A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, SINGLE AND MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	PF-07612577
Study Intervention Name:	PF-06264006 (CTB) & PF-07338233 (AVP)
US IND Number:	NA
EudraCT Number:	2021-005428-39
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4691001
Phase:	1

Brief Title: A Phase 1 Single and Multiple-Dose Study of PF-07612577 (PF-06264006 [CTB] + PF 07338233 [AVP]) in Healthy Adult Participants

Document History

Document	Version Date
Amendment 1	06 September 2022
Original protocol	18 July 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any global protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (06 September 2022)

Overall Rationale for the Amendment: Changes to original protocol, based on regulatory feedback received from Belgian Health Authority.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.3. Justification for Dose and Section 1.2. Schema	Lowered starting dose regimen in Cohort 2 to 400 mg CTB + 900/1350 mg AVP.	Recent PK/PD modeling and simulation suggest that 400 mg CTB and 1350 mg AVP TID doses are likely to achieve the PK/PD target. Therefore, reduced starting dose for CTB in DR1, consistent with Belgian Health Authority feedback.	Substantial
Section 6.6.1. Dose Escalation and Stopping Rules	Added stopping criteria for CTB: CTB C_{max} >100 µg/mL (estimated CTB C_{max} at NOAEL in the 1-month rat toxicology study).	Stopping criteria for CTB C_{max} added, based on Belgian Health Authority feedback.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1. Synopsis, Section 4.1. Overall Design, and Section 9.5. Sample Size Determination	Added optional Cohort 4 (planned to enroll 8 participants who are to receive DR3). Updated the Cohort number of optional Japanese and Chinese Cohorts to Cohort 5 and 6, respectively. Increased total number of participants from 36 to 44.	Additional optional cohort in PART-2 to allow for evaluation up to 1200 mg CTB if needed.	Substantial
Section 1.3. Schedule of Activities, Table 2	Added assessments on Day 3 PART-2: • 12-lead ECG (triplicate) • Vital signs (BP and pulse rate) • Safety laboratory assessments • urinalysis	Additional safety assessments added at Day 3 after steady state achieved to monitor for adverse events, laboratory values, vitals and ECG assessment.	Substantial
Section 1.3. Schedule of Activities, Table 1	Removed ECG assessment at Day -1 in PART-1.	Day 1 time 0 ECG assessment will serve as baseline assessment.	Substantial
Section 1.3. Schedule of Activities, Tables 1 and 2, and Section 10.22. Appendix 2: Clinical Laboratory Tests, Table 13.	Cystatin C: removed note that it is performed on Day -1 only or at Screening.	Local practice updated to perform Cystatin C with all safety labs.	Substantial
Section 10.22. Appendix 2: Clinical Laboratory Tests, Table 13.	Removed eCrCl	Kidney function assessment is already monitored with eGFR (CKD-EPI) and cystatin.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 4.1. Overall Design	Added statement: "Except D1 in PART-1 and DR1 in" PART-2 of the study, the dose levels, frequency of administration, and/or meal condition may be changed based on emerging PK, safety, and tolerability data.	Clarification that Dose 1 and DR1 have fixed doses, all other doses can change after review of new data from prior doses/dose regimens.	Substantial
Section 4.1. Overall Design	Added statement: If the AVP dose CCI mg with CCI mg CTB needs to be evaluated, then the CTB CCI mg CCI will not be evaluated in CCI	Clarification that Period 5 can be either 1200 mg CTB + 1800 AVP or 1600 mg CTB alone.	Substantial
Section 1.2. Schema	Updated Figure 1. C4691001 Study Design and footnotes.	Updated study design to match proposed changes in DR1 (lowered starting CTB dose) and addition of optional Cohort 4 for evaluation of DR3, if needed.	Substantial
Section 8.1 Administrative and Baseline Procedures	Updated blood sampling volume to 291 ml in PART-2.	Additional blood volume needed due to safety lab assessment added on Day 3 in PART-2.	Substantial
Section 1.3. Schedule of Activities, Table 1	The time point of 14 hours post dose was updated to be included in Day 1 instead of Day 2.	To correct a formatting error.	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3. Schedule of Activities, Tables 1 and 2	COVID-19 Questionnaire: clarified in notes that assessment to be done as per local practice. Removed "at least 48 hours before Day 1 or."	Allowed for flexibility when assessment is done as it will depend on local practice.	Nonsubstantial
Section 1.3. Schedule of Activities, Tables 1 and 2	Clarified that PE is to be done at Screening or Day -1 in Period 1 only in PART-1 and at Screening or Day -1 in PART-2.	Clarification.	Nonsubstantial
Section 1.3. Schedule of Activities, Table 1	Clarified that Pregnancy test (β -hCG) WOCBP only is to be conducted at Day -1 Period 1 and Day 2 last period.	Clarification.	Nonsubstantial
Section 1.3. Schedule of Activities, Table 1 and 2	COVID 19 testing: to be done as per local practice.	Updated to state testing will be performed as per local practice to allow for flexibility	Nonsubstantial
Section 1.1. Synopsis and Section 5.2. Exclusion Criteria	Exclusion criteria: removed 2 examples of COVID-19 risks.	Given widespread prevalence of COVID-19 geographical location, either residence or site of travel as risk factors, were removed.	Nonsubstantial
Section 11. References	Updated reference #28: Original text: Investigator's Brochure, PF-07612577. 26 Oct 2021. Updated text: Investigator's Brochure, PF-07612577. Version 2.0. July 2022.	Provided updated reference since the IB V2.0 was updated 22-Jul-2022 following protocol approval.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Double-Blind, Sponsor-Open, Placebo-Controlled, Single and Multiple-Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetics of PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) in Healthy Adult Participants

Brief Title: A Phase 1 Single and Multiple-Dose Study of PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) in Healthy Adult Participants

Regulatory Agency Identification Number(s):

US IND Number:	NA
EudraCT Number:	2021-005428-39
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C4691001
Phase:	1

Rationale: The current study is a Phase 1 study of PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) in approximately 44 healthy adult participants. It is a 2-PART study combining PART-1: Single dose PK, safety and tolerability of various CTB doses alone or when coadministered with AVP, and PART-2: Multiple dose PK, safety and tolerability of CTB + AVP coadministered, including optional Japanese and Chinese cohorts.

Objectives and Endpoints:

PART-1: Single Dose

Objectives	Endpoints
Primary:	**Primary:**
To assess the plasma PK profile of CTB following a single dose of CTB alone or in combination with AVP.	Plasma PK parameters of cis-CTB: ▪ C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn). ▪ If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.
To assess the plasma PK profile of AVP following administration with single doses of CTB in combination with AVP.	Plasma PK parameters of AVP, AVI and HPA: ▪ C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn). ▪ If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.

Objectives	Endpoints
To assess the safety and tolerability following a single dose of CTB alone or in combination with AVP.	▪ Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. ▪ Frequency and magnitude of abnormal laboratory findings. ▪ Changes from baseline in vital sign measurements and 12-lead ECG parameters.

PART-2: Multiple Dose (including optional Japanese and Chinese Cohorts)

Objectives	Endpoints
Primary:	**Primary:**
To assess the plasma PK profile of cis-CTB and trans-CTB[a] following multiple doses of CTB in combination with AVP.	Plasma PK parameters of cis-CTB and trans-CTB[a] on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state): ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn). ▪ If data permit, $t_{½}$, V_z/F, and CL/F.
To assess the plasma PK profile of AVP following multiple doses of CTB in combination with AVP.	Plasma PK parameters of AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state): ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn) ▪ If data permit, $t_{½}$, V_z/F, and CL/F.
To assess the safety and tolerability following multiple doses of CTB in combination with AVP.	▪ Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. ▪ Frequency and magnitude of abnormal laboratory findings. ▪ Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary:	**Secondary:**
To assess the urinary PK[b] profile of cis-CTB, trans-CTB[a], AVP, AVI and HPA on Day 6 following multiple doses of CTB in combination with AVP.	cis-CTB, trans-CTB[a], AVP, AVI and HPA urinary PK parameters (if data permit): ▪ Ae_{tau} and Ae_{tau}%, CL_r.
To assess PK profile of CTB and AVP when administered in combination in Japanese and Chinese participants.	Plasma PK parameters of cis-CTB, AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state) in Japanese and Chinese cohorts: ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn). ▪ If data permit, $t_{½}$, V_z/F, and CL/F.

a. trans-CTB will be measured only on Day 1, Day 6, and Day 7 in Cohort 2 PART-2.
b. cis-CTB, trans-CTB, AVP, AVI and HPA in urine will be measured on Day 6 only in Cohort 2, PART-2.

Overall Design:

This study will consist of PART-1: Single dose and PART-2: Multiple dose, including optional Japanese and Chinese cohorts. PART-1 and PART-2 are randomized, double-blind (participant and investigator blinded and sponsor open) cohorts.

PART-1: Single Dose

PART-1 will include 1 cohort and up to 5 periods with approximately 8 participants in total. This part will have a randomized, double-blind (sponsor-open), 5-period, sequential single dose design. Periods 4 and 5 are optional and may be used to further explore PK at additional doses, based on emerging PK data. In each period, approximately 6 participants will receive a single oral dose of CTB or CTB and AVP combined, and approximately 2 participants will receive the matching placebo under fed state. Each participant may receive either a single dose of CTB, CTB and AVP combined, or matching placebo during each period. In each period, participants on active treatment will receive D1, D2, D3, D4 (optional), or D5 (optional) dose levels, respectively. There will be a washout interval of a minimum of 3 days between doses for a given participant. Participants will be required to stay at the CRU for the duration of the washout interval.

PART-2: Multiple Dose

PART-2 will include up to 5 cohorts, ie, Cohort 2, and up to 4 optional cohorts including optional Cohort 5 (Japanese Cohort) and optional Cohort 6 (Chinese Cohort) with approximately 8 participants each in Cohorts 2, 3 and 4, and six participants each in Cohorts 5 and 6, and up to approximately 36 participants planned in total. This part will have a randomized, double-blind (sponsor-open), sequential multiple-dose design. In Cohorts 2,3 and 4, approximately 6 participants will receive 1 of the dose regimens of CTB and AVP combined, and approximately 2 participants will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted). In Cohorts 5 and 6, approximately 5 participants will receive 1 of the dose regimens of CTB and AVP combined and approximately 1 participant will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted.) From Day 1 to Day 7, CTB and AVP combined or the matching placebo will be administered q8h (ie, TID), with the dose regimen of DR1 (for Cohort 2), DR2 (for optional Cohort 3), DR3 (for optional cohort 4) and either DR1, DR2 or DR3 (for Cohort 5, optional Japanese Cohort and Cohort 6, optional Chinese Cohort).

Number of Participants:

Up to 44 participants (8 in PART-1 and 36 in PART-2) will be randomly assigned to study intervention.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential

participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

Age and Sex:

1. Participants 18 to 60 years of age (or the minimum age of consent in accordance with local regulations), inclusive, at screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, vital signs and standard 12-lead ECGs.

Other Inclusion Criteria:

3. For optional Japanese cohort only: Japanese participants who have 4 Japanese biologic grandparents who were born in Japan.

4. For the optional Chinese cohort only: Chinese participants who were born in mainland China, and both parents are of Chinese descent.

5. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Known allergy to the cephalosporin group of antibiotics.

3. History of HIV infection, hepatitis B or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality [or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case)] that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.9 for additional details).

6. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP. (Refer to Section 6.9 for additional details).

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

8. A positive urine drug test.

9. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility.

Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.25 × ULN;
    - Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - eGFR <90 mL/min (estimated using the CKD-EPI equation).

Other Exclusions Criteria:

12. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).
13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
14. History of sensitivity to heparin or heparin-induced thrombocytopenia.
15. Participants who are unwilling and/or unable to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
16. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

Study Arms and Duration:

Duration of Participant Involvement in the Study:

The total planned duration of participation, from Screening visit to the Follow-up phone call, is approximately 12 weeks for participants in PART-1 (up to 4 weeks for screening, up to 3 weeks of dosing and up to 5 weeks for safety follow-up visit), and 10 weeks for

participants in PART-2 (up to 4 weeks for screening, up to 1 week of dosing and up to 5 weeks for safety follow-up visit).

Study Intervention(s)				
Intervention Name	CTB		AVP	
	PF-06264006	Placebo	PF-07338233	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	PF-06264006 Double-Blind Treatment	Placebo Double-Blind Treatment	PF-07338233 Double-Blind Treatment	Placebo Double-Blind Treatment
Unit Dose Strength(s)	400 mg	0 mg	225 mg	0 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP

Study Arms – PART-1		
Arm Title	CTB or CTB + AVP	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants may receive a single dose of 400 mg CTB + 900 mg AVP, or 800 mg CTB + 1350 mg AVP, or 1200 mg CTB + 1350 mg AVP[a], or 800 mg CTB alone, or 1600 mg CTB alone, or 1200 mg CTB + 1800 mg AVP on Day 1 in up to 5 periods.	Participants will receive a single dose of placebo on Day 1 in up to 5 periods.

a. 1350 mg AVP may be replaced with 900 mg AVP.

Study Arms – PART-2		
Arm Title	CTB + AVP[a]	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants may receive 400 mg CTB + 1350 mg AVP (DR1), or 400 mg/800 mg CTB + 1350 mg AVP[a] TID (DR2) or 800/1200 mg CTB + 1350 mg AVP[a] TID (DR3) for 7 days.	Participants will receive placebo TID for 7 Days.

a. 1350 mg AVP may be replaced with 900 mg AVP.

