12h dosing on Days 1 through 4 and a single last dose given on Day 5. The q12h times (± 30 minutes) for study drug dosing are to be set on Day 1 and reverted back to each day. Study drug will be administered within 30 minutes after ingesting a standard non-high fat meal. Participants will be required to fast for 2 hours and be restricted from having any fluids after each dose of study drug.
13 Adverse event reporting will be continuous to end of study on Day 12.
14 Dense PK sampling done on Days 1 and 5, with pre-dose trough sampling (within 1 hour pre-dose) on Days 2, 3 and 4. On Day 1, samples taken prior to the first dose of study drug and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, and 12 hours after the first dose of study drug. The 12-hour PK sample should be collected prior to administering the second dose of study drug. On Day 5, samples taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4. 6, 8, 12, 24 hours post-dose (Day 6), 36 hours (Day 6), and 48 hours (Day 7). Sampling windows for Days 1 and 5 are ±5 minutes for samples through 4 hours post-dose, ±10 minutes for samples at 6 and 8 hours, and ±30 minutes for samples at 12 hours and beyond. When ECGs and vital signs are scheduled at the same time as PK samples, the sample will be taken at the scheduled time point, with the ECGs and vital signs obtained as close as possible prior to the blood draw.

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3. LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine transaminase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
C_{max}	maximum plasma concentration
COVID-19	Coronavirus disease 2019
CRF	case report form
CRU	Clinical Research Unit
DAIDS	Division of AIDS
EC	Ethics Committee
ECG	electrocardiogram
EOS	end of study
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
HD	high dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
λz	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
Q12H	every 12 hours
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMC	Safety Monitoring Committee
$t_{1/2}$	terminal elimination half-life
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal

4. INTRODUCTION

4.1. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection

Coronaviruses are a large family of single-stranded RNA viruses that infect mammals and birds, causing respiratory infection. In December 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China. Its rapid spread resulted in a dramatically increased number of cases worldwide. In February 2020, the World Health Organization (2020) designated COVID-19 (coronavirus disease 2019) to be caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of December 14, 2024, over 776 million persons with COVID-19 had been identified in 230 countries with an estimated 7 million deaths (World Health Organization 2024). The progression from isolated cases in China in late 2019 to the current worldwide pandemic is underscored by asymptomatic (Chan et al., 2020; Li et al., 2020) and presymptomatic (Arons et al., 2020; Kimball et al., 2020) infection and transmission. Viral entry is most prominent through the nasal passage, where binding of the viral spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor facilitates cell entry (Sungank et al., 2020; Zhou et al., 2020). The ACE2 receptor is localized on mucosal epithelial cells (Hamming et al., 2004; Jia et al., 2006). Expression of ACE2 in human respiratory epithelial cells contributes in part to the pulmonary involvement observed in patients with symptomatic COVID-19 (Cuervo et al., 2020; Ni et al, 2020).

The U.S. Food and Drug Administration (FDA) has authorized or approved two antiviral drugs given by non-parenteral routes for use in outpatients with mild-to-moderate COVID-19 at increased risk for progression to severe COVID, including hospitalization or death: nirmatrelvir with ritonavir (Paxlovid) and molnupiravir (Lagevrio) (Centers for Disease Control and Prevention 2024). Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. In addition, observational studies suggest that nirmatrelvir/ritonavir may be associated with SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment (Charness et al., 2022). National Institutes of Health COVID-19 Treatment Guidelines recommend use of molnupiravir for nonhospitalized adults with mild-to-moderate COVID-19 only when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate (National Institutes of Health 2022). Molnupiravir is not authorized for use in patients <18 years, because it may affect bone and cartilage growth. The use of molnupiravir also presents additional considerations and concerns related to viral mutagenesis in immunocompromised persons and safety in persons of reproductive age (Infectious Diseases Society of America 2022). There remains a significant need for safe and effective non-parenteral treatments for ambulatory patients with mild-to-moderate COVID-19 who are at risk for progression to severe COVID-19.

4.2. CDI-988

Cocrystal Pharma is developing CDI-988 for the oral treatment of nonhospitalized patients with symptomatic mild to moderate COVID-19. SARS-CoV-2 is a member of the family Coronaviridae, the largest of the positive sense, single-stranded RNA viruses. The coronavirus 3C-like protease (3CL pro) is a chymotrypsin-like cysteine protease that cleaves two SARS-CoV-2 polyproteins at 11 sites to produce 16 functional non-structural proteins essential for viral replication, such as the viral 3CL pro, papain-like protease, helicase, and RNA-dependent RNA polymerase. The 3CL pro gene is highly conserved among coronaviruses, including pandemic SAR-CoV-2 variants of concern. Humans do not produce a homologous 3CL pro. The inhibition of 3CL pro can effectively block viral RNA replication and transcription and further block viral proliferation. Therefore, the 3CL pro is considered an important therapeutic target for diseases caused by coronaviruses, including COVID-19.

CDI-988 is a peptidomimetic 3CL pro inhibitor with high affinity for binding to the highly conserved SARS-CoV-2 3CL pro catalytic site. Accelerated SARS-CoV-2 clearance with CDI-988 treatment administered orally to symptomatic persons not requiring hospitalization has the potential to lessen pulmonary involvement, reduce symptom duration and hospital admissions, and lower disease severity.

CDI-988 is a peptidomimetic covalent inhibitor of SARS-CoV-2 3CL pro. Peptidomimetic inhibitors typically have a two-step process where they initially mimic the natural peptide substrate and form a non-covalent complex that is spatially close to the catalytic residue (Cys-145), it then undergoes a nucleophilic interaction to catalyze the formation of cysteine-participating covalent bonds. The binding of CDI-988 to SARS-CoV-2 3CL protease active site prevents the cleavage of the viral polyproteins, thus impairing viral replication and infectious virus production.CDI-988 has a higher affinity for SARS-CoV-2 3CL pro's catalytic residues than nimatrelvir, which is a component of Paxlovid used to treat SARS-CoV-2 infection in defined populations.

In vitro studies evaluated the antiviral activity of CDI-988 against a broad-spectrum panel of coronaviruses that cause human disease, including pandemic SARS-CoV-2 variants of concern (Beta, Delta, and Omicron variants), SARS-CoV, Middle Eastern respiratory syndrome-CoV, and those related to milder infections human CoV strains (hCoV)229E, OC43, and NL63. CDI-988 had good broad-spectrum anti-coronavirus activity as measured by a reduction in virus cytopathic effect, viral nucleocapsid, genomic RNA, or infectious virus in appropriate cell lines and primary 3-dimensional human bronchial epithelial cells Furthermore, CDI-988 significantly reduced SARS-CoV-2 genome copies in that model by as much as 4 orders of magnitude (99.99%) at 48 and 72 hours post-virus challenge in a dose-dependent manner in primary human bronchial epithelial cells. Antiviral efficacy was demonstrated for hCoV infections in multiple cell lines with EC_{50} values ranging between <0.32 to 4.8 μM and a selectivity index of 5.2 to >53. CDI-988 had synergistic antiviral activity when used in combination with inhibitors of

coronavirus RNA-dependent RNA polymerase that have been FDA-approved to treat SARS-CoV-2 infections (remdesivir and molnupiravir) and GS-441524.

Secondary pharmacology testing, conducted in vitro, comprised cytotoxicity and off-target binding characterization. Short-term cytotoxicity testing demonstrated no significant cytotoxicity at concentrations up to 10 µM. Off-target inhibitory effects were found at 10 µM against agonist radioligands for cannabinoid CB1, kappa-opioid, mu-opioid, glucocorticoid, and vasopressin V_{1A} receptors with 92%, 89%, 66%, 90%, and 96% inhibition, respectively, and antagonist radioligands for calcium L channel (dihydropyridine site) and dopamine transporter with 93% and 55% inhibition, respectively. These off-target interactions of CDI-988 have a safety margin to in vitro efficacy of 2 to >31-fold. No effects were observed in the acute toxicity studies at high oral doses to suggest these interactions would have clinical implications.

