A PHASE 1, RANDOMIZED, 2-WAY CROSSOVER, OPEN LABEL STUDY TO ESTIMATE THE EFFECT OF PF-04965842 ON MATE1/2K ACTIVITY, USING METFORMIN AS A PROBE, IN HEALTHY PARTICIPANTS

Investigational Product Number:	PF-04965842
Investigational Product Name:	Not Applicable (N/A)
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Short Title: A Phase 1 Study of PF-04965842 Effect on MATE1/2K Activity in Healthy Participants

[redacted]

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary of Changes and Rationale**
Original protocol	1 November 2018	Not Applicable (N/A)

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1. PROTOCOL SUMMARY

1.1. Synopsis

Rationale

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[1,2] Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves until late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years,[3] it was concluded that symptoms associated with AD seem to persist well into the second decade of a child's life and likely longer. At every age, more than 80% of PEER study participants had symptoms of AD and/or were using medication to treat their AD.

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a topical treatment in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant interferon [IFN] interferon-gamma [IFN-γ], mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous [IV] immunoglobulin).[4] Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.[5,6]

Other systemic agents to treat AD are under clinical development or recently approved. Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL) -4 and -13, was approved by the FDA in March 2017 and received marketing authorization in Europe in September 2017, and offers a novel mechanism of action for the treatment of moderate to severe AD. However, the approved dosing for Dupilumab as an initial dose of 2 × 300 mg subcutaneous injections followed by 300 mg every other week injections may limit the desirability of this route of treatment.

Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-22, IL-31, and IFN-γ require Janus kinase 1 (JAK1) for signal transduction; this suggests that selective JAK1 inhibitors that modulate the activity of these cytokines represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[7]

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. PF-04965842 has a high degree of selectivity against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over tyrosine kinase 2 (TYK2), as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof of concept (POC) study (B7451006) that evaluated participants with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

Preclinical in vitro inhibition studies showed that the unbound maximum observed concentration (C_{max})/ 50% inhibitory concentration (IC_{50}) ratio is 0.24 and 0.13 for multidrug and toxic compound extrusion transporter (MATE)1 and MATE2K, respectively, suggesting that PF-04965842 has a potential to inhibit these drug transporters in vivo as ratios exceed the in vitro regulatory threshold unbound C_{max}/IC_{50} ratio of 0.02.[8] Therefore, a clinical interaction study with a sensitive MATE1 and MATE2K substrate is needed to assess the effect of PF-04965842 on the activity of these transporters. The primary purpose of this study is to assess the effect of PF-04965842 on the in vivo pharmacokinetics (PK) of metformin, a sensitive substrate for MATE1 and MATE2K.[8] Metformin is also a substrate for organic cation transporter (OCT)1 and OCT2. However, PF-04965842 is not an inhibitor of OCT2 (C_{max}/IC_{50} ratio is >300) and despite the unbound PF-04965842 C_{max}/IC_{50} ratio for OCT1 being just above 0.02 (0.03), inhibition of OCT1, a hepatic uptake transporter, is not expected to increase plasma metformin exposures as OCT1 does not modulate metformin clearance as it is primarily excreted unchanged in urine. Both MATE1 and MATE2K are renal transporters that are expressed in the apical membrane of the renal proximal tubules thus play an important role in tubular secretion and reabsorption of drug molecules in the kidney. Therefore, significant MATE1/2K inhibition would primarily impact the renal clearance of substrates for these transporters with having minimal effects, if any, on plasma exposures.

N^1-methylnicotinamide (NMN), a metabolite of niacin, has been reported to be an endogenous biomarker for assessing MATE/OCT2 inhibition. Renal clearance of NMN was shown to be reduced by ~70% by pyrimethamine, a potent MATE/OCT2 inhibitor.[9] As such, NMN is being assessed in this study to further investigate the utility of this endogenous substance as a biomarker for MATE activity in comparison to metformin, the gold standard for assessing MATE activity in drug-drug interaction (DDI) studies.[8]

Objectives and Endpoints

Objectives:	Endpoints:
Primary:	**Primary:**
• To estimate the effect of PF-04965842 on MATE1/2K activity via the pharmacokinetic assessment of a single, oral dose of metformin in healthy participants.	• Metformin CL_r.
Secondary:	**Secondary:**
• To evaluate the PK, safety and tolerability of a single oral dose of metformin when co-administered with PF-04965842.	• Metformin AUC_{inf}, C_{max}, T_{max}, AUC_{last}, CL/F, Vz/F, t½, Ae, and Ae%. • Vital signs, laboratory tests and adverse events.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• To evaluate the effects of PF-04965842 on N^1-methylnicotinamide. • To correlate the effects of PF-04965842 on N^1-methylnicotinamide versus metformin. • To enableexploratory research through the collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• N^1-methylnicotinamide AUC_{24}, C_{max}, Ae and CL_r. • Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

