Protocol Number: CC-42344-P1-001

A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of the Influenza A Virus Replication Inhibitor CC-42344

Investigational Drug: CC-42344

Sponsor:
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1. PROTOCOL SYNOPSIS

Protocol Number: CC-42344-P1-001

Title: A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of the Influenza A Virus Replication Inhibitor CC-42344

Objectives

Part 1: Single-Ascending Dose

The primary objective of Part 1 is to assess the safety and tolerability of increasing doses of CC-42344 when given as a single oral dose to cohorts of healthy participants. Secondary objectives are to assess the pharmacokinetics (PK) of CC-42344 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 CC-42344 when administered orally to cohorts of healthy participants. A secondary objective is to assess the PK of CC-42344 when given as multiple oral doses to cohorts of healthy participants.

Study Design

This is a single-center, randomized, double-blind, placebo-controlled phase 1 study of the influenza A virus replication inhibitor CC-42344 given orally to healthy participants.

Part 1: Participants will be randomly assigned within each cohort to receive a single dose of CC-42344 or placebo. Doses will escalate in sequential dose cohorts. It is planned that 4 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo in each cohort). Each cohort in Part 1 will include the initial dosing of a sentinel group (1 CC-42344 and 1 placebo) at least 24 hours before dosing the remaining 6 subjects in the cohort (5 CC-42344 and 1 placebo). The remainder of the cohort will only be dosed if, in the opinion of the investigator, there is no significant safety concern identified in the sentinel subjects within the first 24 hours after administration of the dose (CC-42344 or placebo). The following regimens are planned:

- Cohort 1A (N=8): 100 mg CC-42344 or placebo.
- Cohort 1B (N=8): 200 mg CC-42344 or placebo.
- Cohort 1C (N=8): 400 mg CC-42344 or placebo on Days 1 and 9 (food effect).
- Cohort 1D (N=8): 800 mg CC-42344 or placebo.

Cohort 1C will be a two-period sequential food-effect cohort 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.

After the study was conducted, it was found that the Cohort 1C PK data were not interpretable due to issues with the execution of the assay for plasma CC-42344 levels at the contracted laboratory. Therefore, an additional cohort (Cohort 1C-2) will be enrolled to generate the 400 mg PK and food-effect data. This cohort will comprise 6 participants, all of whom will receive a single 400-mg dose of open-label CC-42344 on Day 1 under fasted conditions and a single 400-mg dose of open-label CC-42344 on Day 9 under fed conditions. The study entry criteria, activities, and assessments will be the same as those described for the main study.

Part 2: Participants will be randomly assigned to receive repeated oral doses of CC-42344 or placebo. Doses will escalate between sequential dose cohorts. It is planned that 3 cohorts will be dosed for 14 days and 2 additional cohorts will be dosed for 5 days, with 8 healthy participants per cohort (6 active and 2 placebo).

The following regimens are planned:

- Cohort 2A (N=8): 50 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2B (N=8): 100 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2C (N=8): 200 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2D (N=8): 400 mg CC-42344 or placebo once daily for 5 days.
- Cohort 2E (N=8): 400 mg CC-42344 or placebo twice daily for 5 days.

Summary of Participant Eligibility Criteria

Inclusion Criteria:

1. Healthy males or healthy, non-pregnant, non-lactating females aged 18 to 55 years.
2. Body weight of at least 50 kg.
3. Body mass index ≥18.0 and ≤32.0 kg/m^2. If outside this range, eligible at investigator's discretion.
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), vital signs, 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 study confinement.
6. Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test, if required and per site policy.
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, tubal ligation 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. 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, 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. Contraception requirements do not apply for participants in an exclusively same-sex relationship. Female participants should not donate eggs for 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 to no longer produce sperm - verbal confirmation through medical history review acceptable); 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. Males with pregnant partners may participate if they agree to use a barrier method of contraception.
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 any 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 2 years 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. Current regular smokers or users of e-cigarettes or nicotine replacement products are excluded. Social smokers who have had 3 or less tobacco- or nicotine-containing

products (including tobacco, e-cigarettes and marijuana) in the 3 months prior to first study drug administration are permitted if willing to abstain from smoking during the confinement period.

6. 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).
7. Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the investigator at screening.
8. Clinically significant abnormal biochemistry, hematology, coagulation, or urinalysis as judged by the investigator.
9. Positive alcohol breath test or urine test for drugs of abuse at screening or Day -1.
10. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance of <80 mL/min using the Cockcroft-Gault equation.
11. 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 results consistent with Gilbert's syndrome may be enrolled at the discretion of the investigator.
12. Positive test result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening.
13. Evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of dosing), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, renal, psychiatric, or neurological disease.
14. Acute illness (gastrointestinal, infection [e.g., influenza] or known inflammatory process) at screening or Day -1.
15. 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.
16. Supine resting bradycardia (pulse heart rate [HR] <40 bpm) or a supine resting tachycardia (HR >100 bpm) during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.

17. Hypertension, defined as a supine resting systolic blood pressure >140 mm Hg or a supine resting diastolic blood pressure >90 mm Hg during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.
18. Hypotension, defined as a supine resting systolic blood pressure <90 mm Hg or a supine resting diastolic blood pressure <40 mm Hg during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.
19. Known personal or family history of congenital long QT syndrome or known family history of sudden death.
20. Has donated blood or plasma within 30 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.
21. Taking, or have taken, any prescribed medication in the 14 days before dosing or over-the-counter drug, including herbal remedies, in the 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.
22. Failure to satisfy the investigator of fitness to participate for any other reason.

Investigational Drug

CC-42344

Study Drug Doses and Route of Administration

CC-42344 or placebo given orally. Study drug will be provided in capsule form. Part 1 will include single-ascending doses of CC-42344 100 mg, 200 mg, 400 mg, and 800 mg. The 400-mg food-effect cohort will receive a second dose on Day 9. Part 2 will include multiple doses of CC-42344 50 mg, 100 mg, and 200 mg once daily (QD) for 14 days, and 400 mg QD and 400 mg BID for 5 days.