GLP safety pharmacology studies confirmed that CDI-988, when administered at single oral doses up to 1000 mg/kg, had no effect on CNS or respiratory function in rats and was not associated with any cardiovascular changes in dogs at peak plasma concentrations established in toxicokinetic (TK) work of 6.35 to 6.78 µg/mL. Dose concentrations approaching those did exhibit inhibitory potential against hERG potassium currents in vitro with an $IC_{50} \geq 8.8$ µM (5.34 µg/mL).

In a single oral dose GLP toxicity study with a 14-day extended recovery period conducted in SD rats with CDI-988, there were no test article-related clinical signs, or effects on body weight, food consumption, ophthalmologic, serum chemistry, urinalysis, gross (necropsy) evaluation, organ weight, and histopathological parameters. Test article-related hematology changes were noted at the end of the recovery phase, including decreased monocyte counts in male animals at ≥100 mg/kg and females at 300 mg/kg, and coagulation parameter changes at 1000 mg/kg in male and female animals on Day 3 comprising decreased fibrinogen. None of these changes were considered adverse. The maximum tolerated dose (MTD) and NOAEL in this study was 1000 mg/kg, corresponding to an $AUC_{0\text{-}24h}$ and C_{max} of 7390 h*ng/mL and 874 ng/mL for males and 18300 h*ng/mL and 1050 ng/mL for females.

In a single oral dose GLP toxicity study with a 14-day extended recovery period conducted in Beagle dogs with CDI-988, there was no mortality nor changes in body weight, food consumption, ophthalmologic examination, body temperature, clinical pathology, gross pathology, and histopathology. Clinical signs at 300 and 1000 mg/kg were limited to small/medium amounts of food-like vomitus and abnormal stool (mucoid/watery stool) on the day of dosing (Day 1) with the degree of incidence being dose related. All of the changes were completely reversible on the following days. The NOAEL was assigned as 1000 mg/kg. The corresponding $AUC_{0\text{-}24h}$ and C_{max} of CDI-988 at the NOAEL were 46500 ± 13300 h*ng/mL and 6780 ± 2700 ng/mL for males, and 54300 ± 22900 h*ng/mL and 6350 ± 1600 ng/mL for females, respectively.

The completed in vitro GLP genotoxicity studies demonstrated no mutagenic potential (bacterial reverse mutation test and chromosomal aberration assay in CHO cells).

The NOAELs from the rat and dog acute toxicology studies provided human equivalent doses (HED), calculated according to FDA guidance Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, of 9,680 and 33,300 mg to a 60-kg person for the rat and dog, respectively, and 7260 and 25000 mg to a 45-kg person for the rat and dog, respectively.

Repeat oral dose toxicity testing in rats and dogs was assessed using 7-day dose range finding and 14-day GLP studies at doses up to 1000 mg/kg/day (HD). In the rat 7-day study, there were no mortalities or any moribund animals. CDI-988-related clinical signs were limited to salivation and piloerection at the HD. Macroscopic changes were confined to white solid material in the stomach at the HD. Microscopic changes comprised minimal to mild, non-adverse, diffuse follicular atrophy in bilateral thyroid glands of males at ≥100 mg/kg/day and females at ≥300 mg/kg/day. Focal erosion in the pyloric mucosa of the stomach was noted in two males at the HD, but the relationship with test article treatment was uncertain. The microscopic findings in the stomach and thyroid can be non-specific observations consistent with stress. In rats, stress/glucocorticoids are associated with focal erosions/ulcers in the stomach glandular mucosa and decreases in thyroid stimulatory hormone function, which subsequently results in follicular epithelial atrophy.

In the 14-day rat GLP study, there was one death in an HD male on Day 12; the cause of death was undetermined and given the isolated occurrence a relationship to CDI-988 is uncertain. At 1000 mg/kg/day clinical signs of hunched posture, salivation, unkempt, and abnormal respiratory sounds were found chiefly at the HD that reversed in a 7-day recovery. Raised platelets and white blood cell counts, and serum total bilirubin were noted at the HD; all reversed in recovery. Microscopic findings occurred in the thyroids comprising minimal colloid vacuolation and minimal follicular epithelial atrophy in dosing phase animals at ≥30 mg/kg/day and minimally to mildly decreased thyroid weights in males at ≥200 mg/kg/day. Microscopic thyroid findings reversed, but minimally decreased thyroid weights persisted in the HD recovery males. Females at the HD had mildly decreased uterine weights which persisted at the end of the recovery phase but were without macroscopic or microscopic findings. The NOAEL assigned by the Contract Research Laboratory that conducted the study was 200 mg/kg/day on the basis of the one death at 1000 mg/kg/day that was of uncertain relationship to CDI-988. Given this uncertainty and no findings judged to be adverse in other animals at any dose level, including 1000 mg/kg/day, the HD is considered a better representation of the NOAEL. At the HD, the with corresponding mean $AUC_{0\text{-}24h}$ and C_{max} on Day 14 of 19,200 h*ng/mL and 1230 ng/mL for males, 27,200 h*ng/mL and 1880 ng/mL for females, respectively.

In the dog 7-day study, there was no mortality, and clinical signs were limited to soft/watery stool observed in males at ≥100 mg/kg/day and females at the HD, and small amounts of food-

like vomit observed in both sexes at the HD. Decreased food consumption was observed in some animals at the HD. The 14-day GLP study also had no mortality. Clinical signs at ≥100 mg/kg/day included sporadic food-like/white frothy or cloudy vomitus, and abnormal stool (soft/mucoid/watery stool) with dose-related incidence. Transient light to moderate salivation at ≥300 mg/kg/day and white material in pans/bedding was noted at the HD. A slight body weight decrease was noted at the HD in females. Hematology changes were limited to slight to mildly decreased absolute reticulocyte count across all the test article dose groups that lacked any consistent dose response. Serum chemistry changes at ≥100 mg/kg/day included slight to moderate increases in alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase and minimal to mild decreases in total protein, albumin, total cholesterol, triglycerides, and globulin. Those changes correlated with the non-adverse microscopic finding of moderate diffuse hepatocellular cytoplasmic vacuolation. Organ weight changes consisted of increased mean absolute and relative liver weights for males and females at ≥100 mg/kg/day. All findings reversed in recovery. The NOAEL was set at 1000 mg/kg/day with corresponding mean $AUC_{0\text{-}24h}$ and C_{max} on Day 14 of 105000 ± 47800 h*ng/mL and 11000 ± 5770 ng/mL for males, and 77200 ± 37100 h*ng/mL and 9080 ± 3220 ng/mL for females, respectively.

More detailed information about nonclinical studies with CDI-988 can be found in the Investigator's Brochure.

4.3. Risk/Benefit Assessment

Anticipated risks of CDI-988 are low based on the mechanism of action and preclinical safety data that includes in vitro and in vivo pharmacology, pharmacokinetic, and toxicology studies. The benefit-risk balance for this study is considered favorable given the overall limited risks to study participants in this sequential-cohort dose-escalation study of CDI-988 administered orally.