In PART-1 and PART-2, treatment sequences and the dosing regimen may be adjusted during the study based on emerging safety, tolerability, and PK data. The provisional dosing regimens for Parts 1 and 2 are provided in Table 6 and Table 7, respectively. Except D1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data. Dose escalation of CTB (and AVP, when applicable) to higher doses will be based on all available (a minimum of 24 hours post-dose) safety data in a minimum of 5 participants (4 active and 1 placebo) at the previous dose levels of CTB and/or AVP. AVP dose for PART-1 may be 900 mg, 1350 mg, or 1800 mg (in Period 5 only) as long as PK exposures for AVI in the next higher cohort are not projected to be higher than PK stopping limit (AVI AUC ≤ 354 µg.hr/ml- NOAEL in the 14-day pivotal repeat-dose toxicology study in rats). In PART-2, at least 6 days of safety data in a minimum of 5 participants (4 active and 1 placebo) from Cohort 2 will be reviewed prior to proceeding to optional Cohorts 3, 4, 5 and/or 6.

PART-1: Single Dose

PART-1 includes 1 cohort and up to 5 periods (Period 4 and 5 are optional). In each period, approximately 6 participants will receive a single oral dose of CTB or CTB and AVP combined, and approximately 2 participants will receive the matching placebo, all under fed conditions. Each participant may receive either a single dose of CTB, CTB and AVP combined, or matching placebo during each period. In each period, participants on active treatment will receive D1, D2, D3, D4 (optional), or D5 (optional) dose levels, respectively (Section 4.3). The washout period between doses is planned to be a minimum of 3 days.

PART-2: Multiple Dose

PART-2 is planned with up to 5 cohorts (Cohorts 3, 4,5 and 6 are optional). In Cohorts 2, 3 and 4, approximately 6 participants will receive 1 of the dose regimens of CTB and AVP combined and approximately 2 participants will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted). In Cohorts 5 and 6, approximately 5 participants will receive 1 of the dose regimens of CTB and AVP combined, and approximately 1 participant will receive the matching placebo orally under fed state (except Day 7 which will be administered fasted). From Day 1 to Day 7, CTB and AVP combined or the matching placebo will be administered q8h (ie, TID), with the dose regimen of DR1 (for Cohort 2), DR2 (for optional Cohort 3), DR3 (for optional Cohort 4), and either DR1, DR2 or DR3 (for Cohort 5, optional Japanese Cohort and Cohort 6, optional Chinese Cohort) (Section 4.3).

Statistical Methods:

There are no formal statistical hypotheses for this study.

PART-1: Single Dose

A sample size of approximately 8 participants (6 active, 2 placebo) for this single-cohort, cross-over study has been chosen based on the need to minimize first exposure of healthy

participants to CTB + AVP and the requirement to provide adequate safety and tolerability information and PK information at each dose level.

PART-2: Multiple Dose

A sample size of approximately 36 participants (8 participants each in Cohorts 2, 3 and 4: six on CTB + AVP, 2 on matching placebo and 6 participants each in Cohorts 5 and 6: five on CTB + AVP, 1 on matching placebo) for this 5-cohort (1 cohort and 4 optional cohorts) multiple dose study has been selected to provide adequate PK, safety and tolerability information. This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability, and PK data in these populations.

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. The plasma PK parameters will be summarized descriptively by dose. No formal inferential statistics will be applied to the PK data apart from the comparisons of CTB PK parameters when CTB is administered in combination with AVP or alone in PART-1, and food effect on CTB and AVP in PART-2.

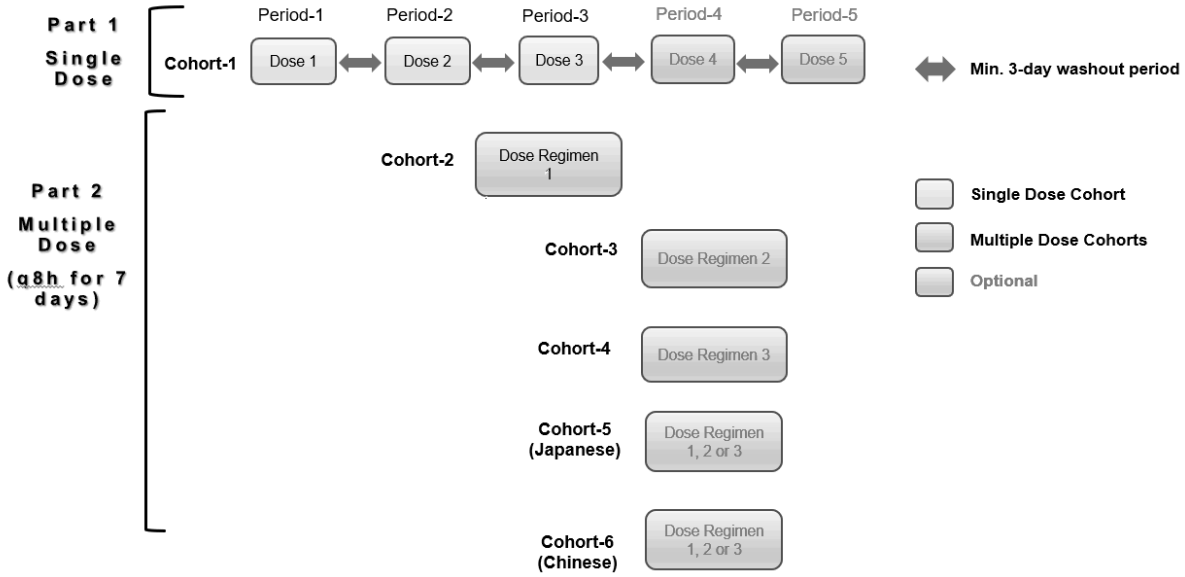
Ethical Considerations:

This study will be conducted in healthy participants who are not expected to receive any clinical benefit from participation in the study. Potential risks from CTB + AVP include nausea and vomiting, hypersensitivity, pseudomembranous colitis and convulsions/seizures.

The trial-specific risks and burdens for participants includes the requirement to be confined during study intervention in the CRU, the potential increased risk of acquiring SARS-CoV-2 infection by undergoing procedures at a study facility, they may experience discomforts undergoing study assessments (eg, blood samples, ECGs), and the need to be compliant with lifestyle and dietary restrictions.

1.2. Schema

Figure 1. C4691001 Study Design



PART-1: Dose 1 = 400 mg CTB + 900 mg AVP; Dose 2 = 800 mg CTB + 1350 mg AVP; Dose 3 = 800 mg CTB alone; Dose 4 = 1200 mg CTB + 1350 mg AVP*; Dose 5 = 1600 mg CTB alone or 1200 mg CTB + 1800 mg AVP.

PART-2: DR1 = 400 mg CTB + 1350 mg AVP* q8h for 7 days; DR2 = 400 mg/800 mg CTB + 1350 mg AVP* q8h for 7 days; DR3 = 800 mg/1200 mg CTB + 1350 AVP q8h for 7 days.

* 1350 mg AVP may be replaced with 900 mg AVP, based on safety, tolerability and PK data.

Note that except Dose 1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURE section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**														**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**												**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Informed consent	X																	• Informed consent should be obtained prior to undergoing any study-specific procedures. The time frame for obtaining a signature on the ICD should be changed if the screening window is revised. • See Section 10.1.3 for additional information.

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	→	→	X			• Participants will be confined in the CRU for all periods. Discharge from CRU in last period only after completion of all procedures and sample collection.
Inclusion/exclusion criteria	X	X																• Inclusion/exclusion criteria are still being assessed on Day -1. • To be conducted for Period 1 only. • See Section 5.1 and Section 5.2
Medical history	X																	• See Section 8.1.1
Medication history	X	X														X		• See Section 8.1.1
PE		X															X	• PE to be done at Screening or Day -1 in Period 1 only. • Brief PE to be done for PE findings or new/open AEs, at the discretion of the PI. • See Section 8.3.1

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Demography	X																	• See Section 8.1.1
Contraception check	X	X													X	X	X	• Day 2 to be conducted for last Period only, unless discharged earlier at discretion of the investigator. • See Section 10.4
12-Lead ECG (triplicate)	X		X				X		X	X					X		X	• All ECGs are collected in triplicate, except at screening. • See Section 8.3.3
Vital Signs (pulse rate, BP)	X		X				X								X		X	• See Section 8.3.2
COVID-19 questionnaire	X	X																• Review COVID-19 related signs and symptoms. To be done as per local procedures.
COVID-19 testing		X																• Testing for COVID-19 by PCR wil be performed as per local procedures. • See Section 8.3.5

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Study intervention administration																		• All doses to be administered within 30 minutes of completing standard breakfast. • See Section 5.3.2 and Section 4.1
CTB or Placebo			X															
AVP or Placebo			X															• Will not be administered when CTB/placebo is given alone.
Blood samples for:																		
Pregnancy test (β-hCG) WOCBP only	X	X													X		X	• To be conducted at Day -1 Period 1 and Day 2 last period,prior to discharge from CRU. • See Section 8.3.6

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Safety laboratory assessments	X	X													X		X	• Participants should fast for at least 4 hours prior to lab collection. • See Section 10.2
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X																	
eGFR (CKD-EPI)	X																	
Serum FSH (for post-menopausal women only)	X																	

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Retained Research Sample for Genetics (Prep D1)			X															• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • To be conducted for Period 1 only. • See Section 8.6.2
Retained Research Sample for Biomarkers (Prep B2)			X															• If not collected on designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • To be conducted for Period 1 only. • See Section 8.7.4
Plasma PK (cis-CTB, AVP, AVI and HPA)			X	X	X	X	X	X	X	X	X	X	X	X	X		X	• See Section 8.5.1

Table 1. Study Schedule of Assessment - PART-1: Single Dose

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Period 1 to Period 5**													**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**											**Day 2**	**29 to 36 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention. • Minimum 3 day washout period between doses.
Hours After Dose			0	0.5	1	1.5	2	2.5	3	4	6	8	12	14	24			
Urine Samples for:																		
Urine drug testing	X	X																• To be conducted for Period 1 only. • See Section 8.1.1
Urinalysis	X	X													X		X	

Table 2. Study Schedule of Assessment - PART-2: Multiple Dose (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**										**35 to 42 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention.
Informed consent	X												• See Section 10.1.3 for additional information.
CRU confinement		X	→	→	→	→	→	→	→	X			
Inclusion/exclusion criteria	X	X											• Inclusion/exclusion criteria are still being assessed on Day -1. • See Section 5.1 and Section 5.2
Medical history	X												• See Section 8.1.1
Medication history	X	X									X		• See Section 8.1.1
PE		X										X	• PE to be done at Screening or Day -1. • Brief PE to be done envisioned for PE findings during previous PE or new/open AEs, at the discretion of the PI. • See Section 8.3.1
Demography	X												• See Section 8.1.1
Contraception check	X	X								X	X	X	• See Section 10.4

Table 2. Study Schedule of Assessment - PART-2: Multiple Dose (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**										**35 to 42 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention.
12-lead ECG (triplicate)	X		X		X			X	X			X	• 12-lead ECG to be measured at 0hr, 2hr, and 8hr post morning dose on Day 1, Day 3, Day 6 and Day 7. Triplicate 12-lead ECG for baseline to be measured at 3 time points prior to dosing on Day 1. • See Section 8.3.3
Vital Signs (BP and pulse rate)	X		X		X			X	X			X	• BP and pulse rate to be measured at 0hr, 2hr, and 8hr post morning dose on Day 1, Day 3, Day 6 and Day 7. • See Section 8.3.2
COVID-19 questionnaire	X	X											• Review COVID-19 related signs and symptoms. To be done as per local practice.
COVID-19 testing		X				X							• Testing for COVID-19 by PCR will be performed as per local procedures. • See Section 8.3.5

Table 2. Study Schedule of Assessment - PART-2: Multiple Dose (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**										**35 to 42 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention.
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	→	→	→	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.
Study intervention administration													• See Section 5.3.2 and Section 4.1
CTB and AVP or Placebo (q8h)			X	X	X	X	X	X	X				• Dosing Days 1 - 6 to be administered in fed state. • Single morning dose to be administered on Day 7 in the fasted state.
Blood samples for:													
Pregnancy test (β-hCG) WOCBP only	X	X								X		X	• To be conducted prior to discharge from CRU. • See Section 8.3.6
Safety laboratory assessments	X	X	X		X			X	X			X	• Participants should fast for at least 4 hours prior to lab collection. • See Section 10.2
eGFR (CKD-EPI)	X												

Table 2. Study Schedule of Assessment - PART-2: Multiple Dose (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**										**35 to 42 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention.
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X												
Serum FSH (for post-menopausal women only)	X												
Retained Research Sample for Genetics (Prep D1)			X										• Prep D1 Retained Research Samples for Genetics: If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.6.2
Retained Research Sample for Biomarkers (Prep B2)			X										• If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit. • See Section 8.7.4

Table 2. Study Schedule of Assessment - PART-2: Multiple Dose (Including Optional Japanese and Chinese Cohorts)

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Screening**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**F/U**	**ET/ Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**										**35 to 42 Days**		• All screening activities should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28 to 35 days after final dose of study intervention.
Plasma PK (trans-CTB, cis-CTB, AVP, AVI and HPA)			X					X	X	X		X	• Refer to Table 3 for PK collection time points. On Day 1, Day 6 and Day 7, plasma PK samples are collected after morning dose. • trans-CTB plasma PK analysis to be conducted for Cohort 2 only.
Urine Samples for:													
Urine drug testing	X	X											• See Section 8.1.1
Urinalysis	X	X			X			X	X			X	
Urine PK			X					X					• Refer to Table 3 for urine PK collection time points. On Day 6 only, urine PK samples are collected after morning dose at 0 - 8 hr interval.