Safety Assessments

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

Pharmacokinetic Assessment

Plasma CC-42344 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 up to 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.
  - 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, 32 healthy participants will be enrolled into 4 cohorts, each with 8 participants. An additional 6 participants will be enrolled into an open-label cohort to repeat the Part 1 PK and food-effect investigation with 400 mg.
- In Part 2, 24 healthy participants will be enrolled into 3 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 CC-42344 will be considered evaluable and will not be replaced.
- Planned number of sites: one (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						End of Study Visit[10]
	Day -28 to -1	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	X					
Demographic data	X							
Medical history	X	X	X					
Prior medication history	X	X						
Vein assessment	X							
Physical examination[1]	X	X			X (abbrev)		X (abbrev)	X (abbrev)
Height	X							
Weight	X	X						
12-lead ECG[2]	X	X	X		X	X	X	X
Vital signs[3]	X	X	X		X	X	X	X
Randomization			X					
Study Drug				X				
Adverse event reporting[4]				X	X	X	X	X
Concomitant medications			X			X	X	X
Alcohol breath test[11]	X	X						
Drugs of abuse screen	X	X						
Pregnancy screen[5]	X	X						X
FSH[6]	X							
Serology[7]	X							
Clinical Safety Labs[8]	X	X			X	X		X
Plasma CC-42344 levels[9]			X		X	X	X	
Discharge from Unit							X	

Footnotes

1 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.

2 Electrocardiogram will be taken in triplicate (a least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG once during screening, on Day -1, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±10 minutes after dosing, and 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.

3 Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature and will be collected prior to blood draws following a minimum 5-minute rest in a supine 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 ±10 minutes after dosing, and on Days 2, 3, and 8.

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

5 Females of childbearing potential will be screened for pregnancy. The screening pregnancy test will be by blood sample to detect the presence of β-hCG (collected as part of clinical chemistry sample). On Day -1 and at end of study, pregnancy will be determined by urine dipstick.

6 Only for women of postmenopausal status.

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

8 Standard clinical safety labs will be collected non-fasted.

9 PK samples to be collected before dosing (within 30 minutes) 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. Additional samples to be collected at 72 and 96 hours postdose for Cohorts 1C and 1D. Sampling windows are ±5 minutes for samples through 4 h postdose, ±10 minutes for samples at 6 and 8 h, ±30 minutes for samples from 12 to 48 h, and ±4 h for samples at 72 and 96 h. 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.

10 End of study visit for all cohorts except for the food-effect cohort, Cohort 1C. See Section 2.2 for schedule of events for days 8-16 for Cohort 1C.

11 Alcohol breath testing may be replaced with a question asking that participants confirm that they have refrained from any alcohol intake for the time period outlined in the protocol

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

	Clinical Unit						EOS Visit[9]
	Day 8	Day 9			Day 10	Day 11	Day 16
Assessments		**Pre-dose**	**Dosing**	**Post-dose**			**(+/-1 d)**
Unit Check-in	X						
Informed consent							
Inclusion/exclusion criteria	X	X					
Demographic data							
Medical history							
Prior medication history							
Vein assessment							
Physical examination[1]	X			X (abbrev)		X (abbrev)	X (abbrev)
Height							
Weight	X						
12-lead ECG [2]	X	X		X	X	X	X
Vital signs[3]	X	X		X	X	X	X
High-fat breakfast[4]		X					
Study Drug			X				
Adverse event reporting[5]	X	X	X	X	X	X	X
Concomitant medications	X	X			X	X	X
Alcohol breath test [10]	X						
Drugs of abuse screen	X						
Pregnancy screen[6]	X						X
Clinical Safety Labs[7]	X			X	X		X
Plasma CC-42344 levels[8]		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 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.

12 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 ±10 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.

13 Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature and will be collected prior to blood draws following a minimum 5-minute rest in a supine position. Vital signs will be measured on Day 8, on Day 9 prior to dosing (within 2 hours) and 2 and 4 hours ±10 minutes after dosing, and on Days 10, 11, and 16.

14 High-fat breakfast started and finished within 30 minutes prior to dosing.

15 Adverse event reporting will be continuous to end of study on Day 16.

16 On Day 8 and at end of study, pregnancy will be determined by urine dipstick.

17 Standard clinical safety labs will be collected non-fasted.

18 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, 48, 72, and 96 h after dosing. Sampling windows are ±5 minutes for samples through 4 h postdose, ±10 minutes for samples at 6 and 8 h, ±30 minutes for samples at 12 to 48 h, and ±4 h for samples at 72 and 96 h. 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.

19 End of study visit.

20 Alcohol breath testing may be replaced with a question asking that participants confirm that they have refrained from any alcohol intake for the time period outlined in the protocol

2.3. Part 2: Multiple-Ascending Dose Schedule of Events (Cohorts 2A, 2B, and 2C)

	Screening Day -28 to -1	Clinical Unit															EOS Visit [11] Day 21
		Day -1	Day 1			Day 2-4			Day 5-13			Day 14			Day 15-16 or ET	Day 17-18	
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																
Inclusion/ exclusion criteria	X	X	X														
Demographic data	X																
Medical history	X	X	X														
Prior medication history	X	X															
Vein assessment	X																
Physical examination [1]	X	X			X abbrev			X abbrev						X abbrev			X abbrev
Height	X																
Weight	X	X															
12-lead ECG [2]	X	X	X		X			X						X			
Vital signs [3]	X	X	X		X			X			X			X	X		X
Randomization			X														
Study Drug				X			X			X			X				
Adverse event reporting[4]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screen-ing Day -28 to -1	Clinical Unit														Day 17-18	EOS Visit [11] Day 21
		Day -1	Day 1			Day 2-4			Day 5-13			Day 14			Day 15-16 or ET		
Assessments			Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose			(+/-1 d)
Alcohol breath test [12]	X	X															
Drugs of abuse screen	X	X															
Pregnancy screen [5]	X	X															X
FSH [6]	X																
Serology[7]	X																
Clinical Safety Labs [8]	X	X			X			X			X			X			X
Plasma CC-42344 levels[9]			X [9]		X [9]	X [9]			X [9]			X [9]		X [9]	X [9]	X [9]	
Discharge[10]															X		

Footnotes

1 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.