5. OBJECTIVES AND ENDPOINTS

Part 1: Single-Ascending Dose

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of increasing doses of CDI-988 when given as a single oral dose to cohorts of healthy participants	• Incidence of treatment-emergent AEs • Incidence of clinically significant laboratory abnormalities • Incidence of clinically significant changes from baseline in vital signs • Incidence of clinically significant changes from baseline in ECGs
Secondary	
• To assess the PK of CDI-988 following a single oral dose • To explore the effect of food on the single oral dose PK of CDI-988	• PK parameters: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(inf)}$, λz, $t_{1/2}$ • Difference between fasted and fed conditions in systemic exposure to CDI-988: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(inf)}$

Part 2: Multiple-Ascending Dose

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of multiple-ascending doses of CDI-988 when administered orally to cohorts of healthy participants	• Incidence of treatment-emergent AEs • Incidence of clinically significant laboratory abnormalities • Incidence of clinically significant changes from baseline in vital signs • Incidence of clinically significant changes from baseline in ECGs
Secondary	
• To assess the PK of CDI-988 when given as multiple oral doses	• PK parameters: C_{max}, T_{max}, $AUC_{(0-24)}$ on Days 1 and 10 and λz and $t_{1/2}$ after last dose; trough concentrations on intermediate dosing days. • PK parameters: C_{max}, T_{max}, $AUC_{(0-24)}$ on Days 1 and 5 and λz and $t_{1/2}$ after last dose; trough concentrations on intermediate dosing days.

6. INVESTIGATIONAL PLAN

6.1. Summary of Study Design

This is a randomized, double-blind, placebo-controlled phase 1 study of the SARS-CoV-2 replication and protease inhibitor CDI-988 given orally to healthy participants at up to 2 study sites in Australia. Participants will be recruited from the Clinical Research Unit (CRU) or by direct advertising to the public. Screening assessments must be done within 28 days prior to randomization to determine participant eligibility. Written consent must be obtained before conducting any study procedures.

Part 1: Single-Ascending Dose

In Cohorts 1A–1D and 1F, participants will be randomly assigned within each cohort to receive a single dose of CDI-988 or placebo. Doses will escalate in sequential dose cohorts. It is planned that 5 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo). In addition, 6 healthy participants will be enrolled and dosed with CDI-988 in an open-label ("standard non-high fat meal") food-effect cohort.

Cohorts 1A–1D and 1F will include the initial dosing of a sentinel group (1 CDI-988 and 1 placebo) at least 24 hours before dosing the remaining 6 subjects in the cohort (5 CDI-988 and 1 placebo). The remainder of the cohort will only be dosed if, in the opinion of the investigator and sponsor's medical representative, there is no significant safety concern identified in the sentinel subjects within the first 24 hours after administration of the dose (CDI-988 or placebo). The following regimens are planned:

- Cohort 1A (N=8): 100 mg CDI-988 or placebo.
- Cohort 1B (N=8): 200 mg CDI-988 or placebo.
- Cohort 1C (N=8): 400 mg CDI-988 or placebo on Days 1 and 9 (high-fat food-effect cohort).
- Cohort 1D (N=8): 600 mg CDI-988 or placebo.
- Cohort 1E (N=6): 100 mg CDI-988 on Days 1 and 9 (standard non-high fat food-effect) cohort).
- Cohort 1F (N=8): 1200 mg CDI-988 or placebo on Days 1 and 9 (standard non-high fat food effect cohort).

Cohorts 1C, IE, and 1F will be two-period sequential food-effect cohorts in which participants will receive a single dose of study drug under fasted conditions on Day 1 and a single dose of study drug under fed conditions on Day 9.

Part 2: Multiple-Ascending Dose

Part 2 of the study may be opened after satisfactory review of the safety and PK data from the cohorts in Part 1, as well as preclinical data to support the duration of multiple ascending dose cohorts. Cohort 2a may be started in parallel with the highest dose cohort in Part 1.

Participants will be randomly assigned to receive once-daily doses of CDI-988 or placebo for 10 days (Cohorts 2A-2C), once-daily doses of CDI-988 or placebo for 5 days (Cohort 2D), and twice-daily (q12h) doses of CDI-988 or placebo for 5 days (Cohorts 2E-2F). It is planned that up to 6 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo). A minimum of 6 participants must be dosed in a given cohort to allow dose escalation to proceed.

The following regimens are planned:

- Cohort 2A: 200 mg CDI-988 or placebo once daily for 10 days.
- Cohort 2B: 400 mg CDI-988 or placebo once daily for 10 days.
- Cohort 2C: 800 mg CDI-988 or placebo once daily for 10 days.
- Cohort 2D: 1200 mg CDI-988 or placebo once daily for 5 days.
- Cohort 2E: 1200 mg CDI-988 or placebo twice daily (q12h) for 5 days (9 doses).
- Cohort 2F: 1200 mg CDI-988 or placebo twice daily (q12h) for 5 days (9 doses) with a standard meal.

6.2. Discussion of Design

Study Design: The randomized, double-blind, placebo-controlled design provides the optimal opportunity to differentiate potential adverse events associated with CDI-988 from background events in healthy volunteers. Dose escalation in sequential cohorts with interim review by a Safety monitoring committee (SMC) mitigates risk to study participants in this first-in-human study.

Dose Rationale: The NOAELs from the rat and dog acute toxicology studies provided human equivalent doses (HED), calculated according to FDA guidance Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, of 7260 and 25000 mg to a 45-kg person for the rat and dog study, respectively. Using the lowest HED (7260 mg) and the normal safety factor of 10, the maximum recommended starting dose for this first-in-human clinical trial would be a 726-mg dose to a 45-kg human (the lower limit of the allowable weight range for the study). The lowest HED at the NOAEL in acute rat and dog studies thus provides a safety margin that is >70-fold over the 100-mg starting dose for the first SAD cohort (see Section 4.2 for additional information).

Entry Criteria: Participants will be healthy adults and receive standard assessments to determine eligibility.

Safety Endpoints: The safety assessments of physical examination, vital signs, clinical laboratories, electrocardiogram, and adverse event collection used in this trial are standard assessments for phase 1 studies evaluating the safety of single and repeated dosing.

7. STUDY POPULATION

The participants will comprise healthy adults between the ages of 18 and 55.

Participation in this study is voluntary. The nature of the study will be fully explained to each participant during the informed consent. The participants will have the opportunity to ask questions. An informed consent document will then be signed by the participant and the person performing the consent discussion and retained by the investigator according to Good Clinical Practice. A copy of the signed informed consent document will be given to the participant.

Enrollment eligibility will be based on the results of screening for the following inclusion and exclusion criteria.

7.1. Inclusion and Exclusion Criteria

7.1.1. Inclusion Criteria

1) Healthy males or non-pregnant, non-lactating females aged 18 to 55 years.
2) Body weight of at least 45 kg.
3) Body mass index between ≥18.0 and ≤32.0 kg/m^2. If outside this range, eligible if not considered clinically significant.
4) Good state of health (mentally and physically) in the opinion of the investigator as indicated by a comprehensive clinical assessment (detailed medical history and a complete physical examination), electrocardiogram (ECG), and laboratory investigations (hematology, clinical chemistry, coagulation, and urinalysis).
5) Willing and able to refrain from alcohol and caffeine from 48 hours before first dose through the last dose of study drug.
6) Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test on Day -1.
7) Female participants are eligible to participate if they are not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

    - Not of childbearing potential, defined as surgically sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy - verbal confirmation through medical history review acceptable), or postmenopausal (no menses for 12 months and confirmed by follicle-stimulating hormone (FSH) level ≥40 mIU/mL).
    - Of childbearing potential and agrees to practice true abstinence or agrees to use a highly effective method of contraception consistently from 30 days prior to Day 1 until at least 30 days after dosing. The reliability of sexual abstinence is to be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Highly effective contraception includes hormonal contraception (oral, injected, implanted, or transdermal) plus use of a condom, placement of an intrauterine device or intrauterine system plus use of a condom, tubal ligation plus use of a condom, or a vasectomized male partner

(performed at least 6 months prior) who has been documented to no longer produce sperm – verbal confirmation through medical history review acceptable – plus use of a condom. Contraception requirements do not apply for participants in an exclusively same-sex relationship. Female participants should not donate eggs until at least 30 days after their last dose.