Table 3. Study Schedule of Assessment - PART-2: PK Days (Day 1 [fed], Day 6 [fed], Day 7 [fasted]) in Multiple Dose Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Treatment Period on PK Days**																								**Notes**
Days Relative to Day 1	**Day 1 & Day 6 (fed)**												**Day 7 (fasting)**												**Day 8**	
Planned Hours Post 1st Dose on that day	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	
Vital Signs (BP and pulse rate)	X				X					X			X				X					X				
12-lead ECG	X				X					X			X				X					X				
Study intervention administration																										
CTB and AVP or Placebo (q8h dosing)	X									X		X	X													• Single morning dose on Day 7. All doses to be administered within 30 minutes of consuming standard breakfast or meal; except Day 7 dose, which requires a 10-hour overnight fast.
Blood Samples for:																										
Safety laboratory assessments	X												X													• Participants should fast for at least 4 hours prior to collection. • Collection should occur prior to morning dose on Day 6 and Day 7.
Plasma PK (trans-CTB, cis-CTB, AVP, AVI and HPA)	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	• trans-CTB plasma PK on Day 1, Day 6 and Day 7 to be conducted for Cohort 2 only.

Table 3. Study Schedule of Assessment - PART-2: PK Days (Day 1 [fed], Day 6 [fed], Day 7 [fasted]) in Multiple Dose Cohorts

Visit Identifier Abbreviations used in this table may be found in Appendix 10.	**Treatment Period on PK Days**																								**Notes**
Days Relative to Day 1	**Day 1 & Day 6 (fed)**												**Day 7 (fasting)**												**Day 8**	
Planned Hours Post 1st Dose on that day	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**16**	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**16**	**24**	
CCI [redacted]																										
Urine Samples for:																										
Urine PK (trans-CTB, cis-CTB, AVP, AVI and HPA)	X	→	→	→	→	→	→	→	→	X																• Urine PK analysis for all 5 analytes on Day 6; to be conducted for Cohort 2 only. • On Day 6 only, forced void (discarded) prior to dosing on Day 6. At the end of the collection period, forced void into the collection container (0 - 8hr, on Day 6). • On Day 1 only, "Blank" pre-dose urine samples to be collected within 24 hr prior to the first dose.

2. INTRODUCTION

PF-07612577 is a combination of ceftibuten (CTB) and PF-07338233 (avibactam prodrug [AVP]), referred to in this protocol as CTB + AVP, that is currently being developed for the treatment of cUTI, including pyelonephritis. CTB is a third-generation FDA-approved oral cephalosporin. PF-07338233 is an orally bioavailable prodrug which breaks down rapidly to avibactam (PF-06416494, referred to as AVI), a well-established IV β-lactamase inhibitor with activity against a broad spectrum of β-lactamases.

2.1. Study Rationale

The current study is a Phase 1 study of CTB + AVP in approximately 44 healthy adult participants. It is a 2-part study combining PART-1: Single dose PK, safety and tolerability of various CTB doses alone or when coadministered with AVP, and PART-2: multiple dose PK, safety and tolerability of CTB + AVP coadministered, including optional Japanese and Chinese cohorts.

2.2. Background

ESBL-producing Enterobacterales cause serious infections affecting approximately 200,000 patients and causing 9,100 deaths per year in the US.[1] These pathogens are flagged as a 'Critical' priority by the WHO[2] and a 'Serious Threat' by the CDC.[3] Resistance to antibiotics is increasing, with a 50% increase observed in US hospital cases between 2012 and 2017.[1] Oral treatment for ESBL infection is limited and most patients require OPAT or hospital admission solely to receive IV therapy. UTI is the most common infection caused by ESBL-producing Enterobacterales.

AVP is an orally bioavailable prodrug which breaks down rapidly to AVI in vivo. AVI is a well-established IV β-lactamase inhibitor with activity against a broad spectrum of β-lactamases including ESBLs and serine carbapenemases. CTB is a third-generation FDA-approved oral cephalosporin whose clinical utility against Enterobacterales has been eroded by the spread of ESBLs. The combination of CTB with AVP is expected to provide an effective and well-tolerated oral treatment option for ESBL-producing Enterobacterales infections. The current SOC for treating ESBL-producing Enterobacterales are limited as far as oral options for discharge and community setting care are concerned. Oral antibiotic options for Enterobacterales infections are associated with high and increasing resistance rates, with many patients having no oral option, requiring OPAT or hospital admission solely to receive IV therapy. By offering patients with MDR cUTIs a carbapenem-sparing oral antibiotic option, CTB + AVP has the potential to be a breakthrough versus SOC, supporting early hospital discharge or allowing patients to avoid hospitalization or OPAT IV.

2.2.1. Nonclinical Pharmacology

AVP is an oral prodrug of the BLI, AVI. AVI combined with CAZ (CAZ-AVI; AVYCAZ®) is an approved BL/BLI, whereby AVI restores the microbiological activity of CAZ against class A, class C, and some class D β-lactamases. The microbiological profile of CTB-AVI has been demonstrated in reports from 2 independent organizations (JMI laboratories and IHMA) that specialize in susceptibility testing and surveillance. As highlighted in the reports,

CTB-AVI demonstrates potent activity against many of the key Gram-negative pathogens of interest. This includes Enterobacterales with ESBL, KPC and OXA-48. The inhibitor is known not to inhibit metallo-β-lactamases; therefore, isolates that possess one of these enzymes would be expected to be resistant.

In report 17-SLA-01 (from JMI Laboratories)[4], a total of 253 clinical isolates from the 2015-2016 SENTRY Antimicrobial Surveillance Program organism collection were tested. Randomly selected isolates (212 Enterobacterales [158 molecularly characterized]; 30 *Pseudomonas aeruginosa*; 11 *Acinetobacter baumannii)*. Broth microdilution susceptibility testing with CTB-AVI (inhibitor at fixed concentration of 4 mg/L). The MIC_{90} of CTB-AVI was ≤1 mg/L for all Enterobacterale isolates and selected subsets of different key resistant pathogens (Table 4). As expected, no antibacterial activity of CTB-AVI against NDM containing isolates was observed. The MIC_{90} of CTB-AVI against non-Enterobacterales Gram-negative isolates (ie, *P. aeruginosa* and *A. baumannii*) was >32 mg/L.

Table 4. Antibacterial Activity of CTB and CTB-AVI Against Gram-Negative Bacterial Isolates From JMI Laboratories

		MIC (mg/L)		
Organism (N)[a]	**agent**	**range**	**MIC_{50}**	**MIC_{90}**
Enterobacterales (54)	Ceftibuten	≤0.03 - >32	0.25	32
	Ceftibuten-avibactam	≤0.03 - 16	≤0.03	0.25
Enterobacterales ESBL (50)	Ceftibuten	≤0.03 - >32	4	32
	Ceftibuten-avibactam	≤0.03 – 0.12	≤0.03	0.06
Enterobacterales ESBL + OXA-48 (16)	Ceftibuten	4 - >32	16	32
	Ceftibuten-avibactam	≤0.03 – 0.25	0.06	0.25
Enterobacterales ESBL + KPC (13)	Ceftibuten	2 - >32	16	32
	Ceftibuten-avibactam	≤0.03 – 0.25	0.06	0.12
Enterobacterales pAmpC (28)	Ceftibuten	8 - >32	>32	>32
	Ceftibuten-avibactam	≤0.03 – 1	0.12	1
Enterobacterales NDM-1 (2)	Ceftibuten	>32	>32	NA
	Ceftibuten-avibactam	>32	>32	NA
P. aeruginosa (30)	Ceftibuten	8 - >32	>32	>32
	Ceftibuten-avibactam	1 - >32	>32	>32
A. baumannii (11)	Ceftibuten	8 - >32	32	>32
	Ceftibuten-avibactam	2 - >32	32	>32

a. Not all subsets are being displayed in the table.
Source: Report 17-SLA-01[4]

In report 3471 (from IHMA)[5], a total of 314 randomly selected Enterobacterales (201 wildtype, 28 ESBL, 23 KPC, 22 OXA, 20 cAmpC and 20 pAmpC) were tested from years 2015-2017 (Table 5). The MIC_{90} of CTB-AVI was ≤0.5 mg/L for all Enterobacterales isolates and subset of different key resistant pathogens except cAmpC and pAmpC containing isolates. The MIC_{90} of CTB-AVI was 8 mg/L for cAmpC and pAmpC containing isolates.

Table 5. Antibacterial Activity of CTB and CTB-AVI Against Enterobacterales From IHMA

		MIC (mg/L)		
Organism (N)	**agent**	**range**	**MIC_{50}**	**MIC_{90}**
Enterobacterales (314)	Ceftibuten	≤0.015 - >32	0.25	>32
	Ceftibuten-avibactam	≤0.015 - >32	0.03	0.5
Enterobacterales WT (201)	Ceftibuten	≤0.015 - >32	0.25	16
	Ceftibuten-avibactam	≤0.015 – 16	≤0.015	0.06
Enterobacterales ESBL (28)	Ceftibuten	≤0.015 - >32	4	>32
	Ceftibuten-avibactam	≤0.015 - 8	0.03	0.5
Enterobacterales KPC (23)	Ceftibuten	0.25 - >32	16	>32
	Ceftibuten-avibactam	≤0.015 – 1	0.25	0.25
Enterobacterales OXA (22)	Ceftibuten	≤0.015 - >32	16	>32
	Ceftibuten-avibactam	≤0.015 - >32	0.12	0.5
Enterobacterales cAmpC (20)	Ceftibuten	0.25 - >32	>32	>32
	Ceftibuten-avibactam	≤0.015 - 8	2	8
Enterobacterales pAmpC (20)	Ceftibuten	0.12 - >32	>32	>32
	Ceftibuten-avibactam	≤0.015 - >32	0.12	8

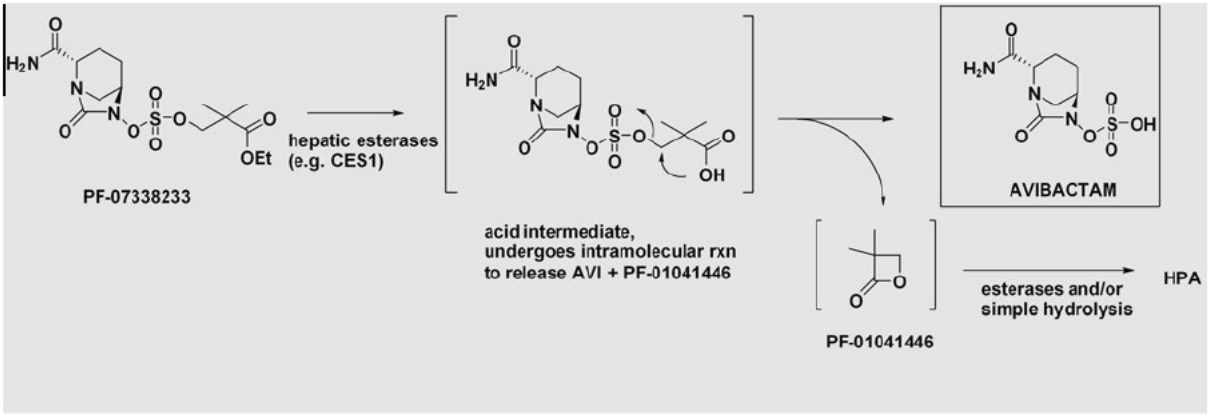
Source: Report 3471 (IHMA)[5]

2.2.2. Nonclinical Pharmacokinetics and Metabolism

2.2.2.1. AVP and AVI

AVP consists of a carboxyethyl ester of the pivaloyl ester of the sulfuric acid of AVI. Based on a series of chemical and in vitro stability studies, the in vivo conversion of AVP to AVI is thought to proceed as follows. After oral administration, AVP is absorbed through the intestine, the carboxyethyl ester is then hydrolyzed, mainly in the liver, to yield ethanol and the pivaloyl ester of AVI. Subsequent hydrolysis of the pivaloyl ester liberates AVI and HPA (Figure 2). The latter reaction has been proposed to proceed via intramolecular cyclization to liberate AVI and the corresponding beta-lactone intermediate.[6] The pivalolactone intermediate would be expected to be rapidly hydrolyzed to HPA. CCI [redacted]

Figure 2. Proposed Mechanism of Conversion of AVP to AVI and HPA



The single dose PK and oral bioavailability of AVP was evaluated in rats, dogs, and NHP. Oral bioavailability was calculated by comparing AVI exposures after PO dosing of the

prodrug to AVI exposures after IV dosing of AVI. Bioavailability was approximately 40% in rat, 80% in NHP, and 100% in dog [Arixa Studies 17003,[7] 17005,[8] 18002,[9] 18003[10]].

The binding of AVP (2.67 µM) and HPA (2.67 µM) to human plasma proteins was evaluated by ultrafiltration [Arixa Study 19004[11]]. Binding of AVP to human plasma protein was moderate at 73.4% (26.6% unbound). Binding of AVI to human plasma protein has been previously determined to be 8% (92% free). HPA had very low binding in human plasma at 1.2% (98.8% unbound).

CCI [redacted] These studies indicate that the prodrug AVP is very rapidly converted to AVI and HPA CCI [redacted]

The ADME of AVI is well understood based on previous studies supporting the IV AVI program. AVI is mainly excreted unchanged in the urine in preclinical species and in humans. Radiolabeled human ADME with IV AVI indicated approximately 90% of the dose was excreted unchanged in urine. AVI was metabolically stable in mouse, rabbit, dog, and human liver microsomes. In vivo studies in rats, dogs, and humans indicated metabolism accounted for approximately 26%, 20%, and 7% of the dose in rats, dogs, and humans, respectively. In rats and dogs, decarbonylation and hydroxylation were the major metabolic pathways, whereas in human, only the decarbonyl metabolite was detected. Unchanged AVI was the major drug-related component in both human plasma and urine.