2 Electrocardiogram will be taken in triplicate (a least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG during screening, on Day -1, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±10 minutes after dosing, and 2 hours ±10 minutes after dosing on Days 2-4 and Day 14. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.

3 Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature and will be collected prior to blood draws following a minimum 5-minute rest in a supine 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 ±10 minutes after dosing, on Days 2-16 and Day 21.

4 Adverse event reporting will be continuous to end of study on Day 21.

5 Females of childbearing potential will be screened for pregnancy. The screening pregnancy test will be by blood sample to detect the presence of β-hCG (collected as part of clinical chemistry sample). On Day -1 and at end of study, pregnancy will be determined by urine dipstick.

6 Only for women of postmenopausal status.

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

8 Standard clinical safety labs will be collected on Day -1, 1-4, 10, 14, and 21.

9 PK sampling to be conducted as follows:

- Day 1: before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h after dosing

- Days 2, 4, 8, 12, and 13: before dosing; note that the Day 2 predose sample serves as the Day 1 24-hour sample
- Day 14: before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, and 96 h after dosing

Sampling windows are within 1 hour predose, ±5 minutes for samples through 4 h post dose, ±10 minutes for samples at 6 and 8 h, and ±30 minutes for samples at 12 to 48 h, and ±4 h for samples at 72 and 96 h. 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.

10 Discharge from unit following assessment on Day 16 or early termination (ET).

11 End of study visit.

12 Alcohol breath testing may be replaced with a question asking that participants confirm that they have refrained from any alcohol intake for the time period outlined in the protocol

2.4. Part 2: Multiple-Ascending Dose Schedule of Events (Cohorts 2D and 2E)

	Screen-ing Day -28 to -1	Clinical Unit												EOS Visit [11] Day 12
		Day -1	Day 1			Day 2-4			Day 5			Day 6-7 or ET	Day 8-9	
Assessments			Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose	Pre-dose	Dosing	Post-Dose			(+/-1 d)
Check-in		X												
Informed consent	X													
Inclusion/ exclusion criteria	X	X	X											
Demographic data	X													
Medical history	X	X	X											
Prior medication history	X	X												
Vein assessment	X													
Physical examination [1]	X	X			X abbrev			X abbrev			X abbrev			X abbrev
Height	X													
Weight	X	X												
12-lead ECG [2]	X	X	X		X			X			X			
Vital signs [3]	X	X	X		X			X			X	X		X
Randomization			X											
Study Drug [13]				X			X			X				
Adverse event reporting[4]				X	X	X	X	X	X	X	X	X	X	X
Concomitant medications			X	X	X	X	X	X	X	X	X	X	X	X
Alcohol breath test [12]	X	X												

	Screen-ing Day -28 to -1	Clinical Unit											Day 8-9	EOS Visit [11] Day 12
		Day -1	Day 1			Day 2-4			Day 5			Day 6-7 or ET		
Assessments			**Pre-dose**	**Dosing**	**Post-Dose**	**Pre-dose**	**Dosing**	**Post-Dose**	**Pre-dose**	**Dosing**	**Post-Dose**			**(+/-1 d)**
Drugs of abuse screen	X	X												
Pregnancy screen [5]	X	X												X
FSH [6]	X													
Serology [7]	X													
Clinical Safety Labs [8]	X	X			X			X			X			X
Plasma CC-42344 levels [9]			X [9]		X [9]	X [9]			X [9]		X [9]	X [9]	X [9]	
Discharge [10]												X		

Footnotes

1 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.

2 Electrocardiogram will be taken in triplicate (a least 1 minute apart and with all 3 completed within 5 minutes) with 12-lead ECG during screening, on Day -1, on Day 1 pre-dose (within 2 hours) and 2 and 4 hours ±10 minutes after dosing, and 2 hours ±10 minutes after dosing on Days 2-5. ECGs will be measured prior to vital sign measurements with participants in a supine position after a minimum 5-minute rest.

3 Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature and will be collected prior to blood draws following a minimum 5-minute rest in a supine 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 ±10 minutes after dosing, on Days 2-7 and Day 12.

4 Adverse event reporting will be continuous to end of study on Day 12.

5 Females of childbearing potential will be screened for pregnancy. The screening pregnancy test will be by blood sample to detect the presence of β-hCG (collected as part of clinical chemistry sample). On Day -1 and at end of study, pregnancy will be determined by urine dipstick.

6 Only for women of postmenopausal status.

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

8 Standard clinical safety labs will be collected on Day -1, 1-5, and 12.

9 PK sampling to be conducted as follows:

- Cohort 2D (QD dosing)
  - Day 1: before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h after dosing.
  - Days 2, 4: before dosing; note that the Day 2 predose sample serves as the Day 1 24-hour sample
  - Day 5: before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, and 96 h after dosing

- Cohort 2E (BID dosing)
  - Day 1: before dose 1 at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 h after dose 1 (pre-dose 2); 12 hours after dose 2.
  - Days 2, 4: before each dose; note that the Day 2 pre-dose 1 sample serves as the Day 1 dose 2 12-hour sample
  - Day 5: before the final dose (administered the morning of Day 5), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, and 96 h after the final dose
- Sampling windows are within 30 minutes predose, ±5 minutes for samples through 4 h post dose, ±10 minutes for samples at 6 and 8 h, and ±30 minutes for samples at 12 to 48 h, and ±4 h for samples at 72 and 96 h. 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.