8) Male participants must agree to practice true abstinence; be surgically sterilized (performed at least 6 months prior and documented azoospermia 90 days post-procedure to no longer produce sperm) and wear a condom; wear a condom if their partner has had a tubal ligation, or agree to use a condom plus effective contraception (i.e., established use of hormonal contraception - started at least 30 days before Day 1; or placement or an intrauterine device or intrauterine system) for their female partner, if of childbearing potential, from screening and for at least 90 days after dosing and refrain from donating sperm during this period. Contraception requirements do not apply for participants in an exclusively same-sex relationship.
9) Must provide written informed consent before any study procedure is performed.

7.1.2. Exclusion Criteria

1) Participants who have received any investigational drug in a clinical research study within the previous 30 days before screening or 5 half-lives, whichever is longer.
2) Participants who have received a coronavirus disease 2019 (COVID-19) vaccine within 7 days prior to randomization.
3) Participants who are study site or sponsor employees, or immediate family members of a study site or sponsor employee.
4) History of any drug or alcohol abuse in the past 12 months defined as >21 units of alcohol per week for males and >14 units of alcohol per week for females. Where 1 unit = 360 mL of beer, 150 mL wine, or 45 mL of spirits.
5) History of asthma or reactive airway disease. Fully resolved childhood asthma with no history of hospitalizations and no recurrence in adulthood is permitted.
6) Current regular smokers. Social smokers who have had 5 or less tobacco- or nicotine-containing products (including tobacco, e-cigarettes, and marijuana) in the 30 days before first study drug administration are permitted if willing to abstain from smoking during the confinement period.
7) Females of childbearing potential who are pregnant or lactating or planning to become pregnant during the study (female participants of childbearing potential must have a negative pregnancy test at screening and Day -1). A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy - verbal confirmation through medical history review acceptable) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum FSH concentration ≥40 mIU/L).

8) Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the investigator at screening.
9) Clinically significant abnormal biochemistry, hematology, coagulation, or urinalysis as judged by the investigator. A repeat test may be taken at the investigator's discretion.
10) Positive alcohol breath test and/or urine test for drugs of abuse at Screening or Day -1.
11) Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance of <59 mL/min/1.73m^2 using the CKD-EPI equation.
12) Abnormal liver function tests as indicated by alanine aminotransferase (ALT) > 1.5x upper limit of normal (ULN), aspartate aminotransferase (AST) > 1.5x ULN or total bilirubin >1.5x ULN. Note: may be repeated once at the discretion of the investigator. Participants with Gilbert's syndrome may be enrolled at the discretion of the investigator.
13) Positive test result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening
14) Evidence or history of clinically relevant allergic (except for untreated, asymptomatic, seasonal allergies at time of dosing), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, renal, psychiatric, or neurological disease.
15) Acute illness (gastrointestinal, infection [e.g., influenza] or known inflammatory process) at screening or Day -1.
16) Abnormal screening ECG, including QT intervals corrected with Fridericia's formula >450 msec for males or >470 msec for females, or participant has any cardiac rhythm other than sinus rhythm that is interpreted by the investigator to be clinically significant.
17) Known personal or family history of congenital long QT syndrome or known family history of sudden death.
18) Resting bradycardia (pulse heart rate [HR] <40 bpm) or a resting tachycardia (HR >100 bpm) at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
19) Hypertension, defined as a resting systolic blood pressure >140 mm Hg or a resting diastolic blood pressure >90 mm Hg at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
20) Hypotension, defined as a resting systolic blood pressure <90 mm Hg or a resting diastolic blood pressure <40 mm Hg at screening or Day -1. Vital sign measurements should be measured in a seating position and may be repeated at the investigator's discretion.
21) Has donated blood within 30 days or plasma within 7 days prior to screening or had a loss of whole blood of more than 500 mL within the 30 days prior to screening, or receipt of a blood transfusion within one year prior to screening.

22) Taking, or having taken, any prescribed medication in the 14 days before dosing or over-the-counter drug, including herbal remedies, within 7 days before dosing. Exceptions are vitamins, minerals, paracetamol, hormone replacement therapy, and hormonal contraception. Additional exceptions may apply on a case-by-case basis, if considered not to interfere with the objectives of the study as agreed by the principal investigator and sponsor's medical monitor.
23) Failure to satisfy the investigator of fitness to participate for any other reason.

7.2. Removal of Participants from Study Drug or Assessment

7.2.1. Early Discontinuation of Study Drug

A participant must prematurely discontinue study drug under any of the following circumstances:

- The participant wishes to discontinue study drug.
- The investigator wishes the participant to discontinue study drug, especially but not limited to the investigator concluding that further treatment puts the participant at unacceptable risk.
- The participant develops a condition or begins a therapy that would have excluded entry into the study.
- The participant becomes pregnant during the study period. In this circumstance, the pregnancy must be immediately reported by telephone to the sponsor.
- The participant develops an adverse event with the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events that is grade 3 or greater toxicity and related to study drug in the judgment of the investigator.

An EOS visit should be scheduled 7-8 days after the last dose of study drug for participants who discontinue study drug prematurely, provided consent has not been withdrawn.

7.2.2. Participant Withdrawal from the Study

A participant must be withdrawn from the study (and discontinue any study drug) if the participant requests such study discontinuation. The reason for study withdrawal must be recorded in the participant's case report form (CRF). An EOS visit should be scheduled 7-8 days after the last dose of study drug for participants who withdraw from the study prematurely, provided consent has not been withdrawn.

7.2.3. Participant Replacement

In both Parts 1 and 2, replacement participants may be enrolled as follows:

- Participants who withdraw/discontinue after randomization but prior to any dosing may be replaced automatically.

- Participants who withdraw/discontinue after dosing (not due to an adverse event related to CDI-988) may be replaced at the discretion of the sponsor and principal investigator.

8. TREATMENTS

8.1. Treatments Administered

8.1.1. Method of Assignment to Treatment

After informed consent has been obtained and study eligibility has been established, participants will be admitted to the CRU the day before the first dose of study drug.

In both parts of this study, participants will be assigned a screening number and randomized to receive CDI-988 or placebo prior to dosing. CDI-988 dosage is determined based on cohort assignment. A participant is considered randomized when a pharmacy personnel assigns a randomization number/treatment allocation.

8.1.2. Treatment Cohorts

Treatment cohorts are presented for Part 1(single-ascending dose) in Table 1 and for Part 2 (multiple-ascending dose) in Table 2.