AVI is not an inhibitor of CYPs. CCI [redacted]. In vivo interactions with other OAT1 and OAT3 substrates are not expected based on lack of interaction with aztreonam (an OAT1 and OAT3 substrate [AstraZeneca Study D4910C00001[16]]).

2.2.2.2. CTB

Information on the nonclinical PK of CTB was obtained from publicly available regulatory summary documents[17] and published literature.[18]

Oral absorption of CTB was evaluated in mice, rats, rabbits, dogs, and NHPs; oral bioavailability of CTB was approximately 56%, 51%, 21%, 80%, and 20%, respectively. Oral bioavailability of CTB in humans is reported as approximately 70%, based on amount of drug excreted in urine.

The plasma protein binding of CTB is low to moderate across species. Percent bound is approximately 9, 14, and 2% in mouse, rat, and dog, respectively. CTB is approximately 39% bound to plasma proteins in humans.

CTB is cleared predominantly by renal excretion of unchanged drug in preclinical species and in humans.[17,19] CTB drug product is primarily the cis-isomer. Following administration of CTB to rats and dogs, cis-ceftibuten is the primary circulating and urinary component, while trans-ceftibuten was also detected, comprising 4% to 25% of the urinary radioactivity. This is similar to what was observed in a radiolabeled human ADME study, wherein the major radiolabeled species in plasma and urine was cis-ceftibuten, while trans-ceftibuten comprised approximately 11% of the dose. Two additional minor metabolites (<2% of dose) were observed in human ADME study, but were not identified.[17,19]

The potential interaction of CTB with CYP enzymes has not been reported. However, given the lack of CYP metabolism of CTB and the lack of CYP interactions with cephalosporins in general, it is considered unlikely that CTB would interact with CYPs. A clinical DDI study was conducted as part of the Cedax development program. Orally administered CTB did not affect the PK of theophylline, a CYP1A2 probe substrate.[19]

Based on in vitro studies, CTB is a substrate for the renal transporters OAT1 and OAT3, and is also a weak inhibitor of these transporters (IC_{50} values of 247 to 563 μM).[20] Even though both AVI and CTB are substrates and weak inhibitors of OAT1 and OAT3, a PK interaction between the 2 compounds is unlikely based on the weak inhibition (high IC_{50} values) and the lack of interaction observed between AVI and coadministered aztreonam (OAT1/OAT3 substrate and weak inhibitor) or ceftaroline (OAT1/OAT3 weak inhibitor).[21,22]

2.2.3. Nonclinical Safety

In repeat dose toxicity studies, systemic toxicity was not observed for AVP, AVI, and CTB at relatively high doses after repeat dose administration, with the exception of gastrointestinal effects which were generally not considered adverse. The only adverse effect noted with CTB (fatal enteritis) was not a direct effect of CTB, but rather was secondary to disruption of the intestinal flora, was not reproduced in repeat studies, and only manifested after prolonged dosing (≥2 months). Systemic exposures for AVI and CTB in toxicity studies support the proposed clinical exposures.

AVP, AVI, and CTB were evaluated in genetic toxicity studies. AVP was positive in an in vitro micronucleus assay in TK6 cells. This result was not considered relevant following negative results in a liver and stomach Comet assay and a Big Blue mutation assay. Both AVI and CTB were nongenotoxic. AVI has no phototoxicity potential based on a negative result in the in vitro 3T3 Neutral Red Uptake assay.

Developmental and reproductive toxicity studies have been conducted with AVI by IV administration, as well as with an HPA-related compound that releases the major AVP metabolite, HPA, and no risks were identified for fertility, embryo-fetal development, or postnatal development except at higher exposures in rabbits. Developmental and reproductive toxicity studies were conducted with CTB and there were no risks identified for fertility, embryo-fetal development, or postnatal development.

Details of the nonclinical safety program are provided in the IB. The nonclinical safety profile of this test article has been adequately characterized to support progression into clinical trials of up to 2 weeks.

2.2.4. Biopharmaceutics

AVP has a pKa of CCI with apparent solubility of CCI mg/mL at 25˚C in unbuffered water. AVP has CCI at ambient at pH CCI In Arixa's FIH clinical trial and based on comparison to historical IV avibactam PK, the absolute bioavailability of AVP appears to be CCI % at CCI mg dosed under the fed condition. After oral dose of CCI mg and CCI mg of AVP under the fed condition, the fraction of dose excreted/recovered as AVI was CCI % and CCI %, respectively. CCI

CTB has a pKa of CCI It exhibits CCI solubility in the neutral pH and FeSSIF and FaSSIF media (pH >6.8). The literature data suggested the absorption of ceftibuten is carrier mediated and saturable.[23] Also a negative food effect at 400 mg has been reported.[24]

2.2.5. Clinical Overview

CTB + AVP has not been administered in humans; therefore, no PK, safety or efficacy data for the combination treatment are available. PK and safety data for the individual agents (AVP, AVI and CTB) are described below.

2.2.5.1. AVP

A Phase 1 FIH SAD study (C4691002, formerly AV-006-01) of AVP has been completed. It was a randomized, double-blind, placebo-controlled, SAD study in healthy male and female subjects. In this study, following oral administration of AVP CCI mg – as a suspension [CCI mg/mL in Ora-Blend]), there was a rapid appearance of AVI and HPA in the blood. AVI reached a concentration likely to be therapeutic (CCI ng/mL) shortly after dosing with mean concentration maintained above this threshold for approximately 8 hours after dosing CCI mg or CCI mg of AVP. AVP was below the limit of quantification (CCI ng/mL) for all time points for all subjects. Mean apparent elimination half-life was CCI at all dose levels. The increase in systemic exposure with dose was approximately proportional for AVI. The dose of CCI mg AVP provides similar mean AVI C_{max} and C_{8h} concentrations as 500 mg IV AVI (approved dose of AVI in AVYCAZ®). All 3 tested dose levels of AVP were safe and well tolerated in the study.[25] The most frequent TEAEs were dizziness, headache, and abdominal pain (each reported by 2 subjects in the AVP group and no subjects in the placebo group). Treatment-related TEAEs were experienced by 1 subject each in the AVP CCI mg, CCI mg, and CCI mg groups; all of these events were mild to moderate in severity and resolved by the end of the study. No treatment-related TEAEs were reported in the placebo group. No subjects died during the study, experienced SAEs, or discontinued the study due to TEAEs. There were no clinically relevant findings or observations of note in clinical laboratory parameters, vital signs, ECG assessments, or PEs.

2.2.5.2. AVI

The PK of IV-administered AVI has been investigated in 12 clinical pharmacology studies in the CAZ-AVI program after administration of AVI alone or CAZ-AVI by IV infusion in healthy participants and patients with different degrees of renal impairment. The studies in healthy participants included young participants, male and female participants, participants ≥65 years of age, and Japanese and Chinese participants. In addition, AVI PK data is also available from 5 Phase 1 clinical pharmacology studies in the ceftaroline-AVI development program.

The exposure of AVI was dose proportional at doses tested [redacted]mg to [redacted]mg), with no evidence of time-dependent kinetics following multiple dosing. The terminal elimination $t_{½}$ of AVI was approximately 2 hours across studies, and there was no or little accumulation of AVI following repeated IV [redacted]doses. AVI is approximately 100% eliminated through renal excretion, with the majority of AVI excreted as unchanged drug. Exposure of AVI increases with increasing renal impairment such that dose adjustments are required based on renal function. AVI is hemodialyzable. Based on the high degree of CL_r and the minimal metabolism of AVI, no dose adjustment is needed in patients with impaired hepatic function. No dose adjustment is needed based on age, gender, race, or BMI. There are no drug interactions with CAZ, ATM, ceftaroline, and metronidazole.

No SAEs have been reported in the patients treated with AVI alone in Phase 1 studies (including the CAZ-AVI program and the ATM-AVI Phase 1 study). Only 1 discontinuation due to an AE was reported for a subject in an AVI-only treatment group (due to an asymptomatic AE of hyperamylasemia [which was demonstrated to be of salivary amylase]). AEs were generally mild to moderate and reported from a wide range of SOCs. Of note, several subjects had elevations in transaminase levels. In a Phase 1 study in healthy Japanese participants, elevations in liver transaminases in a single subject who received AVI alone was reported as an “other significant AE”.

A thorough QT study of supratherapeutic doses of AVI, with negative results, has been completed for CAZ-AVI and ceftaroline-AVI.

2.2.5.3. CTB

CTB (CEDAX) is a third-generation oral cephalosporin, approved in the US in 1995 at a dose of 400 mg QD. Although approved dose for CTB is 400 mg QD, there is some literature data regarding safe and well-tolerated use of higher doses up to 300 mg TID or 400 mg TID.[26,27]

CTB is rapidly absorbed after oral administration with a short terminal elimination $t_{½}$ of 2.5 hours. With repeated QD dosing for 7 days, CTB accumulation in plasma is about 20% at steady state. The average apparent Vz/F of CTB is 0.21 L/kg (± 1 SD = 0.03 L/kg). CTB is 39% bound to plasma proteins. The protein binding is independent of plasma CTB concentration.

CTB is excreted in the urine; 95% of the administered radioactivity was recovered either in urine or feces. Approximately 56% of the administered dose of CTB was recovered from

urine and 39% from the feces within 24 hours. Since renal excretion is a significant pathway of elimination, patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. Food delays the time of CTB C_{max} by 1.75 hours, decreases the C_{max} by 18%, although AUC is unchanged.

Although CTB systemic exposures in plasma were 40% higher at steady state in elderly participants as compared to young adults, the significance of this finding for clinical use in elderly patients is not clear since renal function was not evaluated in these participants. CTB dosage adjustment in elderly patients may be necessary. CTB plasma $t_{½}$ increased and CL/F decreased proportionately with increasing degree of renal dysfunction, requiring dose adjustment for varying degrees of renal impairment. CTB is hemodialyzable. There are no drug interactions with theophylline and liquid antacid. Although a slight interaction was noted (23% increase in C_{max} and 16% increase in AUC) with ranitidine, it is unlikely to be of any clinical relevance. The safety and efficacy of CTB are described in the USPI. ADRs attributed to CTB in this label are considered ADRs for CTB + AVP.

Additional information on the PK, safety, and tolerability of AVP, AVI, and CTB can be found in the IB.[28]

2.3. Benefit/Risk Assessment

CTB + AVP is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data to support further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of CTB + AVP may be found in the IB, which is the SRSD for this study.

Study C4691001 is the first time that CTB and AVP will be administered together in humans. For healthy participants participating in this single and multipledose study, no clinical benefit is expected. The purpose of the study is to provide the basis for further clinical development of CTB + AVP as a potential new, pharmacological agent for the treatment of participants with cUTI. As of 18 July 2022, the known specific human risks are summarized in the IB. The clinical impact of these potential risks will be minimized through the proposed cautious dose-escalation process wherein higher doses of CTB + AVP will be administered only after lower doses have been found to be well tolerated with an acceptable safety profile. In addition, this study includes standard, intensive, inpatient monitoring of the participants following administration of single and multiple oral doses of the study intervention.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) : AVP		
Potential risks associated with CTB + AVP include the following: nausea and vomiting.	This potential risk is based on the fact that nausea and vomiting are reported at an incidence of 4% and 1%, respectively in the CTB USPI. In addition, AEs of nausea and vomiting were reported by 1 patient in the FIH study of AVP. This information is described in the SRSD for CTB + AVP.	AEs will be monitored and participants will be managed as clinically indicated.
Study Intervention(s) : CTB		
Hypersensitivity is a potential risk of CTB.	The risk of hypersensitivity is described in the USPI for CTB and the SRSD for CTB + AVP.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5.2 Exclusion criteria).
Pseudomembranous colitis is a potential risk of CTB.	The risk of pseudomembranous colitis is described in the USPI for CTB and the SRSD for CTB + AVP.	Participants over 60 years of age and with significant medical history will be excluded from the study (see Section 5.1 Inclusion Criteria, Criterion 1 and Section 5.2 Exclusion criteria, Criterion 1). AEs will be monitored and participants will be managed as clinically indicated and per guidance in the SRSD.
Convulsions/seizures is a potential risk of CTB.	The risk of convulsions/seizures is related to the cephalosporin class and is described in the USPI for CTB and the SRSD for CTB + AVP.	Participants with renal impairment and significant medical history will be excluded from the study (see Section 5.2 Exclusion criteria, Criterion 1). AEs will be monitored and participants will be managed as clinically indicated and per guidance in the SRSD.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments according to the SoA.

2.3.2. Benefit Assessment

For healthy participants in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

CTB + AVP is not expected to provide any clinical benefit to healthy participants in this study. Taking into account the measures to minimize risk to study participants, the potential risks identified in association with the administration of CTB + AVP are clinically acceptable.

3. OBJECTIVES AND ENDPOINTS

PART-1: Single Dose

Objectives	Endpoints
Primary:	**Primary:**
To assess the plasma PK profile of CTB following a single dose of CTB alone or in combination with AVP.	Plasma PK parameters of cis-CTB: ▪ C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn). ▪ If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.
To assess the plasma PK profile of AVP following administration of single doses of AVP in combination with CTB.	Plasma PK parameters of AVP, AVI and HPA: ▪ C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn). ▪ If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.
To assess the safety and tolerability following a single dose of CTB alone or in combination with AVP.	▪ Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. ▪ Frequency and magnitude of abnormal laboratory findings. ▪ Changes from baseline in vital sign measurements and 12-lead ECG parameters.

PART-2: Multiple Dose (including optional Japanese and Chinese Cohorts)

Objectives	Endpoints
Primary :	**Primary :**
To assess the plasma PK profile of cis-CTB and trans-CTB[a] following multiple doses of CTB in combination with AVP.	Plasma PK parameters of cis-CTB and trans-CTB[a] on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state): ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn). ▪ If data permit, $t_{½}$, V_z/F, and CL/F.