10 Discharge from unit following assessment on Day 7 or early termination (ET).

11 End of study visit.

12 Alcohol breath testing may be replaced with a question asking that participants confirm that they have refrained from any alcohol intake for the time period outlined in the protocol

13 Study drug to be administered beginning on Day 1 (Time 0) through Day 5 inclusive:

- Cohort 2D: every 24 hours (±30 minutes) for a total of 5 doses
- Cohort 2E: every 12 hours (±30 minutes) with the final dose the morning of Day 5 for a total of 9 doses

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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
BID	twice per day (bis in die)
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease 2019
CRF	case report form
DAIDS	Division of AIDS
EC	Ethics Committee
ECG	electrocardiogram
EOS	end of study
ET	early termination
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
QD	once a day (quaque die)
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDD	spray-dried dispersion
SMC	Safety Monitoring Committee
$t_{1/2}$	terminal elimination half-life
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal
λz	elimination rate constant

4. INTRODUCTION

4.1. Seasonal Influenza

Seasonal influenza is a global acute respiratory illness caused by influenza A or B viruses. Influenza A virus is the sole cause of influenza pandemics and is responsible for seasonal influenza epidemics in humans. Although usually a self-limited infection, influenza A can result in pneumonia, respiratory failure, and death, especially in persons at increased risk for influenza complications (such as very young, elderly, and those with comorbid conditions). The time from infection to illness (incubation period) is approximately 2 days but ranges from one to four days (World Health Organization 2021). Worldwide, influenza results in estimates of about 3 to 5 million cases of severe illness and up to 650,000 respiratory deaths annually (World Health Organization 2021).

Two classes of antiviral drugs are approved for the treatment of influenza: (1) the neuraminidase inhibitors (inhaled zanamivir, oral oseltamivir, and intravenous peramivir), which are active against both influenza A and B, and (2) the selective inhibitor of influenza cap-dependent endonuclease, oral baloxavir, which is active against influenza A and B. A third class of drugs, the adamantanes (amantadine and rimantadine), is only active against influenza A and is not recommended by the World Health Organization due to a marked increase in resistant isolates (World Health Organization 2021).

Antiviral treatment is recommended as soon as possible for any patient with suspected or confirmed influenza who is hospitalized; has severe, complicated, or progressive illness; or is at higher risk for influenza complications (US Centers for Disease Control and Prevention 2021). In contrast, consideration of early empiric antiviral treatment of non-high-risk outpatients with suspected influenza is recommended to be made based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset (US Centers for Disease Control and Prevention 2021). Antiviral therapy for influenza is considered underused in high-risk patients (World Health Organization 2021). Antiviral therapy for influenza can also be critical for the prevention of illness in household contacts of infected patients (Ikematsu et al., 2020).

Resistance, drug interactions, adverse events, timing of initiation of antiviral influenza therapy, route of administration, and duration of therapy are important considerations in choice of antiviral therapy for influenza (Uyeki et al., 2018). In particular, emergence of resistance can limit the therapeutic utility of anti-influenza treatments (Abed et al., 2021; Beigel and Hayden, 2020; Uehara et al., 2020).

4.2. CC-42344

CC-42344 is a novel oral, potent, and broad-spectrum anti-influenza A agent that targets the cap-binding PB2 domain of the viral polymerase, thereby blocking the viral replication cycle.

In vitro pharmacology studies demonstrated CC-42344 to be a potent and selective influenza A virus inhibitor with low nanomolar potency. It exhibits a high level of viral selectivity for influenza A and has no relevant in vitro inhibitory effects against native human DNA polymerases. In vitro studies with CC-42344 studies indicate that it has a high barrier to resistance. CC-42344 also exhibits synergism in combination with current influenza drugs. In vitro combination of CC-42344 with other anti-influenza or antiviral drugs for other indications showed synergism for influenza A activity. In addition, CC-42344 showed excellent anti-influenza activity against oseltamivir- and baloxavir-resistant influenza A H1N1. In a mouse model of influenza A infection, an oral formulation was tolerated without adverse effects and protected the infected mice from the virus-related pattern of body weight loss and improved their survival at doses ≥25 mg/kg/day.

CC-42344 demonstrated no- to low-level cytotoxicity across a range of proliferating and nonproliferating human cells, no signs of mitochondrial toxicity with proliferating HepG2 liver cells, and no off-target in vitro interactions at likely clinical concentrations. Safety pharmacology testing confirmed that the central nervous and respiratory systems in rats were unaffected, while some slight, non-adverse, and reversible decreases were observed in systolic blood pressure and heart rate in conscious dogs at single oral doses of 1000 mg/kg.

Metabolic profiling using hepatocytes detected 9 metabolites formed from CC-42344 across mouse, rat, dog, monkey, and human; a glucuronide metabolite was the most abundant. CC-42344 showed inhibitory potency in vitro towards all the major human cytochrome P-450 isoforms.

Safety assessments were conducted using rat and dog as the selected species based on coverage for human metabolites observed with hepatocytes. No adverse effects of CC-42344 were identified after single oral doses up to 1000 mg/kg. Repeated oral administration over 14 days identified the liver (hepatocellular cholestasis and necrosis with increased bilirubin and liver enzyme activities), kidneys (renal tubular degeneration with increased serum urea and decreased serum chloride), and meninges (mononuclear inflammation) as target organs associated with adverse effects. These adverse effects reversed after a 7-day recovery period apart from a single case of mononuclear inflammation in the meninges. The no-observed-adverse-effect level (NOAEL) was determined to be 70 mg/kg/day in the dog, the most sensitive species. CC-42344 was negative for mutagenicity in the bacterial reverse mutation assay and for structural chromosomal aberration in cultured Chinese hamster ovary cells, both with and without metabolic activation.

More detailed information about nonclinical and preclinical studies with CC-42344 can be found in the Investigator's Brochure.

