A PHASE 1, OPEN-LABEL, FIXED-SEQUENCE STUDY TO ESTIMATE THE EFFECT OF PF-07081532 ADMINISTRATION ON THE SINGLE-DOSE PHARMACOKINETICS OF DABIGATRAN AND ROSUVASTATIN IN OVERWEIGHT OR OBESE ADULT PARTICIPANTS

Study Intervention Number:	PF-07081532
Study Intervention Name:	NA
US IND Number:	160296 (PF-07081532)
[EudraCT/EU CT] Number:	NA
ClinicalTrials.gov ID:	NA
Pediatric Investigational Plan Number:	NA
Protocol Number:	C3991047
Phase:	1

Brief Title: A Drug-Drug Interaction Study to Estimate the Effect of PF-07081532 on the Pharmacokinetics of Dabigatran and Rosuvastatin in Overweight or Obese Adult Participants.

Document History

Document	Version Date
Original protocol	31 January 2023

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-label, Fixed-sequence Study to Estimate the Effect of PF-07081532 Administration on the Single-Dose Pharmacokinetics of Dabigatran and Rosuvastatin in Overweight or Obese Adult Participants.

Brief Title: A Drug-Drug Interaction Study to Estimate the Effect of PF-07081532 on the Pharmacokinetics of Dabigatran and Rosuvastatin in Overweight or Obese Adult Participants.

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Rationale: This is a Phase 1, open-label, fixed-sequence study to estimate the effect of PF-07081532 administration on the single-dose PK of dabigatran (total) and rosuvastatin in otherwise healthy overweight or obese adult participants. The intent of this study is to generate PK, safety, and tolerability data for further clinical development.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of PF-07081532 administration on the single-dose PK of total dabigatran in otherwise healthy overweight or obese participants.	• Dabigatran (total) PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4, and 7.
• To estimate the effect of MD PF-07081532 on the single-dose PK of rosuvastatin in otherwise healthy overweight or obese participants.	• Rosuvastatin PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5, and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with DE in otherwise healthy overweight or obese participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with rosuvastatin in otherwise healthy overweight or obese participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the effects of PF-07081532 on additional PK parameters for total dabigatran.	• Additional plasma PK parameters for total dabigatran: C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$ as data permit, in Periods 1, 4, and 7.
• To evaluate the effects of PF-07081532 on additional PK parameters for rosuvastatin.	• Additional plasma PK parameters for rosuvastatin: C_{max} and T_{max}; and CL/F, Vz/F, $t_{½}$ as data permit, in Periods 2, 5, and 8.
• To evaluate the MD pharmacokinetics of PF-07081532 in healthy overweight or obese participants.	• PF-07081532 plasma pharmacokinetic parameters: AUC_{24}, C_{max}, T_{max}.

* Should it be deemed that too few AUC_{inf} estimates (eg, less than 16 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the dabigatran and rosuvastatin objectives separately.

Overall Design:

This is a Phase 1, open-label, 8-period, fixed-sequence study to evaluate the effect of PF-07081532 administration on the single-dose PK of dabigatran (total) and rosuvastatin in otherwise healthy, overweight or obese, adult female or male participants. The 8 periods will be conducted sequentially without any washout days between periods.

Number of Participants:

Approximately 24 participants will be enrolled in the study.

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 assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. 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

1. Participants aged 18 years or older (or the minimum age of consent in accordance with local regulations) at Screening.

    - Women can be of child-bearing potential, but cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study and may not be taking either oral contraceptives or non-oral hormonal contraceptives (with the exception of implantable progestogen only hormone contraception or intrauterine hormone releasing system), and must avoid vaccination with live attenuated vaccines.

    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 detailed medical history, physical examination (including blood pressure and pulse rate measurement), standard 12-lead ECG, and clinical laboratory tests.

Other Inclusion Criteria:

3. BMI: ≥ 25 kg/m^2 at Screening.

4. Stable body weight, defined as <5 kg change (per participant report) for 90 days before Screening.

Exclusion Criteria

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

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).

    - Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, cholecystectomy or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency).

    - Other medical or psychiatric condition including recent or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    - Known intolerance or hypersensitivity to a GLP-1R agonist(s), rosuvastatin, or DE.

2. Diagnosis of type 1 or type 2 diabetes mellitus or secondary forms of diabetes at screening. **Note:** women with prior diagnoses of gestational diabetes *during pregnancy only* are eligible if they meet the other eligibility criteria.

3. History of myocardial infarction, unstable angina, arterial revascularization, mechanical prosthetic heart valve, stroke, New York Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months of Screening.

4. Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a study participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years (from Screening). Anyone with any history of pancreatic cancer will be excluded, even if it was resected and they were considered 'cured'.

5. Personal or family history of MTC or MEN2, or study participants with suspected MTC per the investigator's judgment.

6. Acute pancreatitis, a history of repeated episodes of acute pancreatitis, or history of chronic pancreatitis.

7. Symptomatic gallbladder disease.

8. Medical history or characteristics suggestive of genetic or syndromic obesity or obesity induced by other endocrinological disorders (eg, Cushing Syndrome).

9. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years from screening.

10. Any lifetime history of a suicide attempt.

11. Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

12. History of HIV infection.

13. Recent history of bleeding, or risks of bleeding, including prior personal or familial history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder, or abnormal coagulation test (INR >1.3) result at Screening.

Prior/Concomitant Therapy

14. Use of any medications that are BCRP, OATP, P-gp and/or CYP3A4/5 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention (Refer to Section 6.9 for additional details).

Diagnostic Assessments (at Screening unless otherwise indicated)

15. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility. Note: At Screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm, and the appropriate cuff selected and used throughout the study.

16. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, 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).

    a. 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 participants.

17. 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:

- HbA1c ≥6.5%.
- 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.
- TSH >1.5x ULN or < LLN.
- INR >1.3.
- Serum calcitonin > ULN.
- Amylase or lipase > ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide not WNL.
- eGFR <75 mL/min/1.73 m2 as calculated by the CKD-EPI equation.
- Positive testing for HIV, HBsAg, HBcAb, or HCVAb. Study participants positive for HCVAb are to be excluded unless known to have been treated with a known curative therapy and negative for HCV RNA. Anyone who has a history of HBV that is treated/cleared is excluded. Hepatitis B vaccination is allowed.
- A positive SARS-CoV-2 test.

Study Arms and Duration:

The total duration of participation from the Screening Visit to the F/U outpatient telephone contact will be approximately 115 days or 16.5 weeks, approximately 8 weeks of which will be conducted on an inpatient basis.

The 54-day inpatient portion of the study will be conducted as follows:

Period 1: 3 days, includes CRU admission on Day -1 (DE 150 mg single dose);

Period 2: 4 days (rosuvastatin 10 mg single dose);

Period 3: 8 days (PF-07081532 titrated to 40 mg QD);

Period 4: 5 days (DE 150 mg single dose + PF-07081532 80 mg QD);

Period 5: 4 days (rosuvastatin 10 mg single dose + PF-07081532 80 mg QD);

Period 6: 20 days (PF-07081532 titrated to 260 mg QD);

Period 7: 5 days (DE 150 mg single dose + PF-07081532 260 mg QD);

Period 8: 5 days, includes discharge day from CRU (rosuvastatin 10 mg single dose + PF-07081532 260 mg QD).

The onsite F/U visit/telephone F/U contact will occur 7-10 days from the last dose of study intervention (Period 8, Day 4) and an outpatient telephone F/U contact will occur 28-35 days from the last dose of study intervention (Period 8, Day 4).

Study Interventions			
Intervention Name	PF-07081532	Rosuvastatin	DE
Arm Name (group of participants receiving a specific treatment or no treatment)	All participants	All participants	All participants
Unit Dose Strength	20 mg, 60 mg, 100 mg	10 mg	150 mg
Route of Administration	Oral	Oral	Oral
Use	Perpetrator	Substrate	Substrate
IMP or NIMP/AxMP	IMP	NIMP/AxMP	NIMP/AxMP

Study Arms								
Arm Title	Period 1: single-dose DE	Period 2: single-dose rosuvastatin	Period 3: PF-07081532 titration	Period 4: single-dose DE + PF-07081532	Period 5: single-dose rosuvastatin + PF-07081532	Period 6: PF-07081532 titration	Period 7: single-dose DE + PF-07081532	Period 8: single-dose rosuvastatin + PF-07081532
Arm Type	Baseline	Baseline	IMP titration only	Experimental (DDI)	Experimental (DDI)	IMP titration only	Experimental (DDI)	Experimental (DDI)
Arm Description	Participants will receive a single 150 mg dose of DE.	Participants will receive a single 10 mg dose of rosuvastatin.	Participants will receive PF-07081532 titrated from 20 mg QD to 40 mg QD over a total of 8 days.	Participants will receive a single 150 mg dose of DE with 80 mg PF-07081532 QD.	Participants will receive a single 10 mg dose of rosuvastatin on a background of 80 mg PF-07081532 QD.	Participants will receive PF-07081532 titrated from 120 mg QD to 260 mg QD over a total of 20 days.	Participants will receive a single 150 mg dose of DE with 260 mg QD PF-07081532.	Participants will receive a single 10 mg dose of rosuvastatin on a background of 260 mg QD PF-07081532.

Based on emerging data from other clinical studies that may become available during the conduct of this study, the titration rate, incremental increases in dose, and/or the PF-07081532 doses at which rosuvastatin and/or dabigatran PK interactions are evaluated may be adjusted. If participants are not able to tolerate titration to higher doses of PF-07081532 (eg, ≥180 mg QD), titration to the next dose level may be delayed temporarily or titration to a maximum tolerated dose may be permitted, **with sponsor approval only**.

Statistical Methods:

The PK data for PF-07081532, rosuvastatin, and dabigatran will be analyzed and reported separately.

Approximately 16 evaluable participants will complete the study.

Natural $\log_e$ transformed AUC_{inf} (as data permit), AUC_{last} and C_{max} of rosuvastatin administered without PF-07081532 or coadministered with PF-07081532 will be analyzed using a mixed effect model with treatment 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 models. 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. The 2 test treatments will be 'rosuvastatin and PF-07081532 80 mg QD' (Period 5) and 'rosuvastatin and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'rosuvastatin without PF-07081532' (Period 2).

Natural $\log_e$ transformed AUC_{inf} (as data permit), AUC_{last} and C_{max} of dabigatran administered alone or coadministered with PF-07081532 will be analyzed and reported separately using the same mixed effect model as described above for rosuvastatin. For dabigatran, the 2 test treatments will be 'dabigatran and PF-07081532 80 mg QD' (Period 4) and 'dabigatran and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'dabigatran alone' (Period 1).

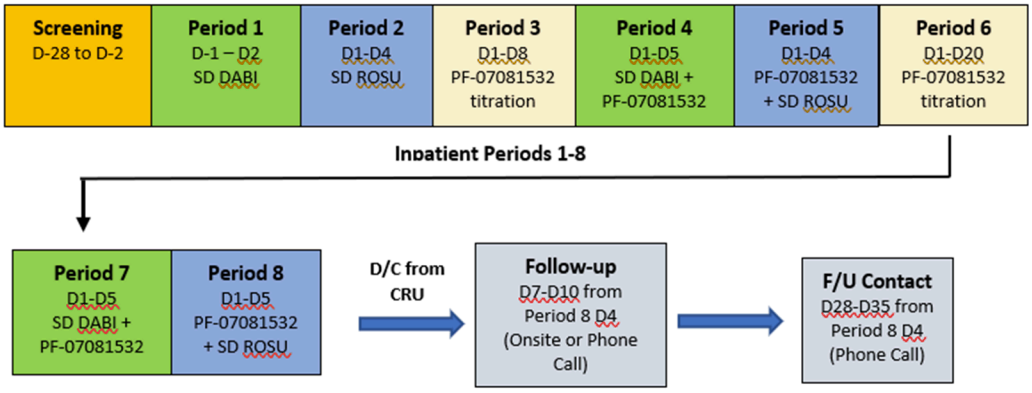
Ethical Considerations:

PF-07081532 is not expected to provide any long-term clinical benefit to the healthy obese adult female and male participants in this study. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

Based on experience with PF-07081532 and other marketed GLP-1R agonists, the potential risks for PF-07081532 include thyroid C-cell tumors, pancreatitis, hypoglycemia, renal function impairment, gastrointestinal adverse reactions, diabetic retinopathy complications, suicidal ideation and behavior, changes in heart rate and blood pressure, weight loss, and/or acute gallbladder disease.

Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods and avoid vaccination with live attenuated vaccines.

1.2. Schema


Screening
D-28 to D-2
Period 1
D-1 – D2
SD DABI
Period 2
D1-D4
SD ROSU
Period 3
D1-D8
PF-07081532
titration
Period 4
D1-D5
SD DABI +
PF-07081532
Period 5
D1-D4
PF-07081532
+ SD ROSU
Period 6
D1-D20
PF-07081532
titration
Inpatient Periods 1-8
Period 7
D1-D5
SD DABI +
PF-07081532
Period 8
D1-D5
PF-07081532
+ SD ROSU
D/C from
CRU
Follow-up
D7-D10 from
Period 8 D4
(Onsite or Phone
Call)
F/U Contact
D28-D35 from
Period 8 D4
(Phone Call)

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES 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. Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	**Screening**	**Period 1 (DE only)**		**Period 2 (ROSU only)**	**Period 3 (PF-07081532 only)**			**Period 4 (PF-07081532 + DE)**		**Period 5 (PF-07081532 + ROSU)**
Day in Study Period[a]	**-28 to -2**	**-1**	**1-2**	**1-4**	**1**	**2-7**	**8**	**1-4**	**5**	**1-4**
Days in Study[b]	**-28 to -2**	**-1**	**1-2**	**3-6**	**7**	**8-13**	**14**	**15-18**	**19**	**20-23**
Informed consent and demography	X									
Outpatient visit (after ≥10 h fast)	X									
Medical history	X									
Eligibility criteria	X	X								
Physical exam[c] (height at Screening only)	X									
Review contraception use - WOCBP Only (Section 5.3.1)	X	X								
Review drug, alcohol/tobacco use	X	X								
COVID-19 screening[d]		X								
C-SSRS and PHQ-9	X	X					X			
Review prior or concomitant treatments	X	X	→	→	→	→	→	→		→
AE monitoring	X	X	→	→	→	→	→	→	→	→
Inpatient stay at CRU		X	→	→	→	→	→	→	→	→
Body weight	X		X[l]		X[l]		X[l]			X[l]
Supine 12-lead ECG	X		X[l]				X[l]			
Single, supine vital signs assessment[e]	X		X[l]		X[l]		X[l]			X[l]

Table 1. Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (DE only)		Period 2 (ROSU only)	Period 3 (PF-07081532 only)			Period 4 (PF-07081532 + DE)		Period 5 (PF-07081532 + ROSU)
Day in Study Period[a]	-28 to -2	-1	1-2	1-4	1	2-7	8	1-4	5	1-4
Days in Study[b]	-28 to -2	-1	1-2	3-6	7	8-13	14	15-18	19	20-23
Rosuvastatin administration				Table 4						Table 4
DE administration			Table 3					Table 3		
PF-07081532 administration[f]					X	X	X		Table 5	Table 4
PF-07081532 PK										
Rosuvastatin PK				Table 4	X[g]					
Dabigatran PK			Table 3					Table 3		
CCI										
Blood Sampling for:[h]										
- Chemistry	X	X					X			
- Calcitonin, amylase, lipase	X	X					X			
- Free T4, TSH, lipid panel, total bile acids	X	X								
- Hematology/ HbA1c	X	X					X			
- FSH[i], HIV, HBsAg, HCVAb, HCV RNA, C-peptide	X									
- PT/INR	X									
- Serum pregnancy test[j]	X	X								
CCI										
Urine Sampling for:										
- Urine drug test[k]	X	X								
- Urinalysis (and microscopy, as appropriate)	X									

Table 1. Overall Schedule of Activities Screening to Period 5

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Screening	Period 1 (DE only)		Period 2 (ROSU only)	Period 3 (PF-07081532 only)			Period 4 (PF-07081532 + DE)		Period 5 (PF-07081532 + ROSU)
Day in Study Period[a]	-28 to -2	-1	1-2	1-4	1	2-7	8	1-4	5	1-4
Days in Study[b]	-28 to -2	-1	1-2	3-6	7	8-13	14	15-18	19	20-23

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of investigational product (DE) on Day 1 of Period 1.

c. Complete physical exam at Screening; otherwise, brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

d. Participants will be screened for COVID-19 according to local procedures prior to being admitted to the clinic for confinement in Period 1. Subsequent testing will also be done according to local procedure if participants develop COVID-19 like symptoms. See also Section 8.3.5 (COVID-19 Specific Assessments). If a participant tests positive for SARS-CoV-2 infection, they will be discharged from the study.

e. Includes BP and PR predose.

f. Dosing to occur QD with breakfast as specified in Section 6.1.1.

g. The rosuvastatin PK sample is to be collected predose (0 hr) on Day 1 of Period 3.

h. Collection following fasting duration specified in Section 5.3.2.

i. FSH for female participants to confirm PM status only. Serum β-hCG for all WOCBP; test result should confirm no pregnancy prior to dosing.

CCI

k. Participants may undergo random urine drug testing at the discretion of the investigator.

l. Assessments to be done on Day 1 of Periods 1, 3, and 5 and prior to IP administration on all days indicated.

Table 2. Overall Schedule of Activities Period 6 to ET

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Period 6 (PF-07081532 only)				Period 7 (PF-07081532 + DE)		Period 8 (PF-07081532 + ROSU)		F/U Visit[q]	F/U Contact Telephone	ET
Day in Study Period[a]	1-5	6-10	11-15	16-20	1-4	5	1-4	5	7-10	28-35	-
Days in Study[b]	24-28	29-33	34-38	39-43	44-47	48	49-52	53[f]	59-62	80-87	-
Outpatient visit (after ≥10 hr fast)									X		
Physical exam											X[c]
Review contraception use - WOCBP Only (Section 5.3.1)									X	X	
Review drug, alcohol/tobacco use									X		
COVID-19 screening[d]											
C-SSRS and PHQ-9[e]	X			X				X	X		X
Review prior or concomitant treatments	→	→	→	→	→		→	X	X	X	
AE monitoring	→	→	→	→	→		→	X	X	X	
Inpatient stay at CRU	→	→	→	→	→		→	X[i]			
Body weight[g]	X		X	X				X[i]	X		X
Supine 12-lead ECG		X[h]						X[i]			X
Single, supine vital signs assessment[j]	X		X	X				X[i]	X		X
Blood Sampling for:[k]											
- Chemistry	X[l]			X[l]				X[i]	X		X
- Calcitonin, amylase, lipase				X[l]				X[i]			X
- Free T4, TSH, lipid panel, total bile acids								X[i]			X
- Hematology/HbA1c				X[l]				X[i]	X		X
- Serum pregnancy test[m]								X[i]			
Rosuvastatin administration							Table 4				
DE administration					Table 3						
PF-07081532 administration[n]	→	→	→	→		Table 5	Table 4				
PF-07081532 PK											X
Rosuvastatin PK	X[o]							Table 4			
Dabigatran PK					Table 3						
CCI											
Urine Sampling for:											
- Urine drug test[p]											
- Urinalysis (and microscopy, as appropriate)											X

a. Day relative to start of dosing Day 1 of that Period.

b. Day relative to first dose of investigational product (DE) on Day 1 of Period 1.

Table 2. Overall Schedule of Activities Period 6 to ET

Visit Identifier Abbreviations used in this table may be found in Appendix 9	Period 6 (PF-07081532 only)				Period 7 (PF-07081532 + DE)		Period 8 (PF-07081532 + ROSU)		F/U Visit[q]	F/U Contact Telephone	ET
Day in Study Period[a]	**1-5**	**6-10**	**11-15**	**16-20**	**1-4**	**5**	**1-4**	**5**	**7-10**	**28-35**	-
Days in Study[b]	**24-28**	**29-33**	**34-38**	**39-43**	**44-47**	**48**	**49-52**	**53**[f]	**59-62**	**80-87**	-

c. Brief exam if findings during previous exam or new/open AEs, if appropriate, at investigator discretion.

d. Participants will be screened for COVID-19 according to local practice prior to being admitted to the clinic for confinement in Period 1. A subsequent test will be done according to local procedure if participants develop COVID-19 like symptoms. See also Section 8.3.5 (COVID-19 Specific Assessments). If participants test positive for SARS-CoV-2 infection, they will be discharged from the study.

e. C-SSRS and PHQ-9 will be administered in Period 6 on Days 5 and 19, and in Period 8 on Day 5 (discharge from CRU).

f. Discharge from CRU.

g. Body weight to be obtained on Days 5, 12 and 19 in Period 6.

h. ECG to be obtained on Day 10 of Period 6.

i. Assessments to be obtained on Day 5 of Period 8 prior to D/C from the CRU.

j. Includes BP and PR predose; to be obtained on Days 5, 12 and 19 in Period 6.

k. Collection following fasting duration specified in Section 5.3.2.

l. Chemistry to be obtained on Days 1 and 20 in Period 6; calcitonin, amylase, lipase and hematology to be obtained on Day 20 in Period 6.

m. Serum β-hCG for all WOCBP

n. Dosing to occur QD with breakfast. Note that there is no PF-07081532 administration on Study Day 53 or anytime thereafter.

o. The rosuvastatin PK sample is to be collected predose (0 hr) on Day 1 of Period 6.

p. Participants may undergo random urine drug testing at the discretion of the investigator.

q. The follow-up visit 7-10 days after the last dose of study intervention (Period 8, Day 4) can be on-site or via telephone call. Whether the follow-up visit is on-site or via telephone call is at the discretion of the Investigator. Regardless of location (ie, on site or telephone call), contraception use, drug, alcohol/tobacco use, concomitant medications and AEs must be reviewed/assessed as appropriate.

Table 3. Schedule of Activities – Period 1 (DE ONLY), Period 4 (DE + PF-07081532 80 mg QD) and Period 7 (DE + PF-07081532 260 mg QD)

Study Day in Period	1									2	3[c]
Hours Relative to Dosing at 0 hr	0	0.5	1	2	3	4	6	8	12	24	48[c]
DE administration	X[a]										
PF-07081532 administration *(Periods 4 and 7 only)*	X[a]									X	X
Blood sampling for:[b]											
- Dabigatran (total) PK	X	X	X	X	X	X	X	X	X	X	X
CCI											

a. Dosing to occur with breakfast as specified in Section 6.1.1.
b. Collection following fasting duration as specified in Section 5.3.2.
c. There is no Day 3 in Period 1 and the 48-hour dabigatran PK sample in Period 1 is the same as the 0-hour sample in Period 2.

Table 4. Schedule of Activities –Period 2 (Rosuvastatin ONLY), Period 5 (Rosuvastatin + PF07081532 80 mg QD), and Period 8 (Rosuvastatin + PF-07081532 260 mg QD)

Study Day in Period	1										2	3	4	5
Hours Relative to Dosing at 0 hr	0	1	2	3	4	5	6	8	10	14	24	48	72	96[c]
Rosuvastatin administration	X[a]													
PF-07081532 administration *(Periods 5 and 8 only)*	X[a]										X	X	X	
Blood sampling for:[b]														
- Rosuvastatin PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X
- Dabigatran (total) PK *(Period 2 only)*	X[d]													
CCI														
- PF-07081532 PK *(Periods 5 and 8 only)*	X[e]													

a. Dosing to occur with breakfast as specified in Section 6.1.1.
b. Collection following fasting duration as specified in Section 5.3.2.
c. The 96-hour PK rosuvastatin samples in Periods 2 and 5 are the same as the 0-hour PK samples on Day 1 in Periods 3 and 6, respectively.
d. For Period 2 only, the 0-hr dabigatran PK sample is the same as the 48-hr PK sample from Period 1.
e. The 0-hr PF-07081532 PK samples in Periods 5 and 8 are the same as the 24-hr PK samples from Day 5 of Periods 4 and 7, respectively.