Table 1: Study Drug Treatment (Part 1, Single-Ascending Dose)

Cohort	Study Drug	No. Bottles	ORA-Sweet™ (mL/bottle)	Frequency
1A	CDI-988 (100 mg) or placebo	1	10	Single dose on Day 1
1B	CDI-988 (200 mg) or placebo	1	20	Single dose on Day 1
1C	CDI-988 (400 mg) or placebo	1	40	Single doses on Day 1 and Day 9
1D	CDI-988 (600 mg) or placebo	2	40	Single dose on Day 1
1E	CDI-988 (100 mg)	1	10	Single doses on Day 1 and Day 9
1F	CDI-988 (1200 mg)	3	40	Single doses on Day 1 and Day 9

Table 2: Study Drug Treatment (Part 2, Multiple-Ascending Dose)

Cohort	Study Drug	No. Bottles	ORA-Sweet™ (mL/bottle)	Frequency
2A	CDI-988 (200 mg/day) or placebo	1	20	Once daily on Days 1 through 10
2B	CDI-988 (400 mg/day) or placebo	1	40	Once daily on Days 1 through 10

2C	CDI-988 (800 mg/day) or placebo	2	40	Once daily on Days 1 through 10
2D	CDI-988 (1200 mg/day) or placebo	3	40	Once daily on Days 1 through 5
2E	CDI-988 (1200 mg/day) or placebo	3	40	Twice daily on Days 1 through 5 (9 doses)
2F	CDI-988 (1200 mg/day) or placebo	3	40	Twice daily on Days 1 through 5 (9 doses) with a standard meal

8.1.3. Dosage Administration

The investigator (or designee) will administer a single oral dose of study drug in Part 1 and once daily oral doses for 5 days or 10 days or twice daily doses for 5 days in Part 2. Please refer to the Pharmacy Manual for more details on dosage administration.

Part 1, Cohorts 1A-1F Day 1 dosing: Administer oral study drug in a fasted state (at least 8 hours of fasting). Study drug will be given as an oral suspension in ORA-Sweet followed by 4 rinses with 20 mL of water. The total rinse volume is 80 mL water for 100-, 200-, and 400-mg doses, 160 mL for the 600-mg dose, and 240 mL for the 1200-mg dose. Subjects are required to fast for 4 hours post-dose. Except for water given with the dose, subjects will not be allowed fluids from 1 hour prior to until 2 hours after dosing.

Part 1, Cohort 1C Day 9 dosing: Drug will be administered within 30 minutes after ingesting a standard high-fat/high-calorie breakfast. A non-standard high-fat breakfast is allowed for participants with specific dietary requirements. The breakfast must be started and finished within 30 minutes prior to dosing. Breakfast is considered completed if ≥75% is consumed within the allowed time window. Post-dose, subjects are required to fast for 4 hours and are not allowed fluids for 2 hours.

Part 1, Cohort 1E and Cohort 1F Day 9 dosing: Drug will be administered within 30 minutes after ingesting a standard non-high fat breakfast. A non-standard breakfast is allowed for participants with specific dietary requirements. The breakfast must be started and finished within 30 minutes prior to dosing. Breakfast is considered completed if ≥75% is consumed within the allowed time window. Post-dose, subjects are required to fast for 4 hours and are not allowed fluids for 2 hours.

Part 2, Cohorts 2A – 2D: Drug will be administered within 30 minutes after ingesting a standard non-high fat breakfast. A non-standard breakfast is allowed for participants with specific dietary requirements. The breakfast must be started and finished within 30 minutes prior to dosing. Breakfast is considered completed if ≥75% is consumed within the allowed time window. Post-dose, subjects are required to fast for 4 hours and are not allowed fluids for 2 hours. All pre-dose PK samples should be collected prior to the meal.

Part 2, Cohort 2E: Drug will be administered twice a day. Participants will be required to fast for 1 hour before and 2 hours after each dose. During this time, water will be allowed as need.

Part 2, Cohort 2F: Drug will be administered twice a day. The morning dose of drug will be administered within 30 minutes after ingesting a standard non-high fat meal. A non-standard meal is allowed for participants with specific dietary requirements. The evening dose of drug will be administered within 30 minutes after ingesting a standard non-high fat snack. All meals must be started and finished within 30 minutes prior to dosing. Meals are considered completed if ≥75% is consumed within the allowed time window. Post-dose, subjects are required to fast for 2 hours and are not allowed fluids for 2 hours. All pre-dose PK samples should be collected prior to the meals.

The investigator (or designee) is responsible for the correct use of the study drug to the participants, confirming that instructions are followed properly, maintaining accurate records of study drug dispensing, and collection of all unused study drug, including empty drug packaging.

8.2. Materials and Supplies

8.2.1. Formulation, Packaging, and Labeling

The drug substance, CDI-988, is manufactured by Aragen Life Science and delivered to Shanghai STA Pharmaceutical Product Co., Ltd, Shanghai, China, for drug product manufacturing. Drug product will be provided by STA to the site pharmacy for suspension prior to oral administration to study participants. The study drug is 100, 200, or 400 mg CDI-988 powder in 60-mL amber bottles with visually-matching placebo.

Powder is mixed at the site pharmacy with 10, 20, or 40 mL of ORA-Sweet for 100-, 200- or 400-mg doses, respectively. The 600-mg cohort will use one 200-mg active or placebo bottle and one 400-mg active or placebo bottle with a total volume of 60 mL of ORA-Sweet. The 800-mg cohort will use two 400-mg active or placebo bottles with a total volume of 80 mL. The 1200-mg cohort will use three 400-mg active or placebo bottles with a total volume of 120 mL. The study drug is prepared as single doses. See the Pharmacy Manual for details on the preparation and handling of dosing solutions.

8.2.2. Storage and Handling

CDI-988 drug product is supplied as powder in 60-mL amber bottles for mixing to an oral suspension with ORA-Sweet prior to use. Matching placebo is supplied in the same manner. The study drug will be stored at 2ºC to 8ºC (36ºF to 46ºF). No other special handling is required.

8.2.3. Final Disposition of Clinical Supplies

At the end of the study, study drug supply and accountability records will be reconciled as to drug shipped, drug consumed, and drug remaining. Any discrepancies noted will be documented.

Final drug accountability reconciliation will be performed at the visit occurring at the end of treatment or early discontinuation. Unused study drug will be destroyed.

8.3. Blinding and Unblinding

This is a randomized, double-blind, placebo-controlled study. Neither the participants nor the study personnel with direct contact with the participant will know which study drug (CDI-988 or placebo) is being administered during the treatment period. Placebo and active drug will be similar in appearance, taste, smell, and quantity. To preserve the blinding of the study, a minimum number of study personnel who do not have direct interactions with the participant's study procedures will see the randomization table before the study is complete. The pharmacy personnel who perform randomization and prepare and dispense the study drug, the bioanalytical laboratory, and the pharmacokineticist will be unblinded. All data will be reviewed blinded by the Safety Monitoring Committee (SMC) for the purposes of escalation of dose cohorts unless the SMC considers it necessary to unblind the data for safety concerns.

Emergency unblinding for adverse events (AEs) will be performed through the code-break envelopes. The principal investigator or designee should make every effort to contact the sponsor directly to discuss the need for emergency unblinding or as soon as practicable after unblinding in the event of a medical emergency where unblinding is essential.

8.4. Concomitant Therapy

No concomitant medications are allowed except for paracetamol, oral contraceptives, and hormone replacement therapy. Exceptions may apply on a case-by-case basis if considered not to interfere with the objectives of the study as agreed by the principal investigator and sponsor's medical monitor. The PI/designee will treat AEs with appropriate concomitant medications if necessary.

9. STUDY ASSESSMENTS

9.1. Pharmacokinetic Assessments

Plasma levels of CDI-988 will be measured by liquid chromatography-mass spectrometry to determine the extent of systemic exposure and standard pharmacokinetic (PK) parameters (e.g., C_{max}, T_{max}, AUC, $t_{1/2}$) will be estimated. Plasma samples for PK assessments will be obtained as detailed in the Schedule of Events (see Section 2).

9.2. Safety Assessments

Safety evaluations will include physical examination, vital signs, electrocardiograms, clinical laboratory data, and collection of adverse events (see Section 9.3).

9.2.1. Physical Examination

Physical examinations will be conducted at the times indicated in the Schedule of Events (see Section 2).

Physical examination will include examination of general appearance, head, ears, eyes, nose, throat, neck (including thyroid), skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system.