4.3. Risk/Benefit Assessment

Anticipated risks of CC-42344 are low based on the mechanism of action and preclinical safety data that includes cytotoxicity and genotoxicity evaluations, safety pharmacology studies, and single- and repeated-dose toxicity studies in rat and dog. The risk-benefit balance for this study is considered favorable given the overall limited risks to study participants in this sequential-cohort dose-escalation study.

5. OBJECTIVES AND ENDPOINTS

Part 1: Single-Ascending Dose

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of increasing doses of CC-42344 when given as 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 CC-42344 following a single oral dose	• PK parameters: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(inf)}$, λz, $t_{1/2}$
• To explore the effect of food on the single oral dose PK of CC-42344	• Difference between fasted and fed conditions in systemic exposure to CC-42344: 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 CC-42344 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 CC-42344 when given as multiple oral doses	• PK parameters: C_{max}, T_{max}, $AUC_{(0-24)}$ on Days 1 and 14 and λz and $t_{1/2}$ after the last dose; predose concentrations on Days 2, 4, 8, 12, and 13.

6. INVESTIGATIONAL PLAN

6.1. Summary of Study Design

This is a single-center, randomized, double-blind, placebo-controlled phase 1 study of the influenza A virus replication inhibitor CC-42344 given orally to healthy participants at a single site in Australia. Participants will be recruited by Linear Clinical Research Ltd. Screening assessments must be done to determine participant eligibility. Written consent must be obtained before conducting any study procedures.

Part 1: Single-Ascending Dose

Participants will be randomly assigned within each cohort to receive a single dose of CC-42344 or placebo. Doses will escalate in sequential dose cohorts. It is planned that 4 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo in each cohort). Each cohort in Part 1 will include the initial dosing of a sentinel group (1 CC-42344 and 1 placebo) at least 24 hours before dosing the remaining 6 subjects in the cohort (5 CC-42344 and 1 placebo). The remainder of the cohort will only be dosed if, in the opinion of the investigator, there is no significant safety concern identified in the sentinel subjects within the first 24 hours after administration of the dose (CC-42344 or placebo). The following regimens are planned:

- Cohort 1A (N=8): 100 mg CC-42344 or placebo.
- Cohort 1B (N=8): 200 mg CC-42344 or placebo.
- Cohort 1C (N=8): 400 mg CC-42344 or placebo on Days 1 and 9 (food effect).
- Cohort 1D (N=8): 800 mg CC-42344 or placebo.

Cohort 1C will be a two-period sequential food-effect cohort 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.

After the study was conducted, it was found that the Cohort 1C PK data were not interpretable due to issues with the execution of the assay for plasma CC 42344 levels at the contracted laboratory. Therefore, an additional cohort (Cohort 1C-2) will be enrolled to generate the 400 mg PK and food-effect data. This cohort will comprise 6 participants, all of whom will receive a single 400-mg dose of open-label CC-42344 on Day 1 under fasted conditions and a single 400-mg dose of open-label CC-42344 on Day 9 under fed conditions. The study entry criteria, activities, and assessments will be the same as those described for the main study.

Additional dose cohort(s) may be added if all previous dosages are well tolerated and accumulated PK and safety data support the addition of higher dose(s).

Part 2: Multiple-Ascending Dose

Part 2 of the study may be opened after satisfactory review of the safety and PK data from the first dose in Cohort 1C.

Participants will be randomly assigned to receive once-daily oral doses of CC-42344 or placebo for 14 days. Doses will escalate between sequential dose cohorts. It is planned that up to 3 cohorts will be dosed with 8 healthy participants per cohort (6 active and 2 placebo).

The following regimens are planned:

- Cohort 2A: 50 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2B: 100 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2C: 200 mg CC-42344 or placebo once daily for 14 days.
- Cohort 2D: 400 mg CC-42344 or placebo once daily for 5 days.
- Cohort 2E: 400 mg CC-42344 or placebo twice daily for 5 days.

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 CC-42344 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 lowest NOAEL of 70 mg/kg/day from the rat and dog 14-day repeated dose GLP toxicology studies provides a human equivalent dose of 1894 mg to a 50-kg person. This corresponds to a 19X safety factor over the proposed Part 1 (single-ascending dose) starting dose of 100 mg and a 2.4X safety factor over the proposed maximum dose of 800 mg.

The doses initially selected for Part 2 (multiple-ascending dose)—50 mg, 100 mg, and 200 mg QD × 14 days—were supported based on the favorable safety profile of single doses of 100 to 800 mg in Part 1 of the study. In addition, at the NOAEL of 70 mg/kg in the 14-day dog study, the most sensitive species, the Day 14 C_{max} and $AUC_{(0-24)}$ were 8,475 ng/mL and 15,450 hr×ng/mL, respectively (mean of males and females). Based on the 200 mg single-dose cohort, and assuming an ~1.5-fold accumulation with QD dosing, the steady-state C_{max} and $AUC_{(0-24)}$ in humans for a 200 mg QD regimen are projected to be 1,410 ng/mL and 3,182 hr×ng/mL, respectively. This provides safety margins of ~6-fold and ~5-fold, respectively. The starting dose of 50 mg is anticipated to result in trough plasma concentrations well in excess of the CC-42344 EC_{90} (concentration resulting in 90% viral activity inhibition) based on modeling of the single-dose PK data.

The additional cohorts planned for Part 2 (multiple-ascending dose)—400 mg QD and 400 mg BID for 5 days—are supported based on the favorable safety profile seen with repeated dosing at up to 200 mg/day for 14 days and single doses of up to 800 mg in the current study. No significant accumulation was seen with QD dosing at up to 200 mg.

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.