Objectives	Endpoints
To assess the plasma PK profile of AVP following multiple doses of CTB in combination with AVP.	Plasma PK parameters of AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state): ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn) ▪ If data permit, $t_{½}$, V_z/F, and CL/F.
To assess the safety and tolerability following multiple doses of CTB in combination with AVP.	▪ Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs. ▪ Frequency and magnitude of abnormal laboratory findings. ▪ Changes from baseline in vital sign measurements and 12-lead ECG parameters.
Secondary :	**Secondary :**
To assess the urinary PK[b] profile of cis-CTB, trans-CTB[a], AVP, AVI and HPA on Day 6 following multiple doses of CTB in combination with AVP.	cis-CTB, trans-CTB[a], AVP, AVI and HPA urinary PK parameters (if data permit): ▪ Ae_{tau} and Ae_{tau}%, CL_r.
To assess PK profile of CTB and AVP when administered in combination in Japanese and Chinese participants.	Plasma PK parameters of cis-CTB, AVP, AVI and HPA on Day 1 (fed, single dose), Day 6 (fed, steady state) and Day 7 (fasted, steady state) in Japanese and Chinese cohorts: ▪ C_{max}, T_{max}, AUC_{tau}, C_{max}(dn), AUC_{tau}(dn). ▪ If data permit, $t_{½}$, V_z/F, and CL/F.
Tertiary/Exploratory :	**Tertiary/Exploratory :**
CCI [redacted]	
To explore the effect of food on PK of cis-CTB, trans-CTB, AVP, AVI and HPA.	In PART-2, comparison of plasma PK parameters of cis-CTB, trans-CTB, AVP, AVI and HPA on Day 6 (fed) versus Day 7 (fasted).
To explore the potential drug-drug interaction when CTB and AVP are co-administered.	In PART-1, comparison of plasma PK parameters of cis-CTB and trans-CTB after administration of Dose 2 (800 mg CTB + 1350 mg AVP) versus after Dose 3 (800 mg CTB alone).
To determine the potential effect of CTB on cardiac repolarization, if data permit.	In PART-1, if supratherapeutic concentrations are achieved, C-QT modeling will be conducted to assess potential effect of CTB on QTc prolongation.

a. trans-CTB will be measured only in Cohort 2 PART-2.
b. cis-CTB, trans-CTB, AVP, AVI and HPA in urine will be measured on Day 6 only in Cohort 2, PART-2.

CCI [redacted]

4. STUDY DESIGN

4.1. Overall Design

The current study is a Phase 1 study of CTB + AVP in healthy adult participants. It is a 2-part study combining PART-1: Single dose PK, safety and tolerability of various CTB doses when administered alone or with AVP, and PART-2: Multiple dose PK, safety and tolerability of CTB + AVP, including optional Japanese and Chinese cohorts. PART-1 and PART-2 are randomized, double-blind (participant and investigator blinded and sponsor open) cohorts.

In both parts, participants will be screened within 28 days of their first dose of investigational product. Participants will be admitted to the CRU on Day -1 or earlier and may be discharged at investigator discretion following completion of assessments per SoA. If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up.

Participants who discontinue for non-safety related reasons prior to completion of the study may be replaced, at the discretion of the PI and sponsor. The replacement participant(s) may or may not be required to complete all periods of the cohort in which they are participating at the discretion of the PI and sponsor.

In PART-1 and PART-2, treatment sequences, actual doses, dose increments, and dosing regimen may be adjusted, and intermediate or alternative dose levels may be substituted during the study based on emerging safety, tolerability, and PK data.

PART-1: Single Dose

PART-1 will include 1 cohort (Cohort 1) with approximately 8 participants planned in total. This part will have a randomized, double-blind (sponsor-open), 5-period, sequential single dose design. Approximately 6 participants will receive either a single dose of CTB or CTB + AVP combined, and approximately 2 participants will receive the matching placebo under fed state. PART-1 will have a cross-over design with up to 5 periods, as Period 4 and 5 are optional. Periods 4 and 5 may be used to further explore PK at additional doses, based on emerging PK data. When on active treatment, participants will receive D1, D2, D3, D4 (optional), and D5 (optional) for each period, respectively, as specified in Table 6. Participants will be dosed in a fed state, as specified in Sections 5.3.2 and 6.1. Provisional dosing scheme in PART-1 is provided in Table 6. Except D1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data. Dose escalation of CTB (and AVP, when applicable) to higher doses will be based on all available (a minimum of 24 hours post-dose) safety data in a minimum of 5 participants (4 active and 1 placebo) at the previous dose levels of CTB and/or AVP. AVP dose for Period 4 onwards may be CCI [redacted] mg based on PK and tolerability data. In addition, AVP dose for Period 5 CCI [redacted] mg if it appears from Period 2 and Period 4 that AVI AUC is less than target (CCI [redacted] µg.hr/mL). If the AVP dose CCI [redacted] mg with CCI [redacted] mg CTB needs to be evaluated, then the CTB CCI [redacted] mg

CCI will not be evaluated in CCI The predicted human exposure and safety margins relative to exposure limits for the doses of AVP and CTB proposed in PART-1 are each provided in Table 8 and Table 9, respectively.

Table 6. Provisional Dosing Scheme in PART-1

		Period 1	Period 2	Period 3	Period 4[a]	Period 5[a]
Cohort 1	N=2	Placebo	D2	D3	D4	D5
	N=2	D1	Placebo	Placebo	D4	D5
	N=2	D1	D2	D3	Placebo	D5
	N=2	D1	D2	D3	D4	Placebo

a. Periods 4 and 5 are optional.
D1 = 400 CTB + 900 AVP; D2 = 800 CTB +1350 AVP; D3 = 800 CTB alone; D4 = 1200 CTB + 1350 AVP*; D5 = CCI
Note that except D1 in PART-1, all other dose levels and/or meal condition may be changed based on emerging PK, safety, and tolerability data.

There will be a washout interval of a minimum of 3 days between doses for a given participant. Participants will be required to stay at the CRU for the duration of the washout interval.

PART-2: Multiple Dose

PART-2 will include up to 5 cohorts, ie, Cohort 2, optional Cohort 3, optional Cohort 4, optional cohort 5 (Japanese Cohort), and optional Cohort 6 (Chinese Cohort), with up to 36 participants planned in total. This part will have a randomized, double-blind (sponsor-open), sequential multiple-dose design. In Cohorts 2,3 and 4, eight participants are planned, with approximately 6 participants receiving CTB and AVP combined, as specified in Table 7 and approximately 2 participants receiving the matching placebo. In optional Cohorts 5 and 6, six participants are planned, with approximately 5 participants receiving CTB and AVP combined, and approximately 1 participant receiving the matching placebo. From Day 1 to Day 7, CTB + AVP or the matching placebo will be administered q8h (ie, TID) with the dose regimen of DR1 (for Cohort 2), DR2 (for optional Cohort 3), DR3 (for optional Cohort 4) and either DR1, DR2 or DR3 (for Cohort 5, optional Japanese Cohort and Cohort 6, optional Chinese Cohort). Participants are planned to be dosed under fed state (after normal breakfast, lunch or dinner), except for on Day 7, where participants are planned to be dosed under fasted state (as specified in Sections 5.3.2 and 6.1). The predicted human exposure and safety margins relative to exposure limits for the doses of CTB proposed in PART-2 are provided in Table 10, respectively.

At least 6 days of safety data in a minimum of 5 participants (4 active and 1 placebo) from Cohort 2 will be reviewed prior to proceeding to optional Cohorts 3, 4, 5 and/or 6. Cohorts 5 and 6 may be enrolled before Cohort 3 or 4.

Safety, tolerability and PK may be evaluated in participants of Japanese descent (defined as having 4 biological Japanese grandparents who were born in Japan) and Chinese descent (defined as being born in mainland China and both parents of Chinese descent) after multiple

dose oral administration of CTB + AVP in PART-2. These cohorts will have all evaluations as specified in SoA for PART-2 cohorts and the dose level in this cohort will be equal or lower than the highest dose level evaluated in healthy Western participants. Frequency of administration will be based on safety, tolerability and PK data from Western participants.

Urine samples will be collected up to 8 hours post dose on Day 6 in Cohort 2 as specified in the SoA.

Table 7. Provisional Dosing Scheme in PART-2*

Cohort #	DR#	Dosing Regimen
Cohort 2	DR1	400 mg CTB + 1350 mg AVP or Placebo
Cohort 3	DR2	400 or 800 CTB + 1350 mg AVP or Placebo
Cohort 4	DR3	800 mg or 1200 mg CTB + 1350 mg AVP or Placebo
Cohort 5	DR1,DR2 or DR3	400, 800 or 1200 mg CTB + 1350 mg AVP or Placebo
Cohort 6	DR1,DR2 or DR3	400, 800 or 1200 mg CTB + 1350 mg AVP or Placebo

* 1350 mg AVP may be replaced with 900 mg AVP, depending on safety, tolerability and/or PK considerations

Except D1 (Dose 1) in PART-1 and DR1 (Dose Regimen 1) in PART-2 of the study, the dose levels, frequency of administration, and/or meal condition may be changed based on emerging PK, safety, and tolerability data. During PART-1 and PART-2, the dose increments and planned doses may be adjusted, as the study progresses dependent upon emerging PK, safety, and tolerability data. Other intermediate doses or lower doses may be administered instead of the planned doses, or changes in dosing frequency or titration schemes may be proposed for PART-2 cohorts if safety/tolerability or PK issues become apparent, if evidence of nonlinear PK dictates the need to escalate more slowly, or if subsequent doses are predicted to result in exposures that exceed the target limits. Any potential altered dose scheme will be equal to or less than a 3.3-fold increase in exposure from the previous highest dose if a higher dose is warranted to achieve exposure. The projected average exposure of the altered dose scheme will not exceed the exposure limit specified in Section 4.3.

In all cohorts (all parts of the study), participants can be released after completing activities specified in SoA. A telephone follow-up contact will occur between 28 to 35 days after the day of last administration of study intervention. At the discretion of the investigator, telephone follow-up contact may be substituted with an on-site visit in case of additional follow-up of open AEs or clinically significant laboratory findings.

The total planned duration of participation, from Screening visit to the Follow-up phone call, may be approximately 12 weeks for PART-1 (up to 4 weeks for screening, up to 3 weeks of dosing and up to 5 weeks for safety follow-up visit), and 10 weeks for PART-2 (up to 4 weeks for screening, up to 1 week of dosing and up to 5 weeks for safety follow-up visit).

Participants who discontinue from the study (due to non-safety reasons) may be replaced at the Sponsor's discretion.

4.2. Scientific Rationale for Study Design

Although CTB and AVP have been administered separately to humans already, the current study is the first to dose both agents together (CTB + AVP) to healthy participants. Although 400 mg QD is the approved dose for CTB, CCI [redacted] Notably, however, very limited CTB data are available at these potential doses and therefore there is significant uncertainty in predicting the doses that will be sufficient to achieve PK targets CCI [redacted] % of the patient population. Therefore, the protocol is written flexibly to allow for potentially studying CCI [redacted] of CTB and AVP in order to collect sufficient data to model and optimize the dose of each component for future studies in patients.

PK data from PART-1 and PART-2 CCI [redacted]. Healthy male and female adults (18-60 years of age) will be enrolled in this study. Although CTB + AVP is nongenotoxic; its effect on embryo-fetal development is currently not known. Therefore, male and female participants are required to follow contraception requirements as specified in Section 5.3.1 and Appendix 4.

PART-1: Single Dose

Crossover design (Period 1 to 3) in PART-1 will permit within- and between-participant assessment of safety, tolerability and PK. To permit an unbiased assessment of safety, the administration of active versus placebo in each period will be double-blinded to site staff (except those involved in preparation of doses) as well as the study participants. A washout period of a minimum of 3 days between different doses is considered sufficient given the short terminal elimination half-lives of CTB and AVP of around 2-3 hours. Analysis of drug interaction when CTB and AVP are co-administered in PART-1 (Dose 2, 800 mg CTB + AVP versus Dose 3, 800 mg CTB alone) will be conducted.

CCI [redacted]

PART-2: Multiple Dose

Steady state is expected to be achieved by Day 2 with q8h repeated dosing. Safety, tolerability and PK data will be collected for 7 days in the multiple dose study to allow for assessment of longer dosing periods on safety and tolerability. An optional Japanese and Chinese cohort is added to PART-2 to collect data that is expected to facilitate further clinical development of CTB + AVP in Japan and China. PK profiles will be collected on Day 1 in the fed state, Day 6 in the fed state (steady-state) and Day 7 in the fasted state. Analysis of food effect when CTB and AVP are co-administered in fed state (Day 6) versus in fasted state (Day 7) will be conducted.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for CTB + AVP, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.2. Collection of Retained Research Samples

Retained Research Samples will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.3. Justification for Dose

The approach for dose selection for this study includes consideration of all relevant information obtained in nonclinical pharmacology and toxicity studies of CTB and AVP, and a FIH SAD study for AVP (C4691002, formerly AV-006-01). Available PK data for the individual agents CTB and AVI is presented in detail in Section 2.2.5. Although the approved dose for CTB is 400 mg QD, there is some limited literature data regarding safe and well-tolerated use of higher doses up to 300 mg TID or 400 mg TID.[26,27] Thus, starting single dose of 400 mg is considered appropriate. PK data from AVP FIH study (C4691002) estimate 900 mg AVP dose as providing similar AVI concentrations as historical data for 500 mg IV AVI, the safe and effective dose of AVI in AVYCAZ® and ATM-AVI programs.