Table 5. Schedule of Activities – Day 5 of Period 4 (DE + PF-07081532 80 mg QD) and Period 7 (DE + PF-07081532 260 mg QD)

Study Day in Period	**5**									
Hours Relative to Dosing at 0 hr	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**10**	**14**	**24[c]**
PF-07081532 administration	X[a]									
Blood sampling for:[b]										
- PF-07081532 PK	X	X	X	X	X	X	X	X	X	X

a. Dosing to occur with breakfast as specified in Section 6.1.1.
b. Collection following fasting duration as specified in Section 5.3.2.
c. Note: the 24-hour samples for Period 4 Day 5 and Period 7 Day 5 are the same as the 0-hour samples in Period 5 Day 1 and Period 8 Day 1, respectively.

2. INTRODUCTION

GLP-1 is a neuroendocrine hormone that is predominantly released from the small intestine in response to food intake.[1] GLP-1 activation of the GLP-1R stimulates insulin release, inhibits glucagon secretion in a glucose-dependent manner, and delays gastric emptying.[2,3] In addition, GLP-1 has been shown to increase satiety and suppress food intake.[4]

PF-07081532 is an orally administered, potent and selective GLP-1R agonist in development as an adjunct to diet and exercise, to improve glycemic control in T2DM, and for chronic weight management in a population that is overweight with co-morbidities or obese.

2.1. Study Rationale

In vitro data indicate the potential for PF-07081532 to inhibit both the BCRP and P-gp transporters, therefore, this study will evaluate the impact of PF-07081532 administration on the PK of rosuvastatin, a sensitive BCRP substrate, and dabigatran, the active moiety of the prodrug and P-gp substrate, DE.

The purpose of this study is to evaluate the effect of 2 dose levels of PF-07081532 on the SD pharmacokinetics of rosuvastatin and dabigatran (total) in otherwise healthy, overweight or obese adult participants, and to generate safety, tolerability, and PK data for further clinical development.

2.2. Background

T2DM is estimated to affect more than 424 million people worldwide,[5] and the prevalence of T2DM within the US is estimated to range from 12% to 14%.[6] Patients with poorly controlled T2DM have an increased risk of developing complications associated with both microvascular and macrovascular disease, including nephropathy, neuropathy, retinopathy, cardiovascular disease and stroke; and are at 2 to 4 times increased risk of mortality than adults who do not have diabetes.[7] While existing pharmacological options for the treatment of diabetes may provide satisfactory glycemic control for some patients, there remains a large number of patients who do not achieve target glycated HbA1c levels, suggesting a need for additional therapeutic options.

Obesity is a chronic disease that is associated with serious co-morbidities, including T2DM, dyslipidemia, hypertension, atherosclerosis, obstructive sleep apnea and certain cancers,[8] and is also associated with increased all-cause mortality.[9] The global burden of obesity is high with more than 600 million adults estimated to have obesity worldwide. In addition, the prevalence of obesity has doubled in more than 70 countries since 1980 and poses a major public health challenge.[10] First line treatment for obesity is lifestyle intervention including diet, exercise, and behavioral therapy. While effective in many patients, lifestyle intervention is often not sustainable, and many patients regain weight after initial weight loss.[11] Pharmacotherapy has been approved for the long-term treatment of obesity and can be a useful adjunct to lifestyle intervention to augment and maintain weight loss.

Marketed injectable GLP-1R agonists have demonstrated robust glycemic efficacy, weight loss, and cardiovascular safety, with more than one marketed agent demonstrating

cardiovascular benefit.[12] Based on the clinical experience with injectable GLP-1R agonists, an oral, small molecule GLP-1R agonist is expected to improve glucose control and reduce HbA1c levels in patients with T2DM, and to decrease appetite and body weight, resulting in weight loss in patients with T2DM and obesity, while avoiding the subcutaneous injection required by currently available peptidic GLP-1R agonists.

2.2.1. Nonclinical Pharmacology

Refer to the IB for details on the nonclinical pharmacology of PF-07081532.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

In rats and monkeys following single IV and oral dosing, PF-07081532 exhibited low CL_p (13 and 0.6 mL/min/kg, respectively), with low to moderate steady-state V_{ss} (0.76 and 0.21 L/kg, respectively), leading to a $t_{½}$ of 1.6 hours in rats and 8.8 hours in monkeys. Renal excretion was negligible in both species, and biliary excretion was minimal in rats. The systemic exposure (assessed by AUC and C_{max}) of PF-07081532 following oral repeat doses generally increased in a dose-proportional manner.

In vitro, PF-07081532 was a substrate for the hepatic uptake transporter, OATP1B3, but not for OATP1B1. Coadministration of an OATP inhibitor with PF-07081532 in monkeys resulted in a notable increase in the plasma AUC exposure of PF-07081532 and corresponding decrease in CL, suggesting a potential role for OATP transport in the uptake-limited CL in monkeys.

PF-07081532 was examined for in vitro inhibition of the various efflux, hepatic uptake, and renal transporters. DDI risk was assessed according to the EMA[13] and the Draft FDA[14] Guidance documents for drug interactions intended to flag potential need for an in vivo DDI study. Based on these guidances, at a clinical dose of 260 mg QD, PF-07081532 may have the potential to inhibit BCRP, OATP1B1, OATP1B3, MATE1, MATE2K, and intestinal MDR1/P-gp.

Further assessment was conducted using a more physiologically relevant static mechanistic model with the projected C_{max} (reversible inhibition) or C_{av} (time-dependent inhibition) in plasma, intestinal lumen, enterocytes, liver, and portal inlet concentrations while incorporating a predicted liver-to-plasma unbound ratio (kpuu = 14.4) and ka, at a clinical dose of 260 mg. No clinically relevant transporter DDIs were predicted using this model.

Refer to the IB for more details on the nonclinical PK and metabolism of PF-07081532.

2.2.3. Nonclinical Safety

PF-07081532 has been evaluated in a comprehensive nonclinical safety package that includes toxicity studies up to 6 months (in rats) and 9 months (in monkeys), as well as reproductive and developmental toxicology studies in rats and rabbits. Based on the nonclinical studies conducted, the target organs and systems identified with PF-07081532 administration include the heart, stomach and liver.

In the 6-month pivotal study with 1-month recovery phase in rats, oral gavage administration of PF-07081532 for 6 months did not result in any mortality or adverse effects in any of the study parameters or endpoints evaluated resulting in the high dose being the NOAEL. The exposure at this dose provided exposure margins of 40× and 29× (C_{max} and AUC_{24}, respectively) over the highest clinical dose planned (260 mg).

In the 9-month pivotal study in cynomolgus monkeys, PF-07081532 was administered by oral gavage with doses titrating up. There were no adverse findings in the endpoints evaluated in this study. The primary effects were consistent with the expected pharmacology of the test article which included decreased body weight associated with decreased food consumption, and secondary changes in clinical chemistry and hematology parameters. At the NOAEL dose, the exposure margins were 5.2× and 4.6× (C_{max} and AUC_{24}, respectively) over the highest clinical dose (260 mg QD) planned.

The NOAELs in the 6-month rat or 9-month monkey pivotal toxicity studies were 100 mg/kg/day in both species, with associated unbound C_{max} of 768 ng/mL and unbound AUC_{24} of 8270 ng•h/mL in rats and unbound C_{max} of 98.5 ng/mL and unbound AUC_{24} of 1300 ng•h/mL in monkeys.

PF-07081532 was not genotoxic in either in vitro or in vivo assays. In addition, PF-07081532 was negative in the 3T3 Neutral Red uptake Phototoxicity Test, indicating that PF-07081532 is not phototoxic.

Refer to the IB for more details on the nonclinical safety of PF-07081532.

2.2.4. Clinical Overview

As of issuance of this protocol, 2 Phase 1 studies evaluating PF-07081532 have been completed. In total, 88 participants have been randomized including 22 healthy adult participants, 51 adult participants with T2DM, and 15 adult participants with obesity. A total of 74 unique participants have been exposed to at least 1 dose of PF-07081532. The safety profile of PF-07081532 was assessed in these 2 completed clinical studies and, to date, administration of PF-07081532 at single doses up to 200 mg and multiple doses up to 180 mg QD has been considered safe, with the majority of the TEAEs being mild in intensity.

One Phase 1 study, C3991003, recently concluded. This inpatient study enrolled participants with T2DM inadequately controlled on metformin, and participants with obesity, to receive PF-07081532 or placebo QD for 42 days. The starting dose for the first cohort of this study was 20 mg QD of PF-07081532, with subsequent dose levels determined based on emerging data; the maximum dose administered was 80 mg QD. While final clinical data from this study are not yet available, as of issuance of this protocol, there have been no deaths, SAEs or AEs of severe intensity reported.

Refer to the IB for more details on the clinical safety of PF-07081532.

2.2.4.1. Clinical Pharmacokinetics

The clinical PK of PF-07081532 in adult participants have been evaluated to date in 2 completed studies (C3991001 and C3991002). The results of these completed studies are summarized in the PF-07081532 IB.

In Study C3991001 following administration of single oral doses of PF-07081532 under fasted conditions to healthy participants, PF-07081532 was absorbed relatively rapidly with a median T_{max} of 1.00 to 4.02 hours (individual T_{max} values ranged between 0.5 and 6 hours). Based on the individual plasma concentration-time profiles, the absorption phase exhibited multiple peaks, especially at the higher dose levels. Mean $t_{½}$ ranged from 18.03 to 20.90 hours across all doses. Plasma C_{max} increased less than proportionally across the entire investigated dose range (from 10 mg to 200 mg), while plasma AUC_{inf} increased less than proportionally from 10 mg to 30 mg and approximately proportionally from 30 mg to 200 mg. Inter-participant variability for PF-07081532 exposure was low to moderate and ranged from 9% to 36% CV for C_{max} and 15% to 44% CV for AUC_{inf} across all doses. Overall, the results indicate that PF-07081532 may be administered without regard to food.

In Study C3991002 following administration of PF-07081532, C_{max} was observed at 1 to 2 hours on Day 1, and 2 to 8 hours following the last dose on Day 28 or 42. Across all dose groups, the mean $t_{½}$ ranged from 20.70 to 26.50 hours. PF-07081532 exposure generally increased in an approximately dose-proportional manner across the dose range studied, and accumulation of less than 2.1-fold was observed. Urinary recovery of unchanged PF-07081532 was low, with less than 0.2% of the dose recovered in the 24-hour dosing interval following last dose administration. Inter-participant variability for PF-07081532 exposure ranged from 17% to 51% CV for C_{max} and 15% to 62% CV for AUC_{tau} across all doses. No substantial differences in PF-07081532 exposure (C_{max} and AUC_{tau}) were observed between participants with T2DM and obesity either after single dose (Day 1, 10 mg) or multiple dose (Day 28, 120 mg and Day 42, 180 mg) administration.

In Study C3991003 following single-dose (Day 1) and multiple-dose (Day 42) administration of PF-07081532, peak plasma PF-07081532 concentrations (C_{max}) were observed at 1 to 2 hours and 2 to 5 hours, respectively. Terminal $t_{½}$ averaged 24.37 to 26.04 hours following multiple-dose administration (Day 42). PF-07081532 exposure (C_{max} and AUC_{τ}) increased in an approximate dose-proportional manner across the dose range studied. Accumulation with QD dosing was less than 2-fold. No substantial differences were observed in the achieved exposures (both C_{max} and AUC_{tau}) between participants with T2DM and obesity either after single-dose (Day 1, 20 mg) or multiple-dose (Day 42, 60 mg) administration.

Refer to the IB for more details on the clinical PK of PF-07081532.