Eligibility for enrollment 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 healthy, non-pregnant, non-lactating females aged 18 to 55 years.
2) Body weight of at least 50 kg.
3) Body mass index between ≥18.0 and ≤32.0 kg/m^2. If outside this range, eligible at investigator's discretion.
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), vital signs, 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 study confinement.
6) Negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test, if required and per site policy.
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, tubal ligation 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. 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, 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. Contraception requirements do not apply for participants in an exclusively same-sex relationship. Female participants should not donate eggs for 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 to no longer produce sperm - verbal confirmation through medical history review acceptable); 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. Males with pregnant partners may participate if they agree to use a barrier method of contraception.
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 any 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 2 years 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) Current regular smokers or users of e-cigarettes or nicotine replacement products are excluded. Social smokers who have had 3 or less tobacco- or nicotine-containing products (including tobacco, e-cigarettes and marijuana) in the 3 months prior to first study drug administration are permitted if willing to abstain from smoking during the confinement period.
6) 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) or is postmenopausal (had no menses for 12 months without an alternative medical cause and a serum FSH concentration ≥40 mIU/L).
7) Participants who do not have suitable veins for multiple venipunctures/cannulation as assessed by the investigator at screening.

8) Clinically significant abnormal biochemistry, hematology, coagulation, or urinalysis as judged by the investigator.
9) Positive alcohol breath test and/or urine test for drugs of abuse at screening or Day -1.
10) Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance of <80 mL/min using the Cockcroft-Gault equation.
11) 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 results consistent with Gilbert's syndrome may be enrolled at the discretion of the investigator.
12) Positive test result for hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening
13) Evidence or history of clinically significant allergic (except for untreated, asymptomatic, seasonal allergies at time of dosing), hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, renal, psychiatric, or neurological disease.
14) Acute illness (gastrointestinal, infection [e.g., influenza] or known inflammatory process) at screening or Day -1.
15) 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.
16) Supine resting bradycardia (pulse heart rate [HR] <40 bpm) or a supine resting tachycardia (HR >100 bpm) during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.
17) Hypertension, defined as a supine resting systolic blood pressure >140 mm Hg or a supine resting diastolic blood pressure >90 mm Hg during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.
18) Hypotension, defined as a supine resting systolic blood pressure <90 mm Hg or a supine resting diastolic blood pressure <40 mm Hg during vital sign measurements at screening or Day -1. Vital sign measurements may be repeated at the investigator's discretion.
19) Known personal or family history of congenital long QT syndrome or known family history of sudden death.
20) Has donated blood or plasma within 30 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.

21) Taking, or have taken, any prescribed medication in the 14 days before dosing or over-the-counter drug, including herbal remedies, in the 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.
22) 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 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.

Participants who discontinue study drug prematurely should continue to have the planned study assessments unless consent to do so is 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, if available, must be recorded in the participant's case report form (CRF). An early termination visit will be conducted unless consent to do so is withdrawn.

7.2.3. Participant Replacement

In both Parts 1 and 2, up to 2 replacement participants may be enrolled per cohort. An exception is participants withdrawn due to an adverse event related to CC-42344, who will be considered evaluable and will not be replaced.

The PK data from the additional participants enrolled in Cohort 1C-2 will replace the uninterpretable PK data from Cohort 1C; however, the safety data from both Cohorts 1C and 1C-2 will be analyzed and included in the clinical study report.

8. TREATMENTS

8.1. Participant Assignment

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

8.2. Method of Assignment to Treatment

In both parts of this study, participants will be assigned a screening number and randomized to receive CC-42344 or placebo prior to dosing. CC-42344 dosage is determined based on cohort assignment. A participant is considered randomized after they are confirmed as eligible for dosing and when a pharmacy personnel or designee assigns a randomization number/treatment allocation.

8.3. Materials and Supplies

8.3.1. Formulation, Packaging, and Labeling

Study drug (CC-42344 or matching placebo) will be administered orally to the participant in capsule form (Shanghai STA Pharmaceutical Product Co., Ltd, Shanghai, China) through the site pharmacy.

The active drug product is manufactured using spray-dried dispersion (SDD) of CC-42344 and hydroxypropyl methylcellulose acetate succinate. The SDD will be filled into capsules, using excipients such as mannitol, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate (or other excipients commonly used in capsule formulations).

The drug product is a 50-mg dose strength capsule with visually matching placebo. The capsules are packaged in 30-count bottles. Study drug treatment by cohort is summarized in Table 1 and Table 2. See the Pharmacy Manual for additional information.

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

Cohort	Study Drug	No. Capsules	Frequency
1A	CC-42344 (50 mg/capsule) or placebo	2	Single dose on Day 1
1B	CC-42344 (50 mg/capsule) or placebo	4	Single dose on Day 1
1C	CC-42344 (50 mg/capsule) or placebo	8/dose	Single doses on Days 1 and 9
1D	CC-42344 (50 mg/capsule) or placebo	16	Single dose on Day 1
1C-2	CC-42344 (50 mg/capsule) open label	8/dose	Single doses on Days 1 and 9

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

Cohort	Study Drug	No. Capsules	Frequency
2A	CC-42344 (50 mg/capsule) or placebo	1/dose	Once daily on Days 1 through 14
2B	CC-42344 (50 mg/capsule) or placebo	2/dose	Once daily on Days 1 through 14
2C	CC-42344 (50 mg/capsule) or placebo	4/dose	Once daily on Days 1 through 14
2D	CC-42344 (50 mg/capsule) or placebo	8/dose	Once daily on Days 1 through 5
2E	CC-42344 (50 mg/capsule) or placebo	8/dose	Twice daily on Days 1 through 5 [A]

A. Final dose the morning of Day 5 (9 planned doses total)

8.3.2. Storage and Handling

The study drug will be stored at 2ºC to 8ºC (35.6ºF to 46.4ºF). No other special handling is required.

8.3.3. 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 on site with permission of the sponsor.

8.4. Dosage Administration

The investigator (or designee) will administer a single dose of study drug in Part 1 (2 doses in Cohort 1C), every day for 14 days in Part 2, Cohorts 2A-2C, every day for 5 days in Cohort 2D, and twice per day for 5 days in Cohort 2E (last dose the morning of Day 5).