The dose levels for this Phase 1 study were selected in order to explore CCI [redacted]

Conclusions From In vitro Studies:

- PK/PD driver for CTB was CCI [redacted]
- For AVI, CCI [redacted]

Results from in vivo studies (studies in progress):

CCI

[redacted]

CCI [redacted]

AVP dose for PART-1 may be 900 mg, 1350 mg, or CCI [redacted] mg (in Period 5 only) as long as average PK exposures for AVI are not projected to be higher than PK stopping limit (AVI AUC ≤354 ug hr /mL NOAEL in the 14 day pivotal repeat dose toxicology study in rats). Dose escalation decisions in PART-1 and PART-2 for CTB + AVP will take into consideration the dose escalation and stopping rules (Section 6.6.1). The safety, tolerability, and PK of a wide range of CTB and AVP doses CCI [redacted]

[redacted] Thus, 400 mg CTB + 1350 mg AVP is proposed as the starting dose regimen (DR1) in PART-2. In addition, PK, safety and tolerability of single dose 800 mg CTB + 1350 mg AVP will be assessed in D2 PART-1 before initiation of multiple dose DR1 (400 mg CTB + 1350 mg AVP) in PART-2. If 400 mg CTB + 1350 mg AVP dose regimen (DR1) is well-tolerated in PART-2, optional Cohort 3 with 400 mg or 800 mg CTB + 900/1350 mg AVP (DR2) will be initiated. Similarly, if 800 mg CTB + 1350 mg AVP dose regimen (DR2) is well-tolerated in PART-2, optional Cohort 4 with dose escalation to 800 mg CTB or 1200 mg CTB + 900/1350 mg AVP (DR3) will be initiated. The highest multiple doses to be evaluated in PART-2 are 1350 mg (6 capsules of 225 mg each) q8h for 7 days for AVP and 1200 mg (3 capsules of 400 mg each) q8h for 7 days for CTB.

CCI [redacted]

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

Table 8. Predicted Human Exposure and Safety Margins of CTB Relative to Exposure Limits at Planned Dose Levels in PART-1

Dose Levels	Dose (mg)	Estimated Human CTB AUC_{inf}	AUC_{inf} safety margin[d]
D1	400 CTB + 900 AVP	60	17 × (rat) and 23 × (dog)
D2	800 CTB + 1350 AVP	120[c]	9 × (rat) and 11 × (dog)
D3	800 CTB	120[c]	9 × (rat) and 11 × (dog)
D4[b]	1200 CTB + 1350 AVP[a]	180[c]	6 × (rat) and 8 × (dog)
D5[b]	1600 CTB alone	240[c]	4 × (rat) and 6 × (dog)
	CCI		

a. AVP 1350 mg may be replaced with AVP 900 mg.
b. D4 and D5 are optional.
c. Assumes dose-proportional increase in human AUC at higher doses.
d. Safety margin calculations based on estimated human AUC_{inf} of 55-60 µg.hr/mL after single dose of 400 mg CTB; rat AUC of 1046 µg.hr/mL at NOAEL in the 1-month toxicology study; and dog AUC of 1379 µg.hr/mL at NOAEL in 1-month and 3-month toxicology studies.

Table 9. Predicted Human Exposure and Safety Margins of AVI Relative to Exposure Limits at Planned Dose Levels in PART-1

Toxicology Study	Dose (mg/kg/day)	C_{max} (µg/mL)	$AUC_{24,ss}$ (µg.hr/mL)	Exposure margin for 900 mg AVP dose[a]	Exposure margin for 1350 mg AVP dose[b]	Exposure margin for 1800 mg AVP dose[c]
5-day repeat dose in rats	2000	61.9	753	7.2	5.7	3.6
14-day pivotal repeat-dose study in rats	1000 (NOAEL)	32.7	354	3.4	2.7	1.7
14-day pivotal repeat-dose study in dogs	1000 (NOAEL)	265	1370	13.2	10.3	6.6

a. All exposure margins were based on the human AVI AUC (104 µg•h/mL) at the projected human dose of 900 mg TID AVP.
b. All exposure margins were based on the human AVI AUC (133 µg•h/mL) at the projected human dose of 1350 mg TID AVP.
c. All exposure margins were based on the human AVI AUC (208 µg•h/mL)) at the projected human dose of 1800 mg TID AVP, assuming dose-proportional increase in AVI exposures from 900 mg to 1800 mg.

Table 10. Predicted Human Exposure and Safety Margins of CTB Relative to Exposure Limits at Planned Dose Levels in PART-2

Dose Regimens	Dose (mg) and Frequency	$AUC_{24,ss}$ safety margin[b]	Cmax safety margin[c]
DR1	400 mg CTB + 1350[a] mg AVP TID	6 × (rat) and 8 × (dog): 400 mg CTB dose	6.4 x (rat): 400 mg CTB dose
DR2	400 mg or 800 mg CTB + 1350[a] mg AVP TID	6 × (rat) and 8 × (dog): 400 mg CTB dose 3 × (rat) and 4 × (dog): 800 mg CTB dose	6.4 x (rat): 400 mg CTB dose 3.2 x (rat): 800 mg CTB dose
DR3	800 mg or 1200 mg CTB + 1350[a] mg AVP TID	3 × (rat) and 4 × (dog): 800 mg CTB dose 2 × (rat) and 2.6 × (dog): 1200 mg CTB dose	3.2 x (rat): 800 mg CTB dose 2.1 x (rat): 1200 mg CTB dose

a. AVP 1350 mg may be replaced with AVP 900 mg.
b. Based on estimated human AUC (540 µg.hr/mL) at the maximum human dose of 1200 mg TID CTB; assuming proporitional increase from lower doses.
c. Based on estimated human C_{max} (15.7 µg/mL at 400 mg CTB dose, 31.4 µg/mL at 800 mg CTB dose, 47.1 µg/mL at 1200 mg CTB dose) and estimated Cmax of 100 µg/mL in 1-month rat toxicology study

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. Use of a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population including, where permitted under local regulations, age, sex, and race, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Participants 18 to 60 years of age (or the minimum age of consent in accordance with local regulations), inclusive, at screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, PE, laboratory tests, vital signs and standard 12-lead ECGs.

Other Inclusion Criteria:

3. For optional Japanese cohort only: Japanese participants who have 4 Japanese biologic grandparents who were born in Japan.

4. For the optional Chinese cohort only: Chinese participants who were born in mainland China, and both parents are of Chinese descent.

5. BMI of 17.5 to 30.5 kg/m2; and a total body weight >50 kg (110 lb).

6. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Known allergy to the cephalosporin group of antibiotics.

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, or HCVAb. Hepatitis B vaccination is allowed.

4. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality [or other conditions or situations related to COVID-19 pandemic (eg, Contact with positive case)] that may

increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.9 for additional details).

6. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP. (Refer to Section 6.9 for additional details).

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational product within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

8. A positive urine drug test.

9. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Baseline standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate-age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate-corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level ≥1.25 × ULN;

- Total bilirubin level ≥1.5 × ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;

- eGFR <90 mL/min (estimated using the CKD-EPI equation).

Other Exclusions Criteria:

12. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces [240 mL] beer, 1 ounce [30 mL] of 40% spirit or 3 ounces [90 mL] of wine).

13. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

14. History of sensitivity to heparin or heparin-induced thrombocytopenia.

15. Participants who are unwilling and/or unable to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures

16. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence

as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- When fasted PK is being evaluated (Day 7 of every cohort in PART-2), participants will receive study intervention at approximately 0800 hours (± 2 hours) following an overnight fast of at least 10 hours.

- When safety labs are being evaluated in PART-1 or -2, participants must fast (except water) for at least 4 hours prior to blood draw.

- When fed PK is being evaluated (Day 1 for each Period in PART-1) and on Days 1 - 6 in PART-2, participants will receive study intervention at approximately 0800 hours (± 2 hours) under fed conditions. Participants should begin breakfast approximately 30 minutes prior to dose administration which should be consumed within 20 minutes. Dose will be administered approximately 30 minutes after starting the breakfast.

- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing, except water consumed during breakfast on the days under fed conditions. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices - see below) may be consumed with meals and the evening snack.

- Lunch will be provided approximately 4 hours after dosing.

- Dinner will be provided approximately 9 to 10 hours after dosing.

- An evening snack may be permitted.

- For dosing conducted under fed conditions, after an overnight fast of 10 hours, participants will start a high-fat/high-calorie breakfast approximately 30 minutes prior to administration of the investigational product. The breakfast will be consumed over approximately 20 minutes with investigational product administered within approximately 10 minutes after completion of the meal. Participants will be encouraged to eat the full meal. If participants are unable to complete the entire meal, the approximate portion of the meal consumed will be documented. No food will be allowed for at least 2 hours post-dose.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.

- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until collection of the final PK sample of each study period.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted;

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing. In PART-2 participants may lie down following the second and third dose of the day on Days 1 through 6.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions includes all prespecified investigational products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.
For the purposes of this protocol, study intervention refers to all of the following:

- PF-06264006, CTB

- Placebo for CTB

- PF-07338233, AVP

- Placebo for AVP

6.1. Study Intervention(s) Administered

Study Interventions				
Intervention Name	CTB		AVP	
	PF-06264006	Placebo	PF-07338233	Placebo
ARM Name (group of patients receiving a specific treatment)	PF-06264006 Double-Blind Treatment	Placebo Double-Blind Treatment	PF-07338233 Double-Blind Treatment	Placebo Double-Blind Treatment
Type	Drug	Placebo	Drug	Placebo
Dose Formulation	Capsule	Capsule	Capsule	Capsule
Unit Dose Strength(s)	400 mg	0 mg	225 mg	0 mg
Dosage Level(s)	400 mg	0 mg	225 mg	0 mg
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Capsules will be provided in blister packs. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement	Capsules will be provided in blister packs. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement	Capsules will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement	Capsules will be provided in bulk. CRU staff will prepare individual doses for administration. Individual dose containers will be labeled by site staff per country requirement
Current/Former Name(s) or Alias(es)	NA	NA	NA	NA

Study Arms – PART-1		
Arm Title	CTB or CTB + AVP	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants may receive a single dose of 400 mg CTB + 900 mg AVP, or 800 mg CTB + 1350 mg AVP, or 800 mg CTB alone, or 1200 mg CTB + 1350 mg[a] AVP, or 1600 mg CTB alone, or 1200 mg CTB + 1800 mg AVP on Day 1 in up to 5 periods.	Participants will receive a single dose of Placebo on Day 1 in up to 5 periods.

a. 1350 mg AVP may be replaced with 900 mg AVP.

Study Arms – PART-2		
Arm Title	CTB + AVP[a]	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants may receive 400 mg CTB + 1350 mg AVP (DR1), or 400 mg/800 mg CTB + 1350 mg AVP[a] TID (DR2) or 800 mg/1200 mg CTB + 1350 mg AVP[a] TID (DR3) for 7 days.	Participants will receive placebo TID for 7 Days.

a. 1350 mg AVP dose may be replaced with 900 mg AVP.

PF-07338233 (AVP) and placebo for AVP will be provided by Pfizer as bulk capsules to the CRU. PF-06264006 (CTB) and matching placebo for CTB will be provided as blistered capsules to the CRU.

Study intervention and placebo will be presented to the participants in individual dosing containers that were supplied by Pfizer.

AVP will be supplied as 225 mg/capsule. Matching placebo capsules will also be provided.

CTB 400 mg capsules along with matching placebo will be supplied as packaged blisters and labeled according to local regulatory requirements. The blisters will be provided to the site for dispensing by the pharmacy.

6.1.1. Administration

When fasted PK is being evaluated (Day 7 of every cohort in PART-2), participants will receive study intervention at approximately 0800 hours (±2 hours) following an overnight fast of at least 10 hours. On all other days throughout the study, participants will receive study intervention under fed conditions. Investigator site personnel will administer study intervention during each period with ambient temperature water to a total volume of approximately 240 mL. Additional water (100 mL) may be given to participants, as needed, to help ingestion of study interventions. Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing. When applicable, CTB and AVP will be dosed simultaneously (within no more than 7 minutes of each other), starting with CTB.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing. In PART-2 participants may lie down following the second and third dose of the day on Days 1 through 6.

6.1.2. Medical Devices

Not applicable

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the PCRU local/site procedures.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Details of dose preparation will be given in a separate EDR. Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

Study interventions and placebo will be prepared by qualified unblinded site personnel according to the IP manual. Blinded study intervention will be administered in a blinded fashion to the participant.

CTB capsules and AVP capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). The capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

6.3. Assignment to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is a double-blind (sponsor-unblinded) study.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention. The investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment

is warranted. Participant safety must always be the first consideration in making such a determination. The investigator should make every effort to contact the medical monitor prior to unblinding a participant's study intervention assignment, unless this could delay further management of the participant.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

In order to maintain this blind, an otherwise uninvolved third party will be responsible for administration of the study intervention. This includes ensuring that there are no differences in time or effort taken to administer the study intervention and no blinded site staff are able to view the administration.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

6.4.3. Blinding of the Sponsor

A limited number of sponsor staff will be unblinded to participants' assigned study intervention in order to permit real time interpretation of the safety and PK data during dose escalation meetings and/or to support clinical development..

6.4.4. Breaking the Blind

The method for breaking the blind in this study will be manual. A sealed envelope that contains the study intervention assignment(s) for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

Once the study is complete, all envelopes (sealed and opened) must be inventoried and retained until authorization for destruction has been provided.

Blood specimens will be obtained from all participants for PK analysis to maintain the study blind at the investigator site. Only the investigator site staff and blinded study monitor, if assigned, will be blinded to study treatment. Other Pfizer personnel will be unblinded to participant treatments in order to permit real-time interpretation of the safety and PK data; and provide information necessary to potentially alter the dose-escalation sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. Specimens from participants randomized to placebo will not be routinely analyzed. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer unblinded personnel and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding for safety reasons.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.6. Dose Modification

Progression to the next dose in PART-1 will occur if the last dose was well tolerated and after satisfactory review of the available safety data. Each dose escalation will be based on review of the safety data up to a minimum of 24 hours postdose, in at least 4 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level.