2.3. Benefit/Risk Assessment

PF-07081532 is not expected to provide any long-term clinical benefit to healthy obese participants. This study is designed primarily to generate safety, tolerability, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB, which is the SRSD for this study. The SRSD for the site sourced rosuvastatin and DE products are the corresponding USPIs.[15,16]

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07081532		
Thyroid C-cell tumors	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, dulaglutide, semaglutide, and exenatide) due to dose-dependent and treatment duration-dependent thyroid C-cell tumors in nonclinical studies in rats and mice at clinically relevant exposures. Of note, similar tumors were not seen in rodent studies with PF-07081532, likely as PF-07081532 does not stimulate rodent GLP-1 receptors.	Potential participants with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 are excluded from the clinical development program. Thyroid function tests are included in the clinical trial protocols to monitor participants' thyroid function.
Pancreatitis	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). One SAE of obstructive pancreatitis has been observed in the PF-07081532 clinical trial program, which was considered to be treatment-related by the investigator, but unrelated by the sponsor.	Per exclusion criteria, potential participants with acute pancreatitis or a history of chronic pancreatitis are not eligible for study entry. Serum amylase and lipase are monitored during clinical studies.
Hypoglycemia	Clinical trials with injectable GLP-1R agonists have not demonstrated an increased risk for hypoglycemia. But when administered in combination with anti-diabetic agents that are known to have an increased risk of hypoglycemia (such as insulin or sulfonylureas), an increased risk for hypoglycemia was observed. Participants with obesity who do not have co-existing T2DM would not be taking anti-diabetic agents and therefore would not be expected to have an increased risk for hypoglycemia. A low overall frequency of generally mild hypoglycemia has been reported in the PF-07081532 clinical development program to date.	Anti-diabetic medications are prohibited in this study, and blood glucose is monitored as a part of the lab assessments during the study. Participants are informed about the signs and symptoms of hypoglycemia and are monitored for these symptoms during the study.
Impairment in renal function	Potential risks are based on product labeling for injectable GLP-1R agonists, and predominantly occur in patients with	Per exclusion criteria, potential participants with significant

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	significant nausea, vomiting, and dehydration. In the clinical trial program only one mild adverse event (Preferred Term Blood creatinine increased) has been observed.	renal impairment are not eligible for study entry. Renal function is monitored by lab assessments of serum BUN, creatinine and eGFR. Hydration will be encouraged, and reduced fluid intake and evidence of dehydration, if detected, will be treated by close clinical follow-up.
Gastrointestinal adverse reactions	The potential risks are based on product labeling for injectable GLP-1R agonists (ie, liraglutide, exenatide, semaglutide and dulaglutide). Gastrointestinal AEs, the majority of which were mild in severity, have been observed in the clinical program with PF-07081532. In nonclinical studies with PF-07081532, gastrointestinal adverse effects were observed in rats and monkeys.	Participants are monitored during the clinical studies to prevent potential sequelae of any severe gastrointestinal reactions, eg, dehydration. Hydration will be encouraged and concomitant medication for nausea is permitted in the study. During the study, PF-07081532 will be titrated from a 20 mg QD dose to 40 mg QD over 8 days, and from 120 mg QD to 260 mg QD over 20 days, in an attempt to minimize gastrointestinal adverse reactions.
Diabetic retinopathy complications	The potential risk is based on the product labeling for the injectable GLP-1R agonist semaglutide and dulaglutide in patients with T2DM. There are no nonclinical or clinical data involving PF-07081532 to suggest an increased risk of diabetic retinopathy complications.	Potential participants with diabetes mellitus are excluded from this clinical study.
Suicidal ideation and behavior	The potential risk is based on the product labeling for the injectable GLP-1R agonists liraglutide and semaglutide for obesity based on long-term studies. Suicidal ideation has not been observed in the PF-07081532 clinical studies to date.	Suicidal ideation and behavior, along with symptoms of depression, will be monitored at specified intervals during the study using the C-SSRS and PHQ-9 questionnaires, with referral to a MHP for further evaluation if needed.
Changes in heart rate	Potential risk is based on the product labeling for the injectable GLP-1R agonists, liraglutide and semaglutide, for T2DM and obesity. Modest increases in HR have been noted in the early clinical studies with PF-07081532, with most values remaining within the normal range.	HR is monitored during the clinical study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Declines in body weight	Decreased appetite and body weight loss have been reported for marketed GLP-1R agonists, and declines in body weight have been noted at higher doses of PF-07081532.	Weight is collected at multiple time points and will be monitored throughout the trial.
Acute gallbladder disease	Potential risk is based on the product labeling for the injectable GLP-1R agonists, semaglutide and liraglutide, for T2DM and obesity. Acute gallbladder disease has not been observed in the PF-07081532 clinical trial program to date.	Participants with symptomatic gallbladder disease are excluded from this clinical study. Participants are monitored for AEs and laboratory tests that may suggest development of acute gallbladder disease.
Study Intervention: Rosuvastatin		
Skeletal muscle effects (eg, myopathy and rhabdomyolysis): Risks increase with use of 40 mg dose, advanced age (≥65 years), hypothyroidism, renal impairment, and combination use with cyclosporine, atazanavir/ritonavir, lopinavir/ritonavir, or simeprevir. Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. These risks can occur at any dose level, but are increased at the highest dose (40 mg) • **Liver enzyme abnormalities:** Persistent elevations in hepatic transaminases can occur. Perform liver enzyme tests before initiating therapy and as clinically indicated thereafter.	Risk based on product labeling.	Participants will be monitored in an inpatient clinical research unit. Liver enzyme levels will be monitored throughout the study. A single 10 mg dose is expected to pose minimal risk to the participants in this study.
Study Intervention: DE		
Risk of bleeding: serious and, sometimes, fatal bleeding. Promptly evaluate signs and symptoms of blood loss.	Risk based on product labeling.	A single oral dose of 150 mg is administered in the study and poses minimal risk. Participants will be monitored in an inpatient clinical research unit.
Other		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk of COVID-19 exposure during study	During the pandemic, study participants could be infected with the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Participants undergo COVID-19 specific assessments prior to admission to study site and according to the SoA.

2.3.2. Benefit Assessment

While PF-07081532 is not expected to provide any significant long-term clinical benefit to the healthy obese participants in this relatively short-term study, potential benefits may include weight loss, receiving medical evaluations/assessments associated with clinical study visits (eg, physical examinations, ECGs, labs), and contributing to the process of developing a potential new therapy for T2DM and obesity.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07081532 may be found in the IB, which is SRSD, for this study.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07081532 are justified by the anticipated benefits that may be afforded to participants who are overweight or obese.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of PF-07081532 administration on the single-dose PK of total dabigatran in otherwise healthy overweight or obese participants.	• Dabigatran (total) PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 1, 4, and 7.
• To estimate the effect of MD PF-07081532 on the single-dose PK of rosuvastatin in otherwise healthy overweight or obese participants.	• Rosuvastatin PK parameters: AUC_{inf} (if data permit* otherwise AUC_{last}) in Periods 2, 5, and 8.
Secondary:	**Secondary:**
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with DE in otherwise healthy overweight or obese participants.	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the safety and tolerability of PF-07081532 administered separately and in combination with rosuvastatin in otherwise healthy overweight or obese participants	• Assessment of TEAEs, clinical laboratory abnormalities, vital signs, body weight, and ECG parameters. • Assessment of mental health as determined by C-SSRS and PHQ-9.
• To evaluate the effects of PF-07081532 on additional PK parameters for total dabigatran.	• Additional plasma PK parameters for total dabigatran: Cmax and T_{max}; and CL/F, V_z/F, $t_{½}$ as data permit, in Periods 1, 4, and 7.
• To evaluate the effects of PF-07081532 on additional PK parameters for rosuvastatin.	• Additional plasma PK parameters for rosuvastatin: Cmax and Tmax; and CL/F, Vz/F, $t_{½}$ as data permit, in Periods 2, 5, and 8.
• To evaluate the MD pharmacokinetics of PF-07081532 in healthy overweight or obese participants.	• PF-07081532 plasma pharmacokinetic parameters: AUC_{24}, C_{max}, T_{max}.
Tertiary:	**Tertiary:**
CCI [redacted]	

* Should it be deemed that too few AUC_{inf} estimates (eg, less than 16 for a single treatment) are obtained from the evaluable participants, AUC_{last} may be selected as the primary endpoint for CSR reporting. This will be considered for the rosuvastatin and dabigatran objectives separately.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, fixed-sequence, 8-period study to evaluate the effect of PF-07081532 administration on the SD pharmacokinetics of dabigatran (total) and

rosuvastatin in otherwise healthy overweight or obese adult participants. The 8 periods will be conducted sequentially without any washout days between periods.

All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. Screening will occur within 28 days of the first dose of study intervention on Day 1 of Period 1. Participants who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and sponsor.

Approximately 24 participants will be enrolled.

The total duration of participation from the Screening Visit to the F/U outpatient telephone contact will be approximately 115 days or 16.5 weeks, approximately 8 weeks of which will be conducted on an inpatient basis.

The 54-day inpatient portion of the study will be conducted as follows:

Period 1: 3 days, includes CRU admission on Day -1 (DE 150 mg single dose);

Period 2: 4 days (rosuvastatin 10 mg single dose);

Period 3: 8 days (PF-07081532 titrated to 40 mg QD);

Period 4: 5 days (DE 150 mg single dose + PF-07081532 80 mg QD);

Period 5: 4 days (rosuvastatin 10 mg single dose + PF-07081532 80 mg QD);

Period 6: 20 days (PF-07081532 titrated to 260 mg QD);

Period 7: 5 days (DE 150 mg single dose + PF-07081532 260 mg QD);

Period 8: 5 days, includes discharge day from CRU (rosuvastatin 10 mg single dose + PF-07081532 260 mg QD).

The onsite F/U visit/telephone F/U contact will occur 7-10 days from the last dose of study intervention (Period 8, Day 4) and an outpatient telephone F/U contact will occur 28-35 days from the last dose of study intervention (Period 8, Day 4).

4.2. Scientific Rationale for Study Design

This is a Phase 1, open-label, fixed-sequence, 8-period drug-drug interaction study to evaluate the effect of PF-07081532 administration on the single-dose pharmacokinetics of dabigatran (total) and rosuvastatin in otherwise healthy overweight or obese adult participants. The intent of this study is to generate safety, tolerability, and PK data for further clinical development.

PF-07081532 was examined for in vitro inhibition of the various efflux, hepatic uptake, and renal transporters. DDI risk was assessed according to the EMA[13] and the Draft FDA[14] Guidance documents for drug interactions, which are intended to flag potential need for an in vivo DDI study. Based on these guidances, at a clinical dose of 260 mg QD, PF-07081532 may have the potential to inhibit BCRP, OATP1B1, OATP1B3, MATE1, MATE2K, and intestinal MDR1/P-gp. Further assessment was conducted using a more physiologically relevant static mechanistic model at a clinical dose of 260 mg QD; no clinically relevant

transporter DDIs were predicted using this model. Given the inconsistent predictions obtained using the 3 modeling approaches, and the strong likelihood that BCRP and P-gp substrates will be administered to the target populations, rosuvastatin will be evaluated as a BCRP substrate, and dabigatran, the active moiety of the prodrug and P-gp substrate DE, will be evaluated in this study to derisk the DDI potential with PF-07081532. Rosuvastatin is also a substrate for OATP; however, previous results using CP-I as a biomarker for OATP inhibition in C3991003 indicate relatively small changes (<13%) from baseline in CP-I AUC_{24} and C_{max} across all PF-07081532 treatment groups that were not considered to be clinically relevant.