Abbreviated exam will include at a minimum assessment of general appearance, head, nose, throat, respiratory system, and cardiovascular system.

9.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and body temperature, will be monitored according to the Schedule of Events (see Section 2).

9.2.3. Electrocardiograms

Triplicate 12-lead ECG(s) will be obtained as outlined in the Schedule of Events (see Section 2) using a digital ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

9.2.4. Clinical Laboratory Tests

Clinical laboratory tests will be performed at the times specified in the Schedule of Events (see Section 2). The following tests will be performed:

- Hematology: hemoglobin, hematocrit, erythrocyte count, mean cell volume, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, reticulocyte count
- Clinical chemistry: Serum concentrations of sodium, potassium, chloride, total bilirubin, indirect bilirubin (screening only), direct bilirubin (screening only), alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST),

urea, creatinine, uric acid, phosphorous, calcium, plasma glucose, total protein, albumin, cholesterol, creatinine kinase, creatinine clearance (screening only)

- Lipid panel: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, Non-HDL cholesterol, triglyceride, LDL/HDL ratio, cholesterol/HDL ratio
- Coagulation: prothrombin time, activated partial thromboplastin time, international normalized ratio
- Urinalysis: specific gravity, pH, protein, glucose, blood, nitrites, leukocyte esterase. Microscopy will be performed if abnormalities noted for protein, blood, or leukocytes, or if clinically indicated.

All clinical laboratory assessments will be analyzed at the participating site's local laboratory. Investigators must document their review of each laboratory report by signing or initialing and dating each report.

9.3. Adverse Events

9.3.1. Definition of Adverse Event

For purposes of this trial, an AE will be defined as **any** new unfavorable or unintended sign, symptom, or disease, or change of an existing condition, which occurs during or after treatment, whether or not considered treatment-related. If clinically significant laboratory values lead to or are associated with clinical symptoms(s), the diagnosis should be reported as an adverse event. Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

After informed consent and before treatment with study drug, study site personnel will note the occurrence and nature of each participant's medical condition(s) in the Medical History section of the CRF. During the remainder of the study, site personnel will again note any change in the condition(s) and the occurrence and nature of any adverse events.

If the study drug is discontinued for a participant, study site personnel must report and clearly document the circumstances and data leading to any such discontinuation, using designated case report forms. For adverse events, the participant should be followed until the event resolves or stabilizes, with frequency of follow-up at the discretion of the investigator.

In cases where the investigator notices an unanticipated benefit to the participant, study site personnel should enter "unexpected benefit" with the actual event term (for example, the complete actual term would be "unexpected benefit—sleeping longer").

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported for tracking purposes. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

9.3.2. Reporting Procedures for All Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and noting any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant. The investigator is responsible for appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, adverse events that are serious or that caused the participant to discontinue the study. The participant should be followed until the event is resolved or explained. Frequency of follow-up is left to the discretion of the investigator.

Adverse event information will be collected from the time of first dose of study drug through Day 8 (Part 1), Day 16 (Cohort 1C), Day 17 (Cohorts 2A -2C) and Day 12 (Cohorts 2D-2F). Participants who discontinue study drug at any time will have adverse events collected through the planned end-of-study visits, *provided consent to continue in the study has not been withdrawn*.

The investigator is responsible for assessing and recording all adverse experiences. Each AE will be recorded and classified for intensity, seriousness, and causality. All AEs either observed by the investigator or reported by the participant will be recorded regardless of causality. The investigator will follow the participant until an AE resolves or stabilizes.

9.3.3. Adverse Event Severity

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events version 2.1 (July 2017) will be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the DAIDS criteria, the following guidelines should be used to grade severity:

- Mild (grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Moderate (grade 2): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicate.
- Severe (grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- Life-threatening (grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

The term “severe” is a measure of intensity and a severe AE is not necessarily serious.

9.3.4. Adverse Event Relationship to Study Drug

The relationship of an AE to the study drug should be based on the judgment of the investigator and assessed using the following guidelines:

- Related: Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
- Probably related: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
- Possibly related: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
- Unrelated: An event that can be determined with certainty to have no relationship to the study drug.

9.3.5. Serious Adverse Event Definition and Reporting Procedures

Any AE that meets the definition of serious noted below and occurs in a participant during the course of the study must be reported to the sponsor by telephone within 24 hours of the investigator becoming aware of the event. In addition, a serious adverse event form (SAE) must be completed by the investigator and faxed to the study sponsor within 24 hours of the investigator becoming aware of the event. In addition, the site investigator must report SAEs to their local Ethics Committee (EC) in accordance with the EC's standard operating procedures and policies.

An SAE is defined as an adverse event that suggests a significant hazard or side effect, regardless of the relationship to study drug. An SAE includes, but may not be limited to, any event that:

- Results in death.
- Is life-threatening. This definition implies that the participant, in the view of the investigator, is at immediate risk of death from the event. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongs existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly or birth defect. This serious criterion applies if a participant exposed to an investigational product gives birth to a child with a congenital anomaly or birth defect.

Medical and scientific judgment will be exercised in deciding whether classification of an AE as serious is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or abuse.

Serious adverse events occurring after a participant is discontinued from the study will only be reported if the investigator believes that the event may have been caused by the study drug or a protocol procedure.

For the purpose of expedited reporting to regulatory agencies, an investigator will be responsible for identifying any adverse event that is serious, unexpected, and believed to be related to study drug. An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure or investigational drug application referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure or investigational drug application listed only "cerebral vascular accidents".

9.4. Safety Monitoring

A medically qualified person will monitor blinded safety data throughout the study. The sponsor (or designee) will review SAEs within time frames mandated by regulatory requirements and will review trends and adverse events at periodic intervals.

A Safety Monitoring Committee (SMC) comprising 3 members will review safety and available PK data prior to dose escalation to the next dose cohort in Parts 1 and 2. The SMC will be composed of the independent medical monitor, principal investigator, and sponsor's medical representative. Other members of the investigational team may join the SMC as non-voting attendees as deemed appropriate. Before dose escalation in the single-ascending dose and multiple-ascending dose cohorts, the SMC will review all available safety and tolerability data for a minimum of 7 participants who have completed the planned safety assessments at least 48 hours after dosing. The following data are required for interim study decisions: adverse events, vital signs, safety laboratory values, and ECGs.

Dose escalation will not occur with any of the following:

- a serious adverse reaction (i.e., a serious adverse event considered at least possibly related to the active drug) in one subject.

- Grade 3 or higher nonserious adverse reactions (i.e., severe nonserious adverse event considered related to the active drug administration) in two participants in the same cohort, independent of whether they occurred within the same system organ class.

The data will be reviewed blinded unless the SMC considers it necessary to unblind the data for safety concerns. Before breaking the code per standard procedures, the potential decisions and actions will be determined.

SMC decisions on whether dose escalation should proceed or planned dose levels should be adjusted will be taken in consensus between the SMC members. If consensus cannot be reached, the investigator, who has the ultimate responsibility for the safety of participants, will make the final decision on whether to continue or stop the study. The SMC's decisions and their rationale will be documented.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standard of Good Clinical Practice; and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The investigator must allow study-related monitoring, audits, and inspection by the EC, sponsor (or designee), government regulatory agencies, and, if applicable, University compliance and quality assurance groups of all trial-related documents and procedures.

The investigator shall prepare and maintain accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules, and regulations.

11. DATA ANALYSIS METHODS

11.1. Determination of Sample Size

No formal sample size calculation was done. Based on experience from previous similar studies, the target number of participants to be enrolled is appropriate for the assessment of safety and tolerability.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

The analysis of safety variables will include all participants who receive study drug.