Part 1, Cohorts 1A-1D Day 1 dosing: Administer oral study drug in a fasted state (at least 8 hours of fasting). Study drug will be given with a 240 mL glass of water. Additional water (up to a total of 480 mL) may be given if needed to ingest all of the capsules in the dose. Dosing should be completed within 5 minutes of ingesting the first capsule. Subjects are required to fast for 4 hours postdose. 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. The breakfast must be started and finished within 30 minutes prior to dosing. Postdose, 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 standardized breakfast. The breakfast must be started and finished within 30 minutes prior to dosing. Postdose, subjects are required to fast for 4 hours and are not allowed fluids for 2 hours.

Part 2, Cohort 2E (BID dosing): Study drug will be administered within 30 minutes after ingesting a standardized breakfast (morning dose) or snack (evening dose). The breakfast or snack must be started and finished within 30 minutes prior to dosing. Postdose, subjects are required to fast for 4 hours and are not allowed fluids for 2 hours. The final dose will be given the morning of the last day of dosing (Day 5).

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.

8.5. 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 (CC-42344 or placebo) is being administered during the treatment period. Placebo and active drug will be the same in appearance, taste, 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. All data will be reviewed blinded by the 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. Emergency unblinding for AEs may be used only if a participant's medical care requires knowledge of the participant's treatment assignment. The investigator should make every effort to contact the sponsor before unblinding a participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor must be immediately notified. In this situation, the sponsor's medical monitor may also become unblinded to the participant's treatment assignment.

In the additional cohort (1C-2) being enrolled to repeat the 400 mg PK and food effect data, no placebo group will be required, thus CC-42344 will be administered in an open-label manner with no blinding or randomization.

8.6. Concomitant Therapy

No concomitant medications are allowed except for vitamins, minerals, 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.

9. STUDY ASSESSMENTS

9.1. Pharmacokinetic Assessments

Plasma levels of CC-42344 will be measured by LC-MS/MS to determine the extent of systemic exposure and standard pharmacokinetic (PK) parameters (such as C_{max}, T_{max}, AUC, and $t_{1/2}$) 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 oral temperature, will be monitored in a supine position after a 5-minute rest period according to the Schedule of Events (see Section 2).

9.2.3. Electrocardiograms

Triplicate 12-lead ECG(s) will be obtained with participants in a supine position 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. There will be a 5-minute rest period before commencing ECGs and at least 1 minute between triplicate measurements with all 3 completed within 5 minutes.

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, white blood cell count, 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)
- 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
- Serology: hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus
- Reproduction (females only): serum β-hCG or FSH (screening) and urine hCG (females of child-bearing potential)

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. A clinically significant laboratory value 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 and method of follow-up are left to the discretion of the investigator and site policy.

Adverse event information will be collected through Day 8 (Part 1), Day 16 (Cohort 1C), and Day 21 (Part 2). Participants who discontinue study drug at any time will have adverse events collected through the planned end of study visit, *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 or designee and faxed to the study sponsor within 24 hours of the investigator becoming aware of the event. In addition, the site investigator or designee 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, as well as between the fasted and fed periods in Part 1, Cohort C. 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 up to 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.
- 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 dose escalation will be taken in consensus between the SMC members. If consensus cannot be reached, the principal 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, including participants in the additional 400 mg food-effect cohort (Cohort 1C-2).

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 CC-42344 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 (LLOQ) [$AUC_{(0\text{-}t)}$] and to infinity [$AUC_{(inf)}$].

Multiple Dose: C_{max}, T_{max}, AUC over the 24-hour dosing interval [$AUC_{(0\text{-}24)}$] on Days 1 and 14, and the elimination rate constant (λz) and half-life ($t_{1/2}$) after the last dose on Day 14.

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

The PK parameters C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(inf)}$ will be compared between the fed and fasted cohorts 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 multiple-ascending dose phase will be assessed by a comparison of the predose plasma concentrations obtained as indicated in the Schedule of Events (see Sections 2.3 and 2.4) 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) and Day 21 (Day 12 in Cohorts 2D and 2E) in Part 2. 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 CC-42344 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.

13. REFERENCES

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14. DOCUMENT HISTORY

Document Version	Date
Version 5.0	17-Dec-2022
Version 4.0	12-Dec-2022
Version 3.0	18-Jun-2022
Version 2.0	17-Jan-2022
Version 1.1	21-Sep-2021
Version 1.0	26-Aug-2021

14.1. Summary of Changes from Version 4.0 to Version 5.0

Section	Change	Rationale
6.1 Summary of Study Design Synopsis Table 2	Added Cohorts 2D and 2E to the multiple-ascending dose (MAD) portion of the study.	Obtain safety and PK data for 400 mg QD and BID dosing of CC-42344 for 5 days to explore additional dosing regimens.
2 Schedule of Events	Added Section 2.4 to define the schedule of events for Cohorts 2D and 2E.	Added additional schedule of events to accommodate the shorter length of treatment for MAD cohorts 2D and 2E (5 days versus 14 days in the initial MAD cohorts). The general scheme for assessments is the same.
6.2 Dose Rationale	Added text supporting 400 mg QD and BID dose regimens.	Provide rationale for additional MAD cohorts (2D and 2E).
8.4 Dosage Administration	Added instructions for BID dosing.	Provide required operational information.
11.2 Statistical and Analytical Plans	Edited to reflect the additional cohorts to be included in the analyses.	Clarity and consistency.

14.2. Summary of Changes from Version 3.0 to Version 4.0

Section	Change	Rationale
6.1 Summary of Study Design Synopsis	Added Cohort 1C-2, an additional cohort to generate replacement 400 mg PK and food-effect data. Six participants will be treated with CC-42344 in a 2-period food design.	Obtain required PK data.
7.2.3 Participant Replacement 11.2 Statistical and Analytical Plans	Stated that the Cohort 1C-2 participants' PK data will replace the uninterpretable PK data from Cohort 1C, however the safety data from both cohorts will be included in the analyses.	Define plans for use of data from addition participants; confirm that safety analyses will include all participants treated with CC-42344.
8.5 Blinding and Unblinding	Noted that CC-42344 will be administered in an open-label manner in Cohort 1C-2.	Specify that treatment assignment will not be blinded in the additional cohort.