The impact of PF-07081532 administration on inflammatory/cardiovascular risk biomarkers will be assessed in this study. CRP is a well-established biomarker of inflammation, and its elevation is a downstream manifestation of pro-inflammatory signaling by IL-6.[17] Both CRP and IL-6 are elevated in obesity and in T2DM.[18-20] Since elevated CRP is also associated with the development of cardiovascular disease, it has sometimes been used as a biomarker for cardiovascular risk.[18,19] Indeed, trials have shown that targeted inhibition of this inflammatory pathway, as measured by changes in CRP concentrations, can reduce the rate of cardiovascular events.[17,21,22] Likewise, fibrinogen is a biomarker for both thrombogenesis and inflammation, and elevated levels are significantly associated with an increased risk of CV and all-cause mortality in patients with CAD.[23]

Weight loss is associated with reductions in CRP and, therefore, inflammation, regardless of the modality used to promote weight loss.[23,24] GLP-1RAs are known to improve glycemic control and reduce body weight, and have exhibited anti-inflammatory effects, including reduction of CRP.[25,26] For example, in overweight and obese individuals with or without T2DM, once-weekly semaglutide 2.4 mg reduced CRP concentrations irrespective of baseline BMI/bodyweight/glycemic status compared with placebo.[27]

Since data suggest a potential anti-inflammatory role for GLP-1RAs in obesity and T2DM (with the potential to reduce cardiovascular risk), and because PF-07081532 Phase 3 studies plan to enroll patients with increased CV risk, hs-CRP, IL-6, and fibrinogen will be collected in the current study as a preliminary assessment of the impact of PF-07081532 on the levels of these biomarkers.

PF-07081532 will be titrated from 20 mg to 260 mg QD and all dosing will be administered with food in order to minimize gastrointestinal related AEs.

Participants will include overweight or obese males and females to represent the target population. Additionally, WOCBP will be permitted with the stipulation that they comply with the contraceptive guidelines provided in Appendix 4.

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data are not available for PF-07081532, 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

CCI [redacted]

4.3. Justification for Dose

PF-07081532: The drug-drug interactions will be assessed at 2 PF-07081532 dose levels, 80 mg QD and 260 mg QD. These doses represent a potential therapeutic dose for T2DM, and the highest dose being assessed in the Phase 2 study (C3991004) for T2DM and obesity, respectively. Exposure margins for the PF-07081532 260 mg QD dose are provided in Section 2.2.3.

The titration to PF-07081532 80 mg QD is planned to occur over an 8-day period in increments of 20 mg to 40 mg QD every 4 days, and from 120 mg QD to 260 mg QD over 20 days, in increments of 20 mg to 40 mg every 4 days (Section 6.1, Table 7). Titration increments as short as 1-2 days have been administered previously in Study C3991002 and were sufficiently tolerated.

Based on emerging data from other clinical studies that may become available during the conduct of this study, the titration rate, incremental increases in dose, and/or the PF-07081532 doses at which rosuvastatin or the dabigatran PK interactions are evaluated may be adjusted. If participants are not able to tolerate titration to higher doses of PF-07081532 (eg, ≥180 mg QD), titration to the next dose level may be delayed temporarily or titration to a maximum tolerated dose may be permitted, **with sponsor approval only**.

Rosuvastatin: In a single dose escalation study, rosuvastatin was safe and well tolerated at doses up to 80 mg.[28] The most common AEs reported were headache and rash. There was no evidence of a relationship between the frequency of AEs and rosuvastatin dose. No SAEs were reported.

After oral administration of rosuvastatin in healthy participants, C_{max} occurred at 3 to 5 hours post dose. Co-administration of rosuvastatin with food had no impact on its exposure. Both C_{max} and AUC increased in an approximately dose-proportional manner. The elimination half-life of rosuvastatin is approximately 19 hours. Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter, OATP1B1, and the efflux transporter, BCRP.[15]

Most DDI studies involving rosuvastatin as a substrate are conducted at the 10 mg or 20 mg dose level.[29-31] The therapeutic dose of rosuvastatin may be as high as 40 mg. Since PF-07081532 may potentially increase rosuvastatin plasma exposure, 10 mg rosuvastatin was selected as a conservative dose in the current study and is expected to be well-tolerated.

Rosuvastatin PK will be assessed following multiple-dose administration of 80 mg QD and 260 mg QD PF-07081532 to steady-state. Residual samples for analysis of rosuvastatin PK may also be utilized for potential analysis of CP-I, an endogenous biomarker of OATP hepatic uptake. In vitro data indicate low risk for PF-07081532 inhibition of OATP, and only minor increases were observed for CP-I exposures in the C3991002 study. However, CP-I

has only been evaluated up to a maximum PF-07081532 dose of 180 mg QD, therefore, data collected in this study are expected to further elucidate whether PF-07081532 affects OATP-mediated uptake in humans at the highest dose (260 mg QD) being assessed in the Phase 2 study (C3991004) for T2DM and obesity. These samples will be analyzed at the discretion of the sponsor. If analysis of these CP-I samples is judged to be useful, the highest dose cohort (260 mg QD) may be assessed first and, if no meaningful effect of PF-07081532 is observed, the lower dose cohort (80 mg QD) may not be assayed.

Dabigatran: Dabigatran is the active moiety of the prodrug, dabigatran etexilate mesylate, and is an oral, direct thrombin inhibitor with antithrombotic effects.[16] The recommended dose of dabigatran etexilate mesylate is 150 mg taken orally twice daily, with or without food, for patients with creatinine clearance >30 mL/min for most indications.

After oral administration of DE in healthy participants, C_{max} occurred at 1 hour post administration in the fasted state. Co-administration of DE with a high fat meal delays the time to C_{max} by approximately 2 hours but has no effect on the bioavailability of dabigatran. The half-life of dabigatran in healthy participants is 12 to 17 hours.[16]

Dabigatran was well tolerated after administration of single oral doses of 10–400 mg DE to healthy participants.[32] Seven of 40 participants reported an AE, all of which were mild to moderate in severity. The most frequently reported AE was headache, but in no case was this considered related to treatment with the study drug. There were no significant findings in vital signs and ECGs, in particular heart rate and PR interval, nor in safety laboratory assessments. There were no deaths, no SAEs, and no AEs leading to withdrawal during the study.

In a drug interaction study with a single dose of verapamil 120 mg, a strong P-gp inhibitor, the AUC and C_{max} of dabigatran (150 mg) increased by 143% and 179%, respectively.[33] The treatments in this study were sufficiently well tolerated despite the increase in dabigatran exposures. The 150 mg dabigatran dose chosen for the current study is expected to be well tolerated.

DE is rapidly converted to dabigatran, which is the main moiety detected in the systemic circulation. Preclinical and clinical data suggest that DE, but not dabigatran, is a substrate of P-gp, therefore, changes in dabigatran exposure reflect an alteration in intestinal P-gp function.[16] A single dose of the perpetrator is sufficient to assess changes in P-gp probe drug absorption, as intestinal P-gp appears to have the most significant impact on DDIs. Therefore, DE will be co-administered with the initial dose of 80 mg and 260 mg PF-07081532 in Periods 4 and 7. (PF-07081532 will continue to be dosed for an additional 4 days in each of Periods 4 and 7 to allow steady-state exposures to be achieved prior to co-administration with single-dose rosuvastatin in Periods 5 and 8, respectively.) Additionally, verapamil, a P-gp inhibitor, was shown to increase dabigatran exposures by a greater magnitude when dosed 1 hour prior to DE administration as compared to simultaneous dosing.[33] Therefore, to assess near maximum intestinal exposures, and thus maximal P-gp modulation by PF-07081532, DE will be administered ~60 min following administration of PF-07081532.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all periods of the study, including the F/U telephone contact visit, approximately 28 to 35 days post last dose of study intervention in Period 8, Day 4.

The end of the study is defined as the date of the last visit (F/U telephone contact) of the last participant in the study.

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 aged 18 years or older (or the minimum age of consent in accordance with local regulations) at Screening.

    - Women can be of child-bearing potential, but cannot be pregnant, breastfeeding, or planning to become pregnant while participating in the study, may not be taking either oral contraceptives or non-oral hormonal contraceptives (with the exception of implantable progestogen only hormone contraception or intrauterine hormone releasing system), and must avoid vaccination with live attenuated vaccines.

    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 detailed medical history, physical examination (including blood pressure and pulse rate measurement), standard 12-lead ECG, and clinical laboratory tests.

Other Inclusion Criteria:

3. BMI: ≥ 25 kg/m^2 at Screening.

4. Stable body weight, defined as <5 kg change (per participant report) for 90 days before Screening.

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).

    - Any condition possibly affecting drug absorption (eg, prior bariatric surgery, gastrectomy, cholecystectomy or any area of intestinal resection, active inflammatory bowel disease or pancreatic insufficiency).

    - Other medical or psychiatric condition including recent or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

    - Known intolerance or hypersensitivity to a GLP-1R agonists, rosuvastatin or DE.

2. Diagnosis of type 1 or type 2 diabetes mellitus or secondary forms of diabetes at Screening. **Note:** women with prior diagnoses of gestational diabetes *during pregnancy only* are eligible if they meet the other eligibility criteria.

3. History of myocardial infarction, unstable angina, arterial revascularization, mechanical prosthetic heart valve, stroke, New York Association Functional Class II-IV heart failure, or transient ischemic attack within 6 months of Screening.

4. Any malignancy not considered cured (except basal cell carcinoma and squamous cell carcinoma of the skin); a study participant is considered cured if there has been no evidence of cancer recurrence in the previous 5 years (from Screening). Anyone with any history of pancreatic cancer will be excluded, even if it was resected and they were considered 'cured'.

5. Personal or family history of MTC or MEN2, or study participants with suspected MTC per the investigator's judgment.

6. Acute pancreatitis, history or repeated episodes of acute pancreatitis, or history of chronic pancreatitis.

7. Symptomatic gallbladder disease.

8. Medical history or characteristics suggestive of genetic or syndromic obesity or obesity induced by other endocrinological disorders (eg, Cushing Syndrome).

9. Known medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic active hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease, primary sclerosing cholangitis, autoimmune hepatitis, overlap syndrome, or prior known drug-induced liver injury.

10. History of HIV infection.

11. History of major depressive disorder or history of other severe psychiatric disorders (eg, schizophrenia or bipolar disorder) within the last 2 years from Screening.

12. Any lifetime history of a suicide attempt.

13. Other medical or psychiatric condition including recent or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

14. Recent history of bleeding, or risk of bleeding, including prior personal or familial history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder, or abnormal coagulation test (INR >1.3) result at Screening.

Prior/Concomitant Therapy:

15. 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 Prior and Concomitant Therapy for additional details.

16. Use of any medications that are BCRP, OATP, P-gp and/or CYP3A4/5 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Refer to Section 6.9 for additional details.

17. Use of pH-altering drugs.

18. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 for additional details.

Prior/Concurrent Clinical Study Experience:

19. Previous administration with an investigational product (drug or vaccine) 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).

20. Previous administration with a GLP-1R agonist within 90 days preceding the first dose of study intervention used in this study.

    Known prior participation in a trial involving PF-07081532 unless placebo treatment was received.

Diagnostic Assessments:

21. A PHQ-9 score ≥15 obtained at Screening or Day -1 in Study.

22. Response of "yes" to question 4 or 5, or on any suicidal behavioral question on the C-SSRS at Screening or Day -1 in Study.

23. A positive urine drug test.

24. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. BP should be measured in triplicate and the average of the 3 BP values should be used to determine the participant's eligibility. Note: At Screening, the participant's arm circumference should be measured (eg, using a flexible anthropometric tape) at the midpoint of the length of the upper arm, and the appropriate cuff selected and used throughout the study.

25. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF interval >450 ms, 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).

    a. If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

26. 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:

    - HbA1c ≥6.5%.
    - 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.
- TSH >1.5× ULN or < LLN.
- Serum calcitonin > ULN.
- INR >1.3.
- Amylase or lipase > ULN.
- Fasting blood glucose ≥126 mg/dL.
- Fasting C-peptide not WNL.
- eGFR <75 mL/min/1.73 m^2 as calculated by the CKD-EPI equation.
- Positive testing for HIV, HBsAg, HBcAb, or HCVAb. Study participants positive for HCVAb are to be excluded unless known to have been treated with a known curative therapy and negative for HCV RNA. Anyone who has a history of HBV that is treated/cleared is excluded. Hepatitis B vaccination is allowed.
- A positive SARS-CoV-2 test.