AVP dose in PART-1 may be 900 mg, 1350 mg, or 1800 mg (in Period 5 only) as long as average PK exposures for AVI are not projected to be higher than PK stopping limit (AVI AUC $\leq$354 ug hr /mL: NOAEL in the 14 day pivotal repeat dose toxicology study in rats). Progression to the next higher optional dose regimen (DR2) in PART-2 may occur if the first DR1 was well tolerated and after satisfactory review of the available safety data. Dose escalation will be based on review of the safety data up to a minimum of 6 days, in at least 4 actively treated participants and at least 1 placebo-treated participant dosed in the previous dose level. If the DR1 dose is not well-tolerated, the dose in DR2 can be modified to be a lower dose than DR1 to allow for dose de-escalation.

6.6.1. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximal tolerated dose has been attained. Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion takes place between the sponsor study team and the investigator. The sponsor study team may not

overrule the investigator's decision to stop dose escalation. If dose escalation is stopped because of any of these criteria, additional cohorts may receive the same or lower doses of the study intervention.

The dose escalation will be terminated based on the following criteria:

- If 50% or more of the participants receiving active drug at a given dose level (but not participants receiving placebo) develop similar clinically significant laboratory, ECG, or vital sign abnormalities, in the same organ class, indicating dose-limiting intolerance.

- Severe nonserious AEs, considered as, at least, possibly related to study intervention administration, in 2 participants at a given dose level (but not participants receiving placebo), independent of within or not within the same system organ class, indicating dose-limiting intolerance.

- Dosing will be paused for any SAE that occurs in a participant receiving active treatment until causality is fully assessed by the PI and sponsor. Dosing may resume if the SAE is determined to be not drug-related by the PI and sponsor. If the SAE is determined to be either drug-related or unknown, either dosing will cease or the SAE will be evaluated by the sponsor's protocol review committee (or similar review group), which is independent of the study team and investigators. If the protocol review committee determines that dosing may resume, a plan that mitigates risks to participants with the resumption of dosing will be implemented. Such a plan could include a revision of inclusion/exclusion criteria, repeating or reducing the dose, or adding appropriate safety monitoring.

- It is determined that the limit of safety and/or tolerability has been reached. This decision will be made following discussions between the study team and the investigator.

- Other findings that, at the discretion of the study team and investigator, indicate that dose escalation should be halted.

- If, at any dose level, the average human exposure ($AUC_{0\text{-}24hr}$) reaches or exceeds the PK stopping limits: CTB $AUC_{inf} \geq 1046$ µg.hr/mL (NOAEL in the 1-month rat toxicology study), AVI $AUC_{0\text{-}24hr} \geq 354$ µg.hr/mL (NOAEL in the 14-day pivotal repeat-dose rat toxicology study), or the average C_{max} reaches or exceeds the C_{max} PK stopping limits: CTB $C_{max} > 100$ µg/mL (estimated CTB C_{max} at NOAEL in the 1-month rat toxicology study), or AVI $C_{max} \geq 32.7$ µg/mL (AVI C_{max} at NOAEL in the 14-day pivotal repeat-dose rat toxicology study).

- If, based on the observed data, the group mean C_{max} or AUC (based on total plasma concentration) of the next planned dose is projected to exceed the escalation limits, that dose will not be explored. Modified doses may be explored if they are not expected to exceed PK stopping criteria.

Progression to the next dose will occur if the last dose was well tolerated and after satisfactory review of the available safety and PK data.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

For this study, any dose of CTB greater than CCI mg or of AVP greater than CCI mg within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up visit.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments (see Appendix 9).

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with CTB or AVP; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE requiring discontinuation in investigator's view;
- Pregnancy;
- Positive COVID-19 test.

If study intervention is permanently discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1. Liver Injury

A participant who meets the criteria as described in Appendix 6 will be withdrawn from study intervention.

7.1.2. ECG Changes

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from the study intervention.

- QTcF >500 ms.
- Change from baseline: QTcF >60 ms and QTcF >450 ms.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Potential Cases of Acute Kidney Injury

Abnormal values in Scr concurrent with presence or absence of increase in BUN that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 µmol/L) in Scr level relative to the participant's own baseline measurement should trigger another assessment of Scr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL [or ≥26.5 µmol/L] in Scr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 µmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal Scr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating Scr, laboratory tests should include serum BUN, serum creatine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal Scr. If ≥2 healthy participants in a given period/treatment arm are noted to have 2 *consecutive* Scr results of ≥0.3 mg/dL (or ≥26.5 µmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

7.1.4. Pregnancy

Pregnancy tests are conducted at each visit and dosing of study intervention will occur only in the presence of a negative pregnancy test. If a participant is confirmed to be pregnant (see Section 8.3.6) during any visit, further dosing with study intervention (if in PART-2) will be discontinued immediately and permanently.

Section 8.4.5.1 describes the follow-up activities if a participant meets the EDP criteria.

7.1.5. COVID-19

If a participant has COVID-19 during the study, this should be reported as an AE or SAE (as appropriate) and appropriate medical intervention provided. If the participant is diagnosed

with COVID-19 during confinement in the CRU, further dosing with study intervention will be discontinued. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

7.1.6. Temporary Discontinuation

Not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Pregnancy.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information.

Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for/attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and Baseline Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

Safety assessments and laboratory results that have been collected for the purposes of this study and could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 519 mL in PART-1 and 291 mL in PART-2. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1.1. Baseline Procedures

Baseline procedures include the collection of medical history, concomitant medication use, demography, physical exam, vital signs, contraception check, COVID-19 assessment (questionnaire and testing), 12-lead ECG completion, eGFR (CKD-EPI), and blood and urine sample collection.

The blood sample includes the following laboratory studies: pregnancy test and FSH for women, and safety labs and screening for HIV, HBV (HBsAg, HBsAb, and HBcAb) and HCV (HCVAb) infections for all participants.

The urine sample includes urine drug testing and urinalysis.

8.1.2. Telehealth Visits

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.2. Efficacy Assessments

No efficacy assessment is planned in this study.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Vital Signs

8.3.2.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2.2. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.3.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using

standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at 3 time points prior to dose administration on Day 1 will serve as each participant's baseline QTcF value.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 24 hours after the last dose of study intervention should

be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.3.5. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection by PCR prior to being admitted to the clinic for confinement and a subsequent COVID-19 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19-like symptoms. Site will review COVID-19 related signs and symptoms using a COVID questionnaire that will be done at screening and at least 48 hours before Day -1 or as per local procedures. Additional testing may be required by local regulations or by the PI.

8.3.6. Pregnancy Testing

A serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue

and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 24 hours after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.4.8. Adverse Events of Special Interest

Not applicable

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Not applicable

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength, or through the wrong route.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

8.5.1. Pharmacokinetic Analysis in Plasma (AVP, AVI, HPA, cis-, and trans-CTB)

One blood sample of approximately 3 mL K_2EDTA, to provide approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of AVP, AVI, and HPA

at time points specified in the SoA. Details of the tubes, additives, and instructions for the use of tubes, collection, processing, aliquoting, handling, storage, and shipment of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

CCI [redacted] Details of the tubes and instructions for the use of tubes, collection, processing, aliquoting, handling, storage, and shipment of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Plasma samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will not be reported in the CSR.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

The plasma samples will be analyzed using validated analytical method/s in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Drug concentration information that may unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the

sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.5.2. Pharmacokinetic Analysis in Urine (AVP, AVI, HPA, cis-CTB, and trans-CTB)

Urine samples will only be collected in Cohort 2 of PART-2 on Day 6 for measurement of AVP, AVI, HPA, cis-CTB and trans-CTB at time points specified in the SoA. Two blank urine samples (approximately 5 mL each) for PK (one for AVP, AVI, and HPA; and the other one for CTB) will be collected within 24 hours prior to dosing on Day 1. For urinary PK, urine samples (0-8 h) will be collected and saved in one container for the duration of the collection interval. Participants will have a forced void into the collection container at the end of the collection interval. After all urine collections are mixed during each interval, 2 urine aliquots, each approximately 5 mL, one for AVP, AVI, and HPA, and the other for CTB will be stored frozen in appropriately labeled tubes for PK analyses. Instructions for the use of tubes, additives, collection, processing, aliquoting, handling, storage, and shipment of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will not be reported in the CSR.

Samples will be analyzed using a validated analytical method/s in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

CCI

CCI

8.5.4. Urine for Qualitative Metabolite Profiling- Day 6, Cohort 2, PART-2 only

An aliquot (≥4 mL) of each of the interval urine samples from Cohort 2 (Day 6) PART-2 of the study (pre-dose and collection interval 0-8 h) will be shipped to the Biotransformation scientist at Pfizer labs in Groton, CT. These samples will be used for metabolite scouting, as needed. These data will not be included in the CSR.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, CCI nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documentation.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.7.1. Specified Gene Expression (CCI Research

Specified gene expression (CCI) research is not included in this study.

8.7.2. Specified Protein Research

Specified protein research is not included in this study.

8.7.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

- 10mL whole blood Prep B2.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention(s). Genes and other analytes (eg, proteins, [redacted] nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documentation.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There are no statistical hypotheses for this study. No formal inferential statistics will be applied to the PK data apart from the comparisons of CTB PK parameters when CTB is administered in combination with AVP or alone in PART-1 and food effect on CTB and AVP in PART-2, as detailed in Section 9.3 below.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and randomization to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Full Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
Safety Analysis Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK Concentration Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.
PK Parameter Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.3.1. General Considerations

The data from each part of the study will be analyzed and reported separately in a single CSR issued at the end of this study.

9.3.2. Primary Endpoint(s) Analysis

The primary endpoints in PART-1 and -2 are related to safety/tolerability with analyses as described in Section 9.3.5.

In addition, primary endpoints in PART-1, and -2 also include the plasma PK endpoints whose analyses are described in Sections 9.3.4.1 and 9.3.4.2.

Evaluation of a drug interaction when CTB and AVP are co-administered versus CTB administered alone will be conducted in PART-1.

9.3.3. Secondary Endpoint(s) Analysis

The secondary endpoints in PART-2 include urinary PK endpoints whose analyses are described in Sections 9.3.4.1 and 9.3.4.2. Secondary endpoint in PART-2 includes plasma PK endpoints for Japanese and Chinese participants whose analyses are described in Sections 9.3.4.1 and 9.3.4.2.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

Tertiary endpoint in PART-2 also includes effect of food on plasma PK of cis-CTB, trans-CTB, AVP, AVI and HPA. Tertiary endpoint in Cohort 2 PART-2 includes metabolite scouting using plasma and urine samples, if data permit. Tertiary endpoints such as metabolite scouting in PART-2 and C-QT modeling may not be reported in the CSR and may be reported separately.

9.3.4.1. PK Analysis

9.3.4.1.1. Derivation of PK Parameters

Plasma PK parameters for cis-CTB, trans-CTB, AVP, AVI and HPA will be derived (if data permit) from the concentration-time data using standard noncompartmental methods following a single oral dose (Table 11) and multiple oral doses (Table 12). Urine cis-CTB, trans-CTB, AVP, AVI and HPA PK parameters are described in Table 12. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 11. Plasma cis-CTB, AVP, AVI, and HPA PK Parameters for PART-1: Single Doses

Parameter	Definition	Method of Determination
AUC_{last}	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the concentration-time curve from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point from the log-linear regression analysis
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression.
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$
AUC_{last}(dn)	Dose normalized AUC_{last}	$AUC_{last}/Dose$
AUC_{inf}(dn)[a]	Dose normalized AUC_{inf}	$AUC_{inf}/Dose$
C_{max}(dn)	Dose normalized C_{max}	$C_{max}/Dose$

dn=dose normalized to a 1 mg dose.
a. If data permit.

Table 12. Plasma and Urine cis-CTB, trans-CTB, AVP, AVI and HPA PK Parameters for PART-2: Multiple Doses

Parameter	Day(s)	Definition	Method of Determination
Plasma			
AUC_{tau}	1, 6, 7	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval, where τ = 8 for TID dosing	Linear/Log trapezoidal method
C_{max}	1, 6, 7	Maximum plasma concentration during the dosing interval	Observed directly from data
T_{max}	1, 6, 7	Time for C_{max}	Observed directly from data as time of first occurrence
C_{min}	6, 7	Minimum observed concentration during the dosing interval	Observed directly from data
PTR	6, 7	Peak-to-trough ratio	C_{max}/C_{min}
R_{ac}	1, 6	Observed accumulation ratio for AUC_{tau}	Day 6 AUC_{tau}/Day 1 AUC_{tau}
$R_{ac,Cmax}$	1, 6,	Observed accumulation ratio for C_{max}	Day 6 C_{max}/Day 1 C_{max}
CL/F[a]	1, 6, 7	Apparent clearance	Dose/AUC_{tau}
$t_{½}$[a]	7	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline are used in the regression
V_z/F[a]	1,6,7	Apparent volume of distribution	Dose/(AUC_{tau} × k_{el})
AUC_{tau}(dn)	1, 6, 7	Dose normalized AUC_{tau}	AUC_{tau}/Dose
C_{max}(dn)	1, 6, 7	Dose normalized C_{max}	C_{max}/Dose
Urine			
Ae_{tau}	6	Amount excreted in urine as unchanged drug over the dosing interval τ	Sum of (urine volume × urine concentration) for each collection over the dosing interval
Ae_{tau}%	6	Percent of dose excreted in urine as unchanged drug over the dosing interval τ	100 × Ae_{tau}/Dose
CL_r	6	Renal clearance	Ae_{tau} /AUC_{tau}

dn=dose normalized to a 1 mg dose.
a. If data permit.