All variables will be summarized by descriptive statistics for each treatment group. The statistics for continuous variables will include mean, median, standard deviation, and number of observations. Categorical variables will be tabulated using frequencies and percentages. Where confidence intervals are presented, they will be two-sided 95% confidence intervals.

11.2.2. Handling of Missing Data

Missing data will not be imputed for safety analyses.

11.2.3. Participant Disposition

Study participant disposition will be summarized by treatment group. Participants who discontinued study drug prematurely or withdrew from the study will be summarized and listed, with reason for early termination/withdrawal.

11.2.4. Participant Characteristics

Demographic and other baseline characteristics will be summarized by treatment group.

11.2.5. Treatment Compliance

As all study drug dosing is administered at the clinical unit, treatment compliance will be evaluated based on the dosing data recorded by the study personnel.

11.2.6. Pharmacokinetic Analyses

The following PK parameters will be estimated from serial plasma concentration data using noncompartmental analysis.

Single Dose: maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}), the elimination rate constant (λz) and half-life ($t_{1/2}$), area under the curve (AUC) to the last time with a concentration ≥ lower limit of quantitation [$AUC_{(0\text{-}t)}$] and to infinity [$AUC_{(inf)}$].

Multiple Dose (Cohorts 2A-2C): C_{max}, T_{max}, AUC over the 24-hour dosing interval [$AUC_{(0\text{-}24)}$] on Days 1 and 10, and the elimination rate constant (λz) and half-life ($t_{1/2}$) after the last dose on Day 10.

Multiple Dose (Cohort 2D): C_{max}, T_{max}, AUC over the 24-hour dosing interval [$AUC_{(0-24)}$] on Days 1 and 5, and the elimination rate constant (λz) and half-life ($t_{1/2}$) after the last dose on Day 5.

Multiple Dose (Cohorts 2E and 2F): C_{max}, T_{max}, AUC over the 12-hour dosing interval [$AUC_{(0-12)}$] on Days 1 and 5, and the elimination rate constant (λz) and half-life ($t_{1/2}$) after the last dose on Day 5.

All analyses will be done using the actual elapsed sampling times since dosing. Plasma concentrations and PK parameters will be summarized using descriptive statistics.

The PK parameters C_{max}, $AUC_{(0-t)}$, and $AUC_{(inf)}$ will be compared between the fed and fasted treatments for Cohorts 1C, 1E, and 1F using an analysis of variance (ANOVA) model with treatment as a fixed effect and subject as a random effect. The geometric mean ratios and associated 90% confidence intervals will be estimated from the statistical model and used to assess the effect of food.

The attainment of steady-state for each dose level in the MAD will be assessed by a comparison of the predose plasma concentrations over time using an ANOVA model with day as a fixed effect and subject as a random effect. Paired comparisons will be done to determine when steady-state has been reached.

Pharmacokinetic parameters will be compared among doses in the single-ascending dose and multiple-ascending dose phases and between phases using descriptive statistics and graphical displays. Relationships between C_{max} and the AUCs and dose for both phases will be assessed using the power model:

$$P = a \times Dose^{b}$$

where P represents the parameter and a and b are constants. A value of b of ~1 with a 95% confidence interval that includes 1 indicates linearity or dose proportionality. The power model will be fit to the individual subject data using nonlinear least squares regression, i.e., SAS PROC NLIN or equivalent.

11.2.7. Safety Analyses

Treatment-emergent AEs are defined as AEs occurring after the first dose of study drug through Day 8 in Part 1 (Day 16 in cohort 1C), Day 17 in Part 2 Cohorts 2A-2C, and Day 12 in Part 2 Cohorts 2D-2F. Duration of treatment will be summarized by treatment group.

The incidence of all reported AEs and treatment-related AEs will be tabulated by treatment group. Adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse events will be listed and summarized by treatment group, MedDRA preferred term, severity, seriousness, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one participant, the AE will be counted once as the worst occurrence. The incidence of AEs will be tabulated by system organ class and treatment group. AEs leading to premature discontinuation of study drug or withdrawal from the study will be summarized and listed in the same manner.

Summary statistics for actual values and for change from baseline will be summarized for laboratory results by treatment group and scheduled visit. Participants with laboratory values outside of the normal reference range at any postbaseline assessment will be identified.

Data to be listed by subject and summarized by treatment will include AEs, vital signs, ECG parameters, and clinical laboratory evaluations. All values outside the clinical reference ranges will be flagged on the data listings. Other data to be listed by subject will include physical examination findings and concomitant medications.

11.2.8. Interim Analyses

As described in Section 9.4, before dose escalation in the single-ascending dose and multiple-ascending dose cohorts, an SMC will review safety and available PK data to determine whether dose escalation may proceed.

12. ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

The investigator is responsible for presenting the risks and benefits of study participation to the participant in simple terms using the informed consent document. The investigator will ensure that written informed consent is obtained from each participant by obtaining the appropriate signatures and dates on the informed consent document before the performance of protocol evaluations or procedures.

12.1. Ethical Review

The investigator will obtain documentation of the EC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing EC are provided in the investigator file.

The sponsor will supply the following to the investigative site for submission to the EC:

- Protocol and amendments.
- Informed consent document and updates.
- Relevant curricula vitae, if required.
- Required safety and SAE reports.
- Any additional submissions required by the site's EC.

The investigator must provide the following documentation to the sponsor or its designee:

- The EC periodic (e.g., quarterly, annual) reapproval of the protocol.
- The EC approvals of any amendments to the protocol or revisions to the informed consent document.
- The EC receipt of safety and SAE reports, as appropriate.

12.2. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the 2013 version of the Declaration of Helsinki or the applicable guidelines on Good Clinical Practice, and all applicable federal, state, and local laws, rules, and regulations.

After reading the protocol, the investigator will sign the protocol signature page and return it to the sponsor or designee.

12.2.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators, and name and address of the research facility are included in the investigator file.

12.2.2. Protocol Amendments and Study Termination

The sponsor will initiate changes to the protocol as necessary (except for changes to eliminate an immediate hazard to a study participant) and seek approval by the EC before implementing. The investigator is responsible for enrolling participants who have met protocol eligibility criteria. Protocol violations must be reported to the local EC in accordance with EC policies.

The sponsor may terminate the study at any time. The EC must be advised in writing of study completion or early termination.

12.2.3. Study Documentation, Privacy, and Records Retention

All records connected with this clinical study will be retained for at least 2 years following the date of an approved marketing application or at least 3 years from the formal discontinuation of CDI-988 development; or 7 years from the end of the study, whichever is longer. All local laws regarding retention of records must also be followed. The study site is required to retain all records until written notification allowing destruction is received from Cocrystal Pharma Australia Pty Ltd.

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and participant medical records in the participant files as original source documents for the study. If requested, the investigator will provide the applicable regulatory agencies and applicable EC with direct access to original source documents.

Records containing participant medical information must be handled in accordance with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule or equivalent (e.g., Privacy Act of 1988) and consistent with the terms of the participant authorization contained in the informed consent document for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the informed consent document. Furthermore, CRFs and other documents should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of participant identities.

12.3. Study Finances

This study is financed by Cocrystal Pharma Australia Pty Ltd.