Other Exclusion Criteria:

27. Participation in a formal weight reduction program (eg, Weight Watchers) within 90 days prior to Screening.
28. 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).
29. Current use of tobacco or nicotine containing products in excess of the equivalent of 5 cigarettes per day.
30. Known or suspected illicit drug use.
31. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.
32. History of sensitivity to heparin or heparin-induced thrombocytopenia. Unwilling or unable to comply with the criteria or procedures in the study.

33. 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 nonhormonal contraception (except for implantable progestogen only hormone contraception or intrauterine hormone releasing systems) for the individual participant from the permitted list of nonhormonal 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 nonhormonal 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 nonhormonal 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 nonhormonal 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

- Participants must abstain from all food and drink (except water) for at least 4 hours prior to any safety laboratory evaluations (at least 12 hours if lipids are to be evaluated) and 10 hours prior to the collection of a predose PK sample.
- Water is permitted until 1 hour prior to study intervention administration. Water may be consumed without restriction beginning 1 hour after dosing.
- Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.
- 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.
- 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.

- 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. 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.

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.

A participant who qualified for this protocol but did not enroll within the 28-day screening window may be re-screened. In this situation, all screening procedures must be repeated, and the participant assigned a new 8-digit SSID number. This criterion would also apply to participants who screened for this study more than 28 days prior to dosing.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products/auxiliary medicinal 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 PF-07081532, rosuvastatin, and DE.

6.1. Study Intervention(s) Administered

Table 6. Study Interventions

Intervention Name	PF-07081532	Rosuvastatin	DE
Arm Name (group of participants receiving a specific treatment or no treatment)	All participants	All participants	All participants
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Capsule
Unit Dose Strength(s)	20 mg, 60 mg, 100 mg	10 mg	150 mg
Dosage Level(s)	PF-07081532 titrated from 20 mg QD to 260 mg QD from Period 3 through Period 8	Single 10 mg doses in Periods 2, 5, and 8	Single 150 mg doses in Periods 1, 4, and 7
Route of Administration	Oral	Oral	Oral
Use	Perpetrator	Substrate	Substrate
IMP or NIMP/AxMP	IMP	NIMP/AxMP	NIMP/AxMP
Sourcing	Provided centrally by the sponsor	Provided locally by the trial site	Provided locally by the trial site
Packaging and Labeling	Study intervention will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in commercial pack. Each commercial pack will be labeled as required per country requirement.	Study intervention will be provided in commercial pack. Each commercial pack will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-07081532	Rosuvastatin (Crestor®)	Dabigatran (Pradaxa®)

Table 7. Study Arms

Arm Title	Period 1: single-dose DE	Period 2: single-dose rosuvastatin	Period 3: PF-07081532 titration	Period 4: single-dose DE + PF-07081532	Period 5: single-dose rosuvastatin + PF-07081532	Period 6: PF-07081532 titration	Period 7: single-dose DE + PF-07081532	Period 8: single-dose rosuvastatin + PF-07081532
Arm Type	Baseline	Baseline	IMP titration only	Experimental (DDI)	Experimental (DDI)	IMP titration only	Experimental (DDI)	Experimental (DDI)
Arm Description	Participants will receive a single 150 mg dose of DE.	Participants will receive a single 10 mg dose of rosuvastatin.	Participants will receive PF-07081532 titrated from 20 mg QD to 40 mg QD over a total of 8 days.	Participants will receive a single 150 mg dose of DE with 80 mg PF-07081532 QD.	Participants will receive a single 10 mg dose of rosuvastatin on a background of 80 mg PF-07081532 QD.	Participants will receive PF-07081532 titrated from 120 mg QD to 260 mg QD over a total of 20 days.	Participants will receive a single 150 mg dose of DE with 260 mg QD PF-07081532.	Participants will receive a single 10 mg dose of rosuvastatin on a background of 260 mg QD PF-07081532.
Associated Intervention Labels	DE	Rosuvastatin	PF-07081532	DE + PF-07081532	Rosuvastatin + PF-07081532	PF-07081532	DE + PF-07081532	Rosuvastatin + PF-07081532

PF-07081532 will be provided by Pfizer as tablets at the CRU.

PF-07081532 will be presented to the participants in individual dosing containers.

PF-07081532 will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Rosuvastatin and dabigatran will be supplied by the CRU.

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive PF-07081532 with the breakfast meal at approximately 0800 hours (±2 hours). Investigator site personnel will administer PF-07081532, rosuvastatin, or DE during each period (as applicable per SoA) with ambient temperature water to a total volume of approximately 240 mL. Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. The study intervention will be administered according to the IP manual.

PF-07081532 must be administered within approximately 10 minutes of completion of the morning meal (Periods 3 through 8).

During the dabigatran DDI assessment periods (Periods 4 and 7), PF-07081532 will be administered first followed by administration of DE approximately 60 minutes later. When DE is administered alone (Period 1), it must be administered approximately 60 minutes after completion of the morning meal.

During the rosuvastatin DDI assessment periods (Periods 5 and 8), PF-07081532 will be administered first and rosuvastatin will be administered approximately 10 minutes later. When rosuvastatin is administered alone (Period 2), it must be administered within approximately 10 minutes of completion of the morning meal.

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.

Administration of study intervention will occur according to the study periods and dosing days listed in the SoA and Table 8.

Table 8. Study Interventions Administered

Study Period	Study Day	Drug and Dosage
Period 1, Days 1-2	1-2	SD DE 150 mg
Period 2, Days 1-4	3-6	SD Rosuvastatin 10 mg
Period 3, Days 1-4	7-10	PF-07081532 20 mg QD
Period 3, Days 5-8	11-14	PF-07081532 40 mg QD
Period 4, Days 1-5	15-19	PF-07081532 80 mg QD + SD DE 150 mg
Period 5, Days 1-4	20-23	PF-07081532 80 mg QD + SD Rosuvastatin 10 mg

Table 8. Study Interventions Administered

Study Period	Study Day	Drug and Dosage
Period 6, Days 1-4	24-27	PF-07081532 120 mg QD
Period 6, Days 5-8	28-31	PF-07081532 160 mg QD
Period 6, Days 9-12	32-35	PF-07081532 200 mg QD
Period 6, Days 13-16	36-39	PF-07081532 220 mg QD
Period 6, Days 17-20	40-43	PF-07081532 240 mg QD
Period 7, Days 1-5	44-48	PF-07081532 260 mg QD + SD DE 150 mg
Period 8, Days 1-5*	49-53*	PF-07081532 260 mg QD + SD Rosuvastatin 10 mg

*No drug administration in Period 8, Day 5 (Study Day 53); participants discharged from the CRU.

Modification of PF-07081532 dosing may be permitted **upon sponsor approval only** (see Section 6.6).

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 IP manual.

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 IP manual. 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 as described in the IP manual.

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 or participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Tablets or 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 tablets or capsules will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

The commercially available products, rosuvastatin and dabigatran, provided by the CRU will be prepared as per the label and in accordance with the protocol 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 rosuvastatin tablets and dabigatran 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

This is a non-randomized, open-label study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

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.

Participants will receive the PF-07081532 doses as described in Table 9.

Table 9. PF-07081532 Dosing Regimens

Period and QD PF-07081532 Dose	Number of PF-07081532 Tablets			Total Number of Tablets
	20 mg	60 mg	100 mg	
Period 3: 20 mg	1	-	-	1
Period 3: 40 mg	2	-	-	2
Period 4: 80 mg	1	1	-	2
Period 5: 80 mg	1	1	-	2
Period 6: 120 mg	1	-	1	2
Period 6: 160 mg	-	1	1	2
Period 6: 200 mg	-	-	2	2
Period 6: 220 mg	1	-	2	3
Period 6: 240 mg	2	-	2	4
Period 7: 260 mg	-	1	2	3
Period 8: 260 mg	-	1	2	3

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of Participants

Participants will be unblinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

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

6.4.3. Blinding of the Sponsor

Sponsor staff will be unblinded to participants' assigned study intervention.

6.4.4. Breaking the Blind

Not applicable.

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; this is vitally important to ensure dosing compliance in light of the potential gastrointestinal AEs. Additionally, if vomiting occurs following oral dosing and up to 4 hours post-dose (twice the median Tmax of PF-07081532), site personnel will examine the emesis for evidence of drug product.

A record of the number of PF-07081532 and rosuvastatin tablets and dabigatran capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

6.6. Dose Modification

Based on emerging data from other clinical studies that may become available during the conduct of this study, the titration rate, incremental increases in dose, and/or the PF-07081532 doses at which rosuvastatin or the dabigatran PK interactions are evaluated may be adjusted. If participants are not able to tolerate titration to higher doses of PF-07081532 (eg, ≥180 mg QD), titration to the next dose level may be delayed temporarily or titration to a maximum tolerated dose may be permitted, **with sponsor approval only**.

6.6.1. Dose Escalation and Stopping Rules

Not applicable.

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 PF-07081532 greater than 1.6 g within a 24-hour time period will be considered an overdose. A single dose of 1.6 g is projected to result in exposure that will exceed that observed at the NOAEL in the pivotal 9-month toxicology study in monkeys, after accounting for species differences in plasma protein binding. There is no specific treatment for an overdose of PF-07081532.

For this study, overdose for rosuvastatin will be as per the respective USPI label.[15]

Any dose of DE greater than 2 × 150 mg capsules within a 24-hour time period (± 12 hours) will be considered an overdose. A specific reversal agent (idarucizumab) is available for DE when reversal of the anticoagulant effect is needed for emergency surgery/urgent procedures

or if AEs of life-threatening or uncontrolled bleeding should occur. Other procedures and agents are also available to remove dabigatran or affect the anticoagulant activity of dabigatran, but their clinical experience is limited. Please see the dabigatran USPI for specific information.[16]

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives (approximately 5 days) after the overdose of study intervention, and as medically appropriate until the next scheduled follow-up.

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

Study participants will abstain from all concomitant treatments, except for the treatment of AEs, as described in the Exclusion Criteria sections of this protocol.

Use of prescription or nonprescription drugs and dietary and herbal supplements (eg, St. John's wort) are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

Systemic therapy with any medications that are moderate or strong CYP3A4/5 inhibitors or moderate or strong CYP3A4/5 inducers within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention are prohibited.

Systemic therapy with inhibitors or inducers of BCRP, OATP and P-gp transporters within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention are prohibited.

Use of pH altering drugs is prohibited; eg, proton-pump inhibitors, H2-blockers, etc.

Use of a GLP-1R agonist is prohibited within 90 days prior to the first dose of study intervention.

Hormonal contraceptives (including oral and non-oral) are prohibited in participants who are WOCBP (see Appendix 4). An exception is made for implantable progestogen only hormone contraception or intrauterine hormone releasing systems.

Females using hormonal contraceptives (including oral and non-oral) or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

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.

Anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF (See Section 6.9.2).

Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

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.

6.9.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07081532; standard medical supportive care must be provided to manage the AEs, including administration of carbohydrates to treat HAEs (see Section 8.3.6).

6.9.2. Management of Nausea and Vomiting

Nausea and vomiting have been reported with administration of GLP-1R agonists and also with administration of PF-07081532. Study participants complaining of nausea may be managed conservatively with bed rest and/or fluid management at the discretion of the investigator. If nausea and vomiting are not amenable to conservative management, anti-emetics (eg, prochlorperazine, promethazine, ondansetron) may be administered at the investigator's discretion with notification to the sponsor and entry in the CRF.

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:

- Criteria for a potential Hy's law case are met (see Appendix 6).
- Intent to become pregnant or pregnancy confirmed by serum β-hCG testing.
- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, dosing with study intervention may be stopped in an individual participant at investigator discretion.
- Based on mental health assessment as outlined in Section 8.3.8.3, should be discontinued from dosing at investigator discretion.
- If the criteria for permanent discontinuation are met, the site should notify the sponsor Medical Monitor or sponsor Clinician.
- Positive SARS-CoV-2 test (see Section 8.3.5).
- Potential or confirmed AKI (see Section 7.1.1).

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for an ET visit. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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, post-treatment study follow-up, and/or future collection of additional information.

7.1.1. 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 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.