9.3.4.2. Statistical Methods for PK Data

For all parts of the study, plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used; for individual participant plots

by time, the actual PK sampling time will be used for plasma samples. Median profiles will be presented on both linear-linear and log-linear scales.

The plasma PK parameters listed in Table 11 and Table 12 will be summarized descriptively by dose.

For PART-1, dose normalized (to 1 mg) AUC_{inf} or AUC_{last} and C_{max} of cis-CTB will be plotted against dose (using a logarithmic scale) and will include individual participant values as well as the geometric means for each dose. These plots may be used to help understand the relationship between the PK parameters and dose for CTB.

For PART-1, drug interaction evaluation for the treatments "800 mg CTB + 900/1350 mg AVP" (Test) versus "800 mg CTB alone" (Reference) and for PART-2, food effect evaluation for fed PK on Day 6 (Test) versus fasted PK on Day 7 (Reference) will be done. For those participants receiving both treatments (Test, Reference), natural log transformed cis-CTB, trans-CTB and AVI AUC_{last}, C_{max}, and AUC_{inf} (if data permit) will be analyzed using a mixed effect model with treatment included as a fixed effect and participant as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

For PART-2, urine amounts of CTB and AVI will be listed and summarized descriptively, if data permit. In PART-2 plasma PK parameters for Japanese and Chinese participants will be compared to Western participants.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.3.5. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and PE and neurological examination information, as applicable, collected during the course of the study will be considered source data and will ***not*** be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized by treatment and time. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480 - 500	>500
Increase from baseline	NA	30 - 60	>60

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTcF value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

In addition, an attempt will be made to explore and characterize the relationship between plasma concentration and QT interval length using a PK/PD modeling approach. If a PK/PD relationship is found, the impact of participant factors (covariates) on the relationship will be examined.

9.3.6. Other Analyses

9.3.6.1. Pharmacogenomic/Biomarker Assessment

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

9.4. Interim Analyses

No interim analysis will be conducted for this study. As this is a sponsor-open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Sample Size Determination

There are no statistical hypotheses for this study.

9.5.1. PART-1: Single Dose

A sample size of approximately 8 participants (6 active, 2 placebo) for this single-cohort, cross-over study has been chosen based on the need to minimize first exposure of healthy participants to CTB + AVP; since these agents have never been co-administered in humans and to address the requirement to provide adequate safety and tolerability information and PK information at each dose level.

9.5.2. PART-2: Multiple Dose

A sample size of up to 36 participants (8 participants each in Cohorts 2, Cohort 3 and Cohort 4): six on CTB + AVP, 2 on matching placebo and 6 participants each in Cohorts 5 and Cohort 6: five on CTB + AVP, 1 on matching placebo) for this 5-cohort (1 cohort and 4 optional cohorts) study has been selected to provide adequate PK, safety, and tolerability information.

This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability, and PK data in these populations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICD.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

Not Applicable

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan and monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 13. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT T bili Alkaline phosphatase Uric acid Albumin Total protein Cystatin C and eGFR (CKD-EPI) <u>Additionally for suspected Hy's law cases:</u> CK Direct and indirect bilirubin GGT PT/INR Total bile acids	<u>Local Dipstick:</u> Urobilinogen Urine bilirubin pH[e] Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase <u>Laboratory:</u> Microscopy and culture[a]	COVID-19 testing (per PCRU procedures) Scr Urine drug screening[c] Pregnancy test (β-hCG)[d] <u>At screening only:</u> • FSH[b] • HBsAg • HBsAb • HBcAb • HCVAb • HIV

[a] Only if UTI is suspected and urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase or both.
[b] For confirmation of postmenopausal status only.
[c] The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
[d] Serum/urine testing is required for pregnancy testing of female participants of childbearing potential.
[e] Can be performed on dipstick or pH-meter device.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Laboratory results that could unblind the study and have been collected for the purpose of the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

CCI [redacted]

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the CRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.

- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology.

- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE DCT (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

- A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  - OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier

method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must

discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to estimate glomerular filtration rate [Scr-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline serum Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations[29]

2021 CKD-EPI Scr Only	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Scr/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽ 0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Scr/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Scr-Scys Combined	**Scr** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽ 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ⩽ 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Scr/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ⩽ 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 ms.
- New prolongation of QTcF to >480 ms (absolute) or by ≥60 ms from baseline.
- New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm.
- New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as SAEs

- QTcF prolongation >500 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex>120 ms).
- New-onset right bundle branch block (QRS complex>120 ms).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and

monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what to be reported as AEs/SAEs.

10.9. Appendix 9: Prohibited Concomitant Medications That May Result in DDI

There are no known prohibited concomitant medications for PF-07612577 (PF-06264006 [CTB] + PF-07338233 [AVP]) at the time of the IB update (Version 2.0).

Possible drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

10.10. Appendix 10: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A. baumanni	Acinetobacter baumannii
Abs	absolute
ADL	activity/activities of daily living
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
Ae_{tau}	amount excreted in urine as unchanged drug over the dosing interval τ/tau
Ae_{tau}%	percent of dose excreted in urine as unchanged drug over the dosing interval τ/tau
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATM	aztreonam
AUC	area under the curve
$AUC_{24,ss}$	area under the plasma concentration-time profile from time zero to the time 24 hours at steady state
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinite time
AUC_{inf}(dn)	dose normalized AUC_{inf}
AUC_{last}	area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration
AUC_{last}(dn)	dose normalized AUC_{last}
AUC_{tau}	area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
AUC_{tau}(dn)	dose normalized AUC_{tau}
AV	atrioventricular
AVI	avibactam
AVP	avibactam prodrug
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
β-hCG	β-human chorionic gonadotropin
BL	β-lactam antibiotic
BLI	β-lactamase inhibitor
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
C_{8h}	plasma concentration 8 hours after dosing
cAmpC	cytosolic type C ampicillinase

Abbreviation	Term
CAZ	ceftazidime
CDC	Centers for Disease Control and Prevention
CCI [redacted]	
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{last}	the last quantifiable concentration
CL_r	renal clearance
CL/F	apparent clearance
C_{max}	maximum observed concentration
C_{max}(dn)	dose normalized C_{max}
C_{min}	minimum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
C-QT	concentration-QT
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial
CTB	ceftibuten
CTIS	Clinical Trial Information System
CTMS	clinical trial management system
cUTI	complicated urinary tract infection
CYP	cytochrome P450
D#	Dose#
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DR#	Dose Regimen#
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EDR	extemporaneous dispensing record
eGFR	estimated glomerular filtration rate
eSAE	electronic serious adverse event

Abbreviation	Term
ESBL	extended spectrum β-lactamase
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
fAUC	area under the unbound concentration–time curve
FaSSIF	fasted state simulated intestinal fluid
FDA	US Food and Drug Administration
FeSSIF	fed state simulated intestinal fluid
FIH	first in human
FSH	follicle-stimulating hormone
fT	fraction of time of dosing interval above a threshold concentration
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HPA	hydroxypivalic acid
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IHMA	International Health Management Associates
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	Intravenous(ly)
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
k_{el}	rate constant for terminal phase
KPC	Klebsiella pneumoniae carbapenemase
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block

Abbreviation	Term
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	medical device regulation
MIC	minimum inhibitory concentration
MIC_{50}	minimum inhibitory concentration required to inhibit the growth of 50% of organisms
MIC_{90}	minimum inhibitory concentration required to inhibit the growth of 90% of organisms
MQI	medically qualified individual
NA	not applicable
NDM	New Delhi metallo-β-lactamase
NHP	non-human primates
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OAT	organic anion transporter
OPAT	outpatient parenteral antimicrobial therapy
OXA	oxacillinase
P. aeruginosa	Pseudomonas aeruginosa
pAmpC	plasmidic type C ampicillinase
PCR	polymerase chain reaction
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
PE	physical examination
PI	principal investigator
PK	pharmacokinetic(s)
pKa	the negative base-10 logarithm of the acid dissociation constant
PO	oral(ly)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PTR	peak to trough ratio
PVC	premature ventricular contraction/complex
q8h	once every 8 hours
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
R_{ac}	observed accumulation ratio for AUC_{tau}
$R_{ac,Cmax}$	observed accumulation ratio for C_{max}
RBC	red blood cell
CCI	[redacted]
SAD	single ascending dose

Abbreviation	Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SD	standard deviation
SoA	schedule of activities
SOC	standard of care; System Organ Class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TID	three times daily
TK6	thymidine kinase 6
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
V_Z/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

11. REFERENCES

1 Centers for Disease Control and Prevention. Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae. Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/esbl-508.pdf. Accessed: 01 May 2021.

2 World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Available from: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. Published 27 Feb 2017. Accessed: 01 May 2021.

3 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf. Accessed: 01 May 2021.

4 JMI Labs Final report (17-SLA-01). Activity of regemonam alone and in combination with b-lactamase inhibitors tested against gram-negative clinical isolates. 18 Jan 2018.

5 IHMA Report (IHMA 3471). MIC Testing of 314 Enterbacteriaceae including molecularly characterized isolates. 18 Sep 2018.

6 Gordon EM, Duncton MAJ, Gallop MA. Orally absorbed derivatives of the b-lactamase inhibitor avibactam. Design of novel prodrugs of sulfate containing drugs. J Med Chem. 2018;61:10340-4.

7 Arixa study number 17003 (Eurofins Study AB79163). A pharmacokinetic (PK) study in male Sprague-Dawley (SD) rats following intravenous (IV) and oral (PO) administrations of Avibactam at 2mg/kg and two prodrugs (AV-006 and AV-007) at 10mg/kg, respectively. 14 Jun 2017.

8 Arixa study number 17005 (Eurofins Study AB81456). Single dose pharmacokinetics and oral bioavailability of avibactam and six prodrugs of Avibactam (AV-006, AV-019, AV-020, AV-021, AV-022 and AV-023) in rats following oral or intravenous administration. 2017.

9 Arixa study number 18002 (CRL study number 01068001). Avibactam, AV-006, AV-016, AV-017 and AV-029: Pharmacokinetic evaluation of intravenous and oral intubation administration in male cynomolgus monkeys. 2018.

[10] Arixa study number 18003 (CRL study number 01068002). Avibactam, AV-006, AV-016, AV-017 and AV-029: Pharmacokinetic evaluation of intravenous and oral intubation administration in male beagle dogs. 2018.

[11] Arixa study number 19004 (Quintara study number 20190314-A016-01). Binding of AV-006 and hyroxypyvalic acid in human plasma. 2019.

[12] Arixa study number 19010 (Quintara study number 2019021502). Investigation of in vitro metabolites of AV-006 formed in rat, dog and human hepatocytes incubations. 2019.

[13] Arixa study number 19006 (Quintara study number 20190220-A016-01 (plasma) 20190308-A016-01 (blood)). Assessment of AV-006 stability in human blood and plasma. 2019.

[14] Arixa study number 19009 (Quintara study number 20190219-A016-01). Assessment of AV-006 stability in human liver S9. 2019.

CCI

[16] AstraZeneca Study Report D4910C00001: A Phase I, randomized, double-blind, 3-part study in healthy young and elderly subjects to assess the safety and tolerability, and investigate the pharmacokinetics of aztreonam and avibactam given alone and in combination (ATM-AVI). 23 Oct 2015.

[17] US Food and Drug Administration, Center for Drug Evaluation and Research. Cedax Summary Basis of Approval (Dec 20 1995). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/050685Orig1s000rev.pdf. Accessed: 01 May 2021.

[18] Nakashimizu H, Kimura Y, Otsubo R, et al. Pharmacokinetics of 7432-S, a new oral cephalosporin, in experimental animals. Chemotherapy. 1989;37(Suppl 1):756-73.

[19] Barr WH, Lin CC, Radwanski E, et al. The pharmacokinetics of ceftibuten in humans. Diagn Microbiol Infect Dis. 1991;14:93-100.

[20] Ueo H, Motohashi H, Katsura T, et al. Human organic anion transporter hOAT3 is a potent transporter of cephalosporin antibiotics, in comparison with hOAT1. Biochem Pharmacol. 2005;70:1104-13.

[21] Study Pfizer-85-11Nov2019. In vitro interaction studies of ceftaroline and ceftaroline fosamil with human BCRP and MDR1 efflux (ABC) transporters, and with human

MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 uptake transporters. December 2020.

[22] Riccobene TA, Su SF, Rank D. Single- and multiple-dose study to determine the safety, tolerability, and pharmacokinetics of ceftaroline fosamil in combination with avibactam in healthy subjects. Antimicrob Agents Chemother. 2013;57(3):1496-504.

[23] Sugawara M, Iseki K, Miyazaki K, et al. Transport characteristics of ceftibuten, cefixime and cephalexin across human jejunal brush-border membrane. Journal of Pharmacy and Pharmacology. 1991;43(12):882-4.

[24] Nakashima, M., Uematsu, T., Takiguchi, Y., et al. Phase I Clinical Studies of 7432-S: Effect of 7432-S on Platelet Aggregation and Blood Coagulation. The Journal of Clinical Pharmacology. 1988;28: 253-258.

[25] Arixa Pharmaceuticals Clinical Study Report AV-006-01. A placebo controlled, double blind, single ascending dose study of AV-006 in healthy subjects. 05 Mar 2020.

[26] Kudo K, Kabe J. Clinical Study of 7432-S in Respiratory Infectious Diseases. 1989; 37(Supple 1): 241-5.

[27] Kishi M, Yamada d, Nasu Y, et al. 7432-S in Complicated Urinary Tract Infections. Chemotherapy. 1989; 37(Supple 1):478-88.

[28] Investigator's Brochure, PF-07612577. Version 2.0. July 2022.

[29] Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385:1737-49.