14.3. Summary of Changes from Version 2.0 to Version 3.0

Section	Change	Rationale
2 Schedule of Events	Optional replacement of alcohol breath testing with a question confirming abstinence	Mitigate risk of COVID-19 in the study clinic, as initially specified in Protocol Clarification Letter 3, dated 21-Feb-22
2 Schedule of Events	Add 72- and 96- hour postdose PK sample for Cohorts 1C and 1D	Better define the terminal elimination half-life, as initially specified in Protocol Clarification Letter 4, dated 24-Mar-22
2.2 Part 1 Cohort 1C Schedule of Events – Period 2	Allow optional extension of washout period between fasted and fed periods in Cohort 1C	Provide operational flexibility, as initially specified in Protocol Clarification Letter 2, dated 04-Feb-22
2.3 Part 2: Multiple-Ascending Dose Schedule of Events	Added specific PK sampling timepoints for Part 2	Provide PK data to support analysis of the multidose PK profile
6.1 Summary of Study Design (and Synopsis)	Changed the planned dose cohorts for the multiple-ascending dose part of the study (Part 2) from 200, 400, and 600 mg QD to 50, 100, and 200 mg QD	Favorable safety profile in Part 1, with PK data supporting predicted trough concentrations above the EC_{90} at the 50-mg QD dose level
6.2 Discussion of Design	Added text regarding the safety of the dose levels planned for Part 2 of the study	Provide rationale for dosing regimens for the multiple-ascending dose cohorts
7.1.2 Exclusion Criteria (and Synopsis)	Criterion 2: Change the allowable length of time between COVID-19 vaccination and randomization from 2 weeks to 7 days and expand the exclusion to cover all vaccines	Relax the COVID-19 vaccination timeframe, as initially specified in Protocol Clarification Letter 3, dated 21-Feb-22; include all vaccines for consistency
8.3.1 Formulation, Packaging, and Labeling	Adjust the number of capsules per dose in Part 2 to match the planned dose levels	Consistency with updated dose levels
8.4 Dosage Administration	Added instructions for a standardized breakfast prior to dosing	Specify controlled predose food intake
General	Editorial, formatting, and/or administrative corrections	Accuracy and consistency

14.4. Summary of Changes from Version 1.1 to Version 2.0

Section	Change	Rationale
2 Schedule of Events	Changed the window for the End of Study Visit from +1 day to +/-1 day for all cohorts	Provide operational flexibility
2.2 Part 1 Cohort 1C Schedule of Events – Period 2	Changed the windows for predose assessments in the fed period of the food effect cohort (Cohort 1C, Day 9): • ECGs and vital sign windows from 30 minutes to 2 hours pre-dose • PK blood draw window from 30 minutes to 1 hour pre-dose	 • Make consistent with other cohorts • Allow time for the completion of a high-fat breakfast prior to dosing
7.1.1 Inclusion Criteria	Changed the upper limit of BMI in inclusion criterion 3 from 30.0 to 32.0 kg/m^2	Correction for consistency with the synopsis
7.1.2 Exclusion Criteria	Changed the required negative pregnancy test in exclusion criterion 6 from Day 1 to Day -1 Changed exclusion criterion 11 by adding the underlined text: Participants with <u>results consistent with</u> Gilbert's syndrome may be enrolled at the discretion of the investigator.	Correction for consistency with the schedule of events Clarification
8.3.1 Formulation, Packaging, and Labeling	Changed the CC-42344 spray-dried dispersion drug product form from 100-mg tablets to 50-mg capsules Updated the number of capsules per dose in Tables 1 and 2	Update drug product information with the planned dose form and strength
8.3.2 Storage and Handling	Changed the storage temperature from 20ºC–25ºC to 2ºC–8ºC	Reflect the actual planned storage temperatures
8.4 Dosage Administration	Added text: Additional water (up to a total of 480 mL) may be given if needed to ingest all of the capsules in the dose. Dosing should be completed within 5 minutes of ingesting the first capsule.	Provide additional details regarding dosing procedures
9.2.4 Clinical Laboratory Tests	Added white blood cell count to the list of required clinical laboratory tests	Correct oversight
9.4 Safety Monitoring	Added the stopping rules that are presented in the synopsis: 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.	Consistency and completeness

Section	Change	Rationale
	• 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.	
1 Protocol Synopsis	Updated to reflect changes noted above	Provide consistency
General	Editorial, formatting, and/or administrative corrections	Accuracy and consistency

14.5. Summary of Changes from Version 1.0 to Version 1.1

Section	Change	Rationale
6.2 Discussion of Design	Changed the dose rationale as follows: The lowest NOAEL of 70 mg/kg/day from the rat and dog 14-day repeated dose GLP toxicology studies provides a human equivalent dose of ~~2333~~ 1894 mg to a ~~60~~ 50-kg person. This corresponds to a ~~23~~19X safety factor over the proposed starting dose of 100 mg and a ~~2.9~~2.4X safety factor over the proposed maximum dose of 800 mg.	Provide the exposure multiples for a 50-kg person, in alignment with the study inclusion criteria.
14 Document History	Added document history and list of changes.	Provide summary and rationale for changes to approved versions of the protocol.

Appendix A: Sponsor Protocol Approval

Protocol Title:	A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of the Influenza A Virus Replication Inhibitor CC-42344
Protocol Number:	CC-42344-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:

Sam Lee

12/18/2022

Sam Lee, PhD
President and Interim Co-Chief Executive Officer
Cocrystal Pharma Australia Pty Ltd.

Date

Appendix B: Investigator Protocol Signature Page

Protocol Title:	A Phase 1 Study in Healthy Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single-Ascending and Multiple-Ascending Doses of the Influenza A Virus Replication Inhibitor CC-42344
Protocol Number:	CC-42344-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