7.1.2. Temporary Discontinuation

If participants are not able to tolerate titration to higher doses of PF-07081532 (eg, ≥ 200 mg QD) titration to the next dose level may be delayed temporarily, with ***sponsor approval only***.

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.
- Safety or behavioral reasons at the discretion of the investigator, including reasons related to mental health assessments.
- Positive SARS-CoV-2 Test.

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.

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 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 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.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

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.

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.

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 535 mL. 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.

8.2. Efficacy Assessments

Not applicable.

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.

Complete physical examinations will be done at the time points specified in the SoA otherwise, brief examinations if findings during a previous examination or new/open AEs, if appropriate at Investigator discretion.

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. Weight will be recorded using a calibrated scale (with the same scale used if possible, for the duration of the study) reporting weight in either pounds (lb) or kilograms (kg), and accuracy to the nearest 0.2 lb (or 0.1 kg); ie, the device must be able to distinguish a difference between 150.4 lb (68.4 kg) versus 150.2 lb (68.3 kg).

Weight measurement should be taken under the following conditions:

- In the morning in a fasting state.
- After void of urine.
- After removal of shoes, bulky layers of clothing and jackets so that only light clothing remains.
- After removal of pocket contents.
- While remaining still during the measurement.

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

Vital signes (systolic BP, diastolic BP and PR) will occur as specified in the SoA. 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. If triplicate measurements are obtained, they should be collected approximately 2 minutes apart.

At Screening, the participant's arm circumference should be measured (e.g., using a flexible anthropometric tape) at the midpoint of the length of the upper arm and the appropriate cuff selected and used throughout the study. 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

Body temperature will be measured at the timepoints listed in the SoA. 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) is not recommended 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.

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) a 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 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥30 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.

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 28-35 days 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 screened for COVID-19 according to local procedures prior to being admitted to the clinic for confinement in Period 1. Subsequent testing will also be done according to local procedure, if participants develop symptoms suggestive of COVID-19. If a participant tests positive for SARS-CoV-2 infection, they will be discharged from the study.

8.3.6. Management of Hypoglycemia

While hypoglycemia is not expected in the study participants, fasting blood glucose will be measured as part of laboratory assessment per the SoA. In addition, as a precaution, participants will be monitored for the signs and symptoms associated with hypoglycemia.

Any episode of hypoglycemia must be captured on the HAE CRF with specific details captured on the HAE Form CRF. For the definition of a hypoglycemic episode and severity categorization see Section 8.3.6.1 below.

For medical management of hypoglycemia, the investigator may administer oral carbohydrate, glucagon, or IV glucose according to his or her medical judgment.

8.3.6.1. Definition and Severity of Categorization of Hypoglycemic Adverse Event (HAE)

The investigator must assess the glucose values reported by the central/local laboratory, as well as any signs or symptoms reported by the study participant.

HAE is defined as **one** of the following:[34]

a. Asymptomatic hypoglycemia: An event not accompanied by typical symptoms of HAE but a glucose value of <70 mg/dL (3.9 mmol/L) using either glucometer (fingerstick blood glucose) at the study site or sponsor-identified central/local laboratory (blood glucose).

b. Documented symptomatic hypoglycemia: An event during which typical symptoms of HAE are accompanied with a glucose value of <70 mg/dL (3.9 mmol/L), using glucometer at the study site or sponsor identified central/local laboratory, and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

c. Probable symptomatic hypoglycemia: An event during which symptoms of HAE are not accompanied by a glucose determination but was presumably caused by a glucose concentration of <70 mg/dL (3.9 mmol/L), and the clinical picture includes prompt resolution with food intake, subcutaneous glucagon, or IV glucose.

Each episode of HAE must be categorized with respect to severity. In order to characterize the event as severe, all 3 criteria below must be met:

1. The participant was unable to treat him/herself. Neurologic impairment, and not the age of the participant, is the explanation for why the participant could not treat him/herself and required the assistance of another person.

2. The participant exhibited at least 1 of the following neurological symptoms:

   - Memory loss.
   - Confusion.
   - Uncontrolled behavior.
   - Irrational behavior.
   - Unusual difficulty in awakening.
   - Suspected seizure.
   - Seizure.
   - Loss of consciousness.

3. Either:

   - If blood glucose was measured and was ≤54 mg/dL (2.7 mmol/L) using glucometer (or central/local laboratory) or
   - If blood glucose was not measured, the clinical manifestations were reversed by oral carbohydrates, subcutaneous glucagon, or IV glucose.

Events that do not meet all the criteria above for severe HAE are characterized as mild or moderate in severity.

8.3.6.2. Glucometer Monitoring of Glucose

Monitoring of FSBG using glucometer measurements is not required per protocol but may be obtained if the investigator or participant notes symptoms of hypoglycemia.

If obtained, FSBG readings will be maintained at the CRU in source documents, and only the glucose results from the laboratory will be reported in the study database.

If an FSBG result is ≤70 mg/dL, a second FSBG should be obtained to confirm the glucose value, in addition to a venous sample that will be sent to the clinical laboratory for confirmation. If the value from this second FSBG is also ≤70 mg/dL, the second value will be recorded as a hypoglycemic AE. FSBG will continue to be monitored until the glucose value returns to >70 mg/dL. Samples m**ay be taken more frequently if deemed necessary by the investigator.**

8.3.7. 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. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

8.3.8.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[35] The "baseline/screening" version of the C-SSRS will be administered at Screening and Day -1 in study. Participants who respond "yes" to Question 4 or 5 (indicating suicidal ideation), or to any suicidal behavioral question on the C-SSRS at screening or Day-1 will not be permitted in the study (see Section 5.2). The "since last visit" version of the C-SSRS will be administered at the time points specified in the SoA. The C-SSRS will be administered by study site staff who have completed training in its administration.

8.3.8.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the guidance document provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will

be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.3.8.2. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a 9 item self-report scale for the assessment of depressive symptoms.[36] The PHQ-9 will be completed by participants and reviewed by site staff at the pre-defined time points outlined in the SoA. A PHQ-9 score of ≥15 at Screening or Day -1 indicates clinically significant depression and serves as an exclusion criterion for this study (see Section 5.2).

8.3.8.3. Referral to a Mental Health Professional

A participant should be referred to a MHP for the following reasons:

- Response of "yes" to question 4 or 5, or on any suicidal behavioral question on the C-SSRS.
- A score of ≥15 on the PHQ-9.
- In the investigator's judgment a risk assessment or exclusion is required.

A clinically qualified MHP is an MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation and behavior in a patient.

Participants who have recurrent suicidal ideation or behavior during the study should be discontinued from the study and treated appropriately. If a study participant endorses a 4 or 5 on the ideation subscale or any behavioral item of the C-SSRS on 2 or more occasions and is confirmed to have active suicidal ideation or behavior on both occasions by a risk assessment conducted by a qualified MHP, then the participant should be discontinued from the study and treated appropriately.

Participants who meet criteria for referral to a MHP but refuse evaluation and/or treatment by a MHP, must be assessed by the investigator to determine if the participant should be discontinued from dosing or from the study.

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.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion 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 28 days 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.

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

Not applicable.

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.

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.

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

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

Blood samples will be collected for measurement of plasma concentrations of rosuvastatin, dabigatran, and PF-07081532 as specified in the SoA.

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 collected for analyses of study intervention plasma concentrations 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.

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

Samples collected for measurement of plasma concentrations of study intervention will be analyzed using a validated analytical method 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.

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.

Instructions for the collection and handling 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.

8.5.1. PK of Rosuvastatin

Samples will be used to evaluate the PK of rosuvastatin. Blood samples of approximately 6 mL, to provide 2 aliquots of plasma volume of approximately 1.2 mL, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of rosuvastatin as specified in the SoA.

8.5.2. PK of Dabigatran

Samples will be used to evaluate the PK of dabigatran. Blood samples of approximately 3 mL, to provide 2 aliquots of plasma volume of approximately 0.6 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of total dabigatran (sum of unconjugated dabigatran and conjugated dabigatran) as specified in the SoA.

8.5.3. PK of PF-07081532

Samples will be used to evaluate the PK of PF-07081532. Blood samples of approximately 3 mL, to provide 2 aliquots of plasma volume of approximately 0.6 mL each, will be collected into appropriately labeled tubes containing K_2EDTA for measurement of plasma concentrations of PF-07081532 as specified in the SoA.

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

CCI [redacted]

8.7. Biomarkers

CCI [redacted]

CCI [redacted]

8.7.3. Specified Gene Expression (RNA) Research

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

8.7.4. Specified Protein Research

Specified protein research is not included in this study.

8.7.5. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.7.6. Retained Research Samples for Biomarkers

CCI [redacted]

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 Hypothesis

No formal statistical hypothesis testing will be conducted in this study.

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 assignment 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.
Safety analysis set	Example: All participants randomly assigned to study intervention and who take at least 1 dose of study intervention.
PK Concentration Set	The PK concentration population is defined as all participants who receive at least 1 dose of rosuvastatin, dabigatran, and/or PF-07081532 and in whom at least 1 plasma concentration value is reported.
PK Parameter Set	The PK parameter analysis population is defined as all participants who receive at least 1 dose of rosuvastatin, dabigatran, and/or PF-07081532 and have at least 1 of the PK parameters of interest calculated. Should vomiting occur after coadministration of rosuvastatin or dabigatran with PF-07081532, the resulting PK parameters

Participant Analysis Set	Description
	from that participant from the corresponding period may be excluded, where further details will be provided in the SAP.

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 and secondary endpoints.

9.3.1. General Considerations

9.3.2. Derivation of Pharmacokinetic Parameters

The plasma PK parameters for rosuvastatin and dabigatran (total) following SD administration (either alone or during coadministration with PF-07081532) will be derived from the concentration-time profiles as detailed in Table 10 below. The plasma PK parameters for PF-07081532 following MD administration will be derived from the concentration-time profiles as detailed in Table 11 below.

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 10. Plasma PK Parameters for Rosuvastatin and Dabigatran

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}).	Linear/Log trapezoidal method.
AUC_{inf}*	Area under the plasma concentration-time profile 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 estimated 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.
$t_{1/2}$*	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 will be used in the regression.
CL/F*	Apparent oral clearance.	$Dose/AUC_{inf}$.
V_z/F*	Apparent volume of distribution.	$Dose/ (AUC_{inf} \bullet k_{el})$.

* as data permit

Table 11. Plasma PK Parameters for PF-07081532

Parameter	Definition	Method of Determination
AUC_{24}	Area under the plasma concentration-time profile from time zero to time 24 hours.	AUC_t (area under the plasma concentration-time profile where t = 0 to 24 hours).
C_{max}	Maximum plasma concentration observed from time zero to 24 hours.	Observed directly from data.
T_{max}	Time for C_{max}.	Observed directly from data as time of first occurrence.

9.3.3. Primary Endpoint(s) Analysis.

The PK data for rosuvastatin, dabigatran (total), and PF-07081532 will be analyzed and reported separately.

Plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment (dosing alone vs. coadministration, as applicable). 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 for plasma samples will be used. Median profiles will be presented on both linear-linear and log-linear scales.

Natural $\log_e$ transformed AUC_{inf} (as data permit), AUC_{last} and C_{max} of dabigatran (total) administered without PF-07081532 on Period 1 or coadministered with PF-07081532 in Period 4 and on Period 7 will be analyzed using a mixed effect model with treatment 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 models. 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. The 2 test treatments will be 'dabigatran and PF-07081532 80 mg QD' (Period 4) and 'dabigatran and PF-07081532 260 mg QD' (Period 7), which will be reported separately in comparison to the reference treatment of 'dabigatran without PF-07081532' (Period 1).

Natural $\log_e$ transformed AUC_{inf} (as data permit), AUC_{last} and C_{max} of rosuvastatin administered alone in Period 2 or coadministered with PF-07081532 on Period 5 and Period 8 will be analyzed and reported separately using the same mixed effect model as described above for dabigatran. The 2 test treatments will be 'rosuvastatin and PF-07081532 80 mg QD' (Period 5) and 'rosuvastatin and PF-07081532 260 mg QD' (Period 8), which will be reported separately in comparison to the reference treatment of 'rosuvastatin without PF-07081532' (Period 2).