12.4. Publications

Cocrystal Pharma Australia Pty Ltd. assures that the key design elements of this protocol will be posted in a publicly accessible registry. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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14. DOCUMENT HISTORY

Document Version	Date	Summary of Changes
Version 6.0	04-Apr-2025	Section 14.9
Version 5.0	17-Dec-2024	Section 14.8
Version 4.2	24-Jul-2024	Section 14.7
Version 4.1	11-Jul-2024	Section 14.6
Version 4.0	12-Jun-2024	Section 14.5
Version 3.2	11-Jun-2024	Section 14.4
Version 3.1	29-Jan-2024	Section 14.3
Version 3.0	25-Jan-2024	Section 14.2
Version 2.0	05-Jul-2023	Section 14.1
Version 1.0	13-Apr-2023	NA

14.1. Summary of Changes from Version 1.0 to Version 2.0

Section	Change	Rationale
2 Schedule of Events	Specified window for pre-dose ECG to be within 2 hours in footnote 9 of schedules 2.1 and 2.3.	Correction to supply missing window.
	Changed windows for post-dose vital signs and ECGs from ± 10 minutes to ± 15 minutes	Provide operational flexibility.
	Specified that standard clinical safety labs may be collected fasted or non-fasted and changed the window for post-dose clinical safety labs from ±10 minutes to ± 1 hour.	Provide operational flexibility.
	Clarified that ECGs are taken only once when specified on non-dosing days.	Clarification.
	Changed MAD Day 10 lipid panel sample from post-dose to pre-dose and noted that subjects will be fasted prior to lipid panel samples.	Specify that lipid panel testing will be performed on fasted blood samples.
8.1 Treatments Administered	Changed the study drug dosage form from capsule to oral suspension that is prepared at site pharmacy from API CDI-988 powder or matching placebo and edited the dosing instructions accordingly.	Adjust dosing information to reflect the change in study drug formulation.

Section	Change	Rationale
9.4 Safety Monitoring	Changed the duration of assessments for dose-escalation review by the SMC from up to 48 hours after dosing to at least 48 hours after dosing.	Specify the minimum duration of safety follow-up required to support dose escalation between cohorts.

14.2. Summary of Changes from Version 2.0 to Version 3.0

Section	Change	Rationale
Synopsis, Section 2.1, Section 2.3, Section 6.1, Section 8.1.2, Section 8.1.3	Added an open-label food-effect cohort (Cohort 1E) consisting of subjects dosed with CDI-988 under fasted conditions on Day 1 and under fed (standard non-high fat meal) conditions on Day 9.	To evaluate the effect of a standard non-high fat meal on drug absorption to better inform the MAD part of the study.
Section 7.1.2	Corrected Exclusion Criteria 18, 19, and 20 to specify that blood pressure and heart rate measurements may be taken at screening or Day -1.	Correction for consistency with synopsis.

14.3. Summary of Changes from Version 3.0 to Version 3.1

Section	Change	Rationale
Section 7.1.2	Corrected Exclusion Criteria 18, 19, and 20 to specify that blood pressure and heart rate measurements may be taken at screening **or Day -1.**	Correction for consistency with synopsis.
Section 2.3	Added a footnote for Cohort 1E stating that a full eligibility review is required on Day 8 and an abbreviated review is sufficient for Day 9.	Clarification.
Section 2.4	Added a footnote stating that eligibility does not need to be re-reviewed between doses during the MAD part of the study.	Clarification.

14.4. Summary of Changes from Version 3.1 to Version 3.2

Section	Change	Rationale
Synopsis, Section 6.1 and Section 8.1	The protocol was updated to allow for up to 2 sites to participate.	Administrative change.
Appendix A and B	Protocol title was corrected.	Correction.

14.5. Summary of Changes from Version 3.2 to Version 4.0

Section	Change	Rationale
Synopsis, Section 4.2, Section 6.1, Section 8.1, Section 11	The study was updated to: • Add Cohort F (1200 mg CDI-988 under fasted conditions on Day 1 and under fed (standard non-high fat meal) conditions on Day 9 • To specify that study treatment during the MAD phase of the study will be under fed (standard non-high fat meal) conditions • Add nonclinical repeat dose toxicology data	The clinical safety data collected to date supports the study of a higher single dose.

14.6. Summary of Changes from Version 4.0 to Version 4.1

Section	Change	Rationale
Section 8.1.3	Detailed instructions on dose timing have been removed. These will instead be provided in the Pharmacy Manual.	To streamline the protocol.

14.7. Summary of Changes from Version 4.1 to Version 4.2

Section	Change	Rationale
Synopsis and Section 6.1	Specified that MAD Cohort 2a may start in parallel with the highest dose cohort in Part 1 and that a minimum of 6 participants must be dosed in a given cohort to allow dose escalation to proceed.	Clarification.
Synopsis, Section 6.1, and Section 8.1.2	Specified that MAD Cohort 2C may receive up to 1200 mg CDI-988	Update based on dose-escalation data from Part 1 of the study.
Section 2.4	The SOE for the MAD part of the study has been updated to reflect the PK sampling schedule and timing of safety lab draws,	Update based on dose-escalation data from Part 1 of the study.

14.8. Summary of Changes from Version 4.2 to Version 5.0

Section	Change	Rationale
Throughout	Minor grammatical and typographical changes made	Correction of grammatical errors
Synopsis, Section 4.2, Section 6.1, Section 8.1, Section 11	Added in Cohort 2D to receive a 1200mg dose for 5 days and Cohort 2C to receive up to 1200mg dose twice daily for 5 days	Updated based on the dose-escalation data from Part 2 Cohorts 2A-2C and the recommendation from the SMC

Section	Change	Rationale
Section 2.5	New SOE added for Cohort 2D	Updated based on the dose-escalation data from Part 2 Cohorts 2A-2C and the recommendation from the SMC
Section 2.6	New SOE added for Cohort 2E	Updated based on the dose-escalation data from Part 2 Cohorts 2A-2C and the recommendation from the SMC
Synopsis, Section 2.5, Section 2.6, Section 7.1.2	Clarificaition of vital sign positioning Clarification of timing of randomization Clarification of timing of assessments	Incorporation of protocol clarification letters 2, 3 and 4
Section 4.1	Updated statistics on SARS-CoV-2	Updated from 2022 to 2024 statistical data

14.1. Summary of Changes from Version 5.0 to Version 6.0

Section	Change	Rationale
Throughout	Minor grammatical and typographical changes made	Correction of grammatical errors
Synopsis, Section 4.2, Section 6.1, Section 8.1, Section 11	Added in Cohort 2F to receive a 1200mg dose given with a standard meal twice daily for 5 days	Updated based on the PK data from Part 2 Cohort 2E the recommendation from the SMC
Section 2.7	New SOE added for Cohort 2F	Updated based on the PK data from Part 2 Cohort 2E the recommendation from the SMC
Section 2.5, Section 2.6, Section 2.7	Clarification of timing of ECG assessments	Incorporation of protocol clarification letter 5

Appendix A
Sponsor Protocol Approval

Protocol Title: A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of Oral CDI-988 in Healthy Adult Participants

Protocol Number: CDI-988-P1-001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice and applicable regulatory requirements.

This study protocol has been approved by the following persons:

Signed: DocuSigned by: Sam Lee B21EFC094510472... Date: 4/2/2025

Sam Lee, PhD
President and Co-CEO
Cocrystal Pharma Australia Pty Ltd.

Appendix B
Investigator Protocol Signature Page

Protocol Title: A Phase 1, Randomized, Double-Blinded, Placebo-Controlled, First-in-Human Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of Oral CDI-988 in Healthy Adult Participants

Protocol Number: CDI-988-P1-001

By signing this protocol, the investigator agrees to conduct the study in accordance with the protocol, generally accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study. In addition, the investigator agrees to provide the sponsor with accurate financial information to allow the sponsor to submit complete and accurate certification and disclosure statements as required by federal regulations.

By signing this protocol, the investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written procedures to ensure that the trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the study.

Investigator's Signature	Print Name	Date

Site Address and Telephone