9.3.4. Other Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, continuous cardiac monitoring, 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 physical examination 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.

9.3.4.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time.

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

Table 12. Safety QTcF Assessment

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

9.3.5. Other Analyses

Tertiary/Exploratory analyses not included in the pharmacokinetic or safety analyses outlined above will be documented in the SAP.

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 an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety and PK assessments.

9.5. Sample Size Determination

A sample size of approximately 24 participants will be enrolled into the study, such that approximately 16 evaluable participants will complete the study. This number of evaluable participants has been selected to provide sufficient precision to detect a 1.5-fold and 1.25-fold difference in AUC_{inf} for dabigatran and rosuvastatin respectively, as described below.

For dabigatran AUC_{inf}:

- The co-administration of DE and PF-07081532 80 mg QD (Period 4) versus DE alone (Period 1, reference treatment).

- The co-administration of DE and PF-07081532 260 mg QD (Period 7) versus DE alone (Period 1, reference treatment).

For rosuvastatin AUC_{inf}:

- The co-administration of rosuvastatin and PF-07081532 80 mg QD (Period 5) versus rosuvastatin alone (Period 2, reference treatment).

- The co-administration of rosuvastatin and PF-07081532 260 mg QD (Period 8) versus rosuvastatin alone (Period 2, reference treatment).

The expected widths of the 90% CIs with 80% coverage probability for these comparisons are shown in Table 13 for a range of possible effects based on a sample size of 16 participants.

Table 13. Expected Widths of the 90% CIs (with 80% Coverage Probability) for Different Possible Estimated Effects and Parameters of Interest

Parameter	Estimated Effect (Test/Reference)	Probable 90% CI	Probable CI Width
Dabigatran: AUC_{inf} (SD=CCI)	75%	CCI	CCI
	100%		
	125%		
	150%		
	200%		
Rosuvastatin: AUC_{inf} (SD=CCI)	75%		
	100%		
	125%		
	150%		
	200%		

For dabigatran, these estimates are based on a conservative standard deviation of CCI (equivalent to a geometric coefficient of variation of CCI %) in log_eAUC_{inf} as obtained from internal clinical studies (B1871043 and B7451026) and literature in healthy participants.[37]

For rosuvastatin, these estimates are based on an assumed standard deviation of CCI (equivalent to a geometric coefficient of variation of CCI %) in log_eAUC_{inf} as observed in a previous internal DDI study in the same population (C3421007).

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

10.1.5.1. Data Monitoring Committee

This study will not use a 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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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.

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 or designee/CRO 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

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 SToD system.

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, and (d) Pfizer Call Center number.

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. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

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 14. 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 Creatinine CystatinC and eGFR Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Direct bilirubin Indirect bilrubin GGT Alkaline phosphatase Uric acid Albumin Total protein	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Laboratory: Microscopy and culture[a]	HbA1c Pregnancy test (β-hCG)[b] Lipid panel: • Total cholesterol • Direct LDL-C • HDL-C • Triglycerides TSH Free T4 Calcitonin Amylase Lipase Serum TBA Fibrinogen Urine drug screening[d] At screening only: FSH[c] C-peptide (fasting) HIV Hepatitis B surface antigen Hepatitis C antibody HCV RNA SARS-CoV-2 PT/INR
	Additional Tests (Needed for Potential DILI): AST/ALT (all repeat) T bili, direct and indirect bili (all repeat) Total bile acids, (repeat) GGT (repeat) Total protein, albumin (repeat), alkaline phosphatase (repeat) CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology (even if screening negative)		

a. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
b. Serum testing will be standard for female participants of childbearing potential.
c. For confirmation of postmenopausal status only.
d. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific). At screening, Period 1 Day-1 and at the discretion of the investigator.

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.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the CSR. Samples to be used for this purpose will be shipped to either a Pfizer-approved BBS facility or other designated laboratory and retained for up to 1 year following the completion of the study.

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 theiropinion 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

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100-fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

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.

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:

<u>Highly Effective Methods That Have Low User Dependency</u>

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.

6. Sexual Abstinence

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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

CCI

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

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	$eGFR = 135 \times (Scr/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

Inker LA et al. N Engl J Med. 2021;385:1737-49.

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: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from time zero to time 24 hours.
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time.
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC_{tau} (AUC_{τ})	area under the plasma concentration-time profile over the dosing interval, tau
AV	atrioventricular
AxMP	auxiliary medicinal product
BBS	Biospecimen Banking System
BCRP	breast cancer resistant protein
β-hCG	b-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CAD	coronary artery disease
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 Collaboration
CL	clearance
C_{last}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL/F	apparent oral clearance
CL_p	plasma clearance
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CP-I	coproporphyrin I
COVID-19	coronavirus disease 2019
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CTIS	Clinical Trial Information System
%CV	percent coefficient of variation
CV	cardiovascular
CYP	cytochrome P450
D	day
D/C	discontinue
DABI	dabigatran
DCT	data collection tool
DDI	drug-drug interaction
DE	dabigatran etexilate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DRE	disease-related event
DU	dispensable unit
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
eSAE	electronic serious adverse event
ET	end-of-treatment
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSBG	fingerstick blood glucose
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide 1
GLP-1R	glucagon-like peptide 1 receptor
HAE	hypoglycemic adverse event
HBcAb	hepatitis B core antibody

Abbreviation	Term
HbA1c	hemoglobin A_{1c}
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
hr	hour(s)
HR	heart rate
HRT	hormone replacement therapy
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IL-6	interleukin-6
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	Investigational Product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRC	internal review committee
IRT	Interactive Response Technology
IV	intravenous(ly)
k_{el}	first-order elimination rate constant
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
LBBB	left bundle branch block
LDL	low-density lipoprotein
LFT	liver function test
LLN	lower limit of normal
MATE	multidrug and toxic compound extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MEN2	multiple endocrine neoplasia syndrome type 2
MDR	medical device regulation
MHP	mental health professional
MQI	medically qualified individual
MTC	medullary thyroid carcinoma
NA	not applicable

Abbreviation	Term
NIMP	noninvestigational medicinal product
NOAEL	no-observed-adverse-effect level
OATP	organic anion transporting polypeptides
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
P-gP	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
ROSU	rosuvastatin
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
Scr	serum creatinine
Scys	serum cystatin C
SD	single dose; standard deviation
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SSID	single subject identifier
ST-T	ST segment to T wave changes on 12-lead ECG
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life.
T2DM	type 2 diabetes mellitus
TB	tuberculosis
TBA	total bile acids
T bili	total bilirubin
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
TOC	table of contents

Abbreviation	Term
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
V_{ss}	volume of distribution at steady state
Vz/F	apparent volume of distribution
WBC	white blood cell
WNL	within normal limits
WOCBP	woman/women of childbearing potential

11. REFERENCES

1. Ørskov C, Holst JJ, Knuhtsen S,et al. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. Endocrinology. 1986;119(4):1467-75.

2. Kreymann B, Williams G, Ghatei MA, et al. Glucagon-like peptide-1 7-36: a physiological incretin in man. Lancet. 1987;2(8571):1300-4.

3. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol. 1997;273(5):E981-8.

4. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101(3):515-20.

5. IDF Diabetes Atlas; 9th Edition. Available from: IDF Diabetes Atlas. Accessed 05 Nov 2022.

6. Menke A, Casagrande S, Geiss L,et al. Prevalence of and trends in diabetes among adults in the United States,1988-2012. JAMA. 2015;314(10):1021-9.

7. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405-12.

8. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.

9. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013;309(1):71-82.

10. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13-27.

11. Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr. 2001;74(5):579-84.

12. Drucker DJ. The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. Diabetes. 2018;67:1710-9.

13. CHMP. Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev. 1 Corr. 2. 2012. Available from: Guideline on the investigation of drug interactions (europa.eu). Accessed: 29 Jan 2023.

14. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). In vitro metabolism and transporter mediated drug-drug interaction studies. Available from: In Vitro Metabolism- and Transporter- Medicated Drug-Drug Interaction Studies Guidance for Insudtry (fda.gov) Accessed: 29 Jan 2023.

15. Rosuvastatin. US Prescribing Information (USPI). Parsippany, NJ: Actavis Pharma, Inc. Available from: 079167Orig1s000lbl.pdf (fda.gov). Accessed 27 Dec 2022.

16. Pradaxa. Highlights of Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. Available from: PRADAXA (dabigatran etexilate mesylate) capsules for oral use Label (fda.gov). Accessed 27 Dec 2022.

17. Ridker PM. From CANTOS to CIRT to COLCOT to clinic: will all atherosclerosis patients soon be treated with combination lipid-lowering and inflammation-inhibiting agents? Circulation. 2020;141(10):787–789.

18. Avan A, Tavakoly SB, Ghayour-Mobarhan M, et al. Serum C-reactive protein in the prediction of cardiovascular diseases: overview of the latest clinical studies and public health practice. J Cell Physiol. 2018;233(11):8508–8525.

19. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016;118(1):145–156.

20. Szmitko PE, Wang CH, Weisel RD, et al. New markers of inflammation and endothelial cell activation: part I. Circulation. 2003;108(16):1917–1923.

21. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–1131.

22. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med. 2019;381(26):2497–2505.

23. Cui Z, Ma M, Zhao G, et al. Blood fibrinogen level as a biomarker of adverse outcomes in patients with coronary artery disease: A systematic review and meta-analysis. Medicine 2022;101:33(e30117).

24. Askarpour M, Khani D, Sheikhi A, et al. Effect of bariatric surgery on serum inflammatory factors of obese patients: a systematic review and meta-analysis. Obes Surg. 2019;29(8):2631– 2647.

25. Mazidi M, Karimi E, Rezaie P, et al. Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. J Diabet Complicat. 2017;31(7): 1237–1242.

26. Katsiki N, Ferrannini E. Anti-inflammatory properties of antidiabetic drugs: a "promised land" in the COVID-19 era? J Diabet Complicat. 2020;34(12):107723.

27. Verma S, Bhatta M, Davies M, et.al. Effects of once-weekly semaglutide 2.4 mg on C-reactive protein in adults with overweight or obesity (STEP 1, 2, and 3): Exploratory analyses of three randomised, double-blind, placebo-controlled, phase 3 trials. eClinicalMedicine 2023;55: 101737.

28. Martin, PD, Warwick MJ, Dane AL, et al. A double-blind, randomized, incomplete crossover trial to assess the dose proportionality of rosuvastatin in healthy volunteers. Clin Ther 2003;25(8):2215-24.

29. Martin P, Gillen M, Ritter J, et al. Effects of fostamatinib on the pharmacokinetics of oral contraceptive, warfarin, and the statins rosuvastatin and simvastatin: results from Phase I clinical studies. Drugs RD 2016;16(1):93-107.

30. Cooper KJ, Martin PD, Dane AL, et al. Effect of itraconazole on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther 2003;73(4):322-9.

31. Stopfer P, Giessmann T, Holh K, et al. Effects of metformin and furosemide on rosuvastatin pharmacokinetics in healthy volunteers: implications for their use as probe drugs in a transporter cocktail. Eur J Drug Metab Pharmacokinet 2018;43(1): 69-80.

32. Stangier J, Rathgen K, Stähle H, et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male participants. Br J Clin Pharmacology 2007;64:292-303.

33. Hartter S, Sennewald R, Nehmiz G, et al. Oral bioavailability of dabigatran etexilate (Pradaxa®) after co-medication with verapamil in healthy participants. Br J Clin Pharmacology 2012;75(4):1053-1062.

34. American Diabetes Association. Standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1): S13-S28.

35. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

36. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.

37. Hartter S, Sennewald R, Nehmiz G, et al. Oral bioavailability of dabigatran etexilate (Pradaxa®) after co-medication with verapamil in healthy subjects. British Journal of Clinical Pharmacology 2013;75(4)(Apr):1053-62.