Overall Design

This is a Phase 1, randomized, 2-way crossover, open label study of the effect of PF-04965842 on metformin PK in healthy adult participants. The effect of PF-04965842 on NMN PK and its correlation to the effect on metformin PK will also be assessed. Participants will be randomized to 1 of 2 treatment sequences as described below. A total of 12 healthy male and/or female participants will be enrolled in the study so that 6 participants will be enrolled in each treatment sequence. Each treatment sequence will consist of 2 periods. Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequence as the participant who discontinued.

Participants will be screened within 28 days of the first dose of investigational product. Participants will report to the clinical research unit (CRU) the day prior to Day 1 (ie Day -1) dosing in Period 1 for both treatment sequences. In both sequences, participants will remain in the CRU for a total of 8 days and 7 nights (including Period 1 and Period 2). To adequately remove any drug effects of metformin (plasma half-life ~ 6 hours/whole blood half-life ~ 18 hours), there will be a minimum 4-day washout period between metformin dosing events from Period 1 to Period 2. The minimum 3-day washout for

PF-04965842 in Sequence 2 is sufficient as the half-life of PF-04965842 is ~3-5 hours. The metformin PK will be assessed over 48 hours.

Number of Participants

A total of approximately 12 healthy male and/or female participants will be enrolled in the study so that approximately 6 participants will be enrolled in each treatment sequence.

Intervention Groups and Duration

Treatment Sequences

Sequence	Period 1	Washout	Period 2
Sequence 1 (N = 6)	Treatment A	At least 4 days from metformin administration	Treatment B
Sequence 2 (N = 6)	Treatment B	At least 4 days from metformin + PF-04965842 administration[a]	Treatment A

Abbreviations: N = number of enrolled participants; QD = once daily.

Treatment A (Reference): Single oral administration of metformin 500 mg on Day 1.

Treatment B (Test): Concomitant single oral administration of metformin 500 mg on Day 1 and oral administration of PF-04965842 200 mg QD for 2 days on Days 1-2.

a. At least a 3-day washout is required from the last dose of PF-04965842.

- All treatments administered on Day 1 will be administered following a moderate-fat meal. PF-04965842 can be dosed with or without food on Day 2 in Treatment B.

Data Monitoring Committee: No

Statistical Methods

Natural log transformed area under the curve from zero to infinity (AUC_{inf}), area under the plasma concentration-time curve from 0 to the time of last measurement (AUC_{last}), maximum observed concentration (C_{max}) and renal clearance (CL_r) of metformin will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Additionally, area under the plasma concentration-time curve from 0 to 24 hours (AUC_{24}), C_{max} and CL_r of NMN will also be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Metformin alone will be the

Reference treatment (Treatment A), while the metformin co-administered with PF-04965842 will be the Test treatment (Treatment B).

A sample size of 12 participants will provide 90% confidence intervals for the difference between treatments of ±0.134, ±0.161 and ±0.148 on the natural log scale for metformin AUC_{inf}, C_{max} and CL_r, respectively, with 80% coverage probability. The following table presents the width of 90% confidence interval for different estimated effects (Table 4):

Sample Size Determination

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
CL_r	60%	51.73, 69.60	17.88
	70%	60.35, 81.20	20.85
	80%	68.97, 92.80	23.83
	90%	77.59, 104.40	26.81
	100%	86.21, 115.99	29.79
AUC_{inf}	100%	87.47, 114.32	26.84
	120%	104.97, 137.18	32.22
	160%	139.96, 182.91	42.95
	200%	174.94, 228.63	53.69
C_{max}	100%	85.10, 117.50	32.39
	120%	102.13, 141.00	38.88
	160%	136.17, 188.00	51.83
	200%	170.21, 235.00	64.79

Abbreviation: CI = confidence interval

These calculations are based on estimates of within participant standard deviations of 0.156, 0.188 and 0.173 for $\log_e AUC_{inf}$, $\log_e C_{max}$ and $\log_e CL_r$ of metformin, respectively, as obtained from internal and/or external data in previous clinical studies with metformin.[10, 11]

1.2. Schema

Not Applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section (Section 8) 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. Schedule of Activities

Visit Identifier	Screening	Period 1					Period 2[a]			ET	Phone call
Days Relative to Day 1	-28 to -2	-1	1	2	3	4	1	2	3		28-35 days after last dose of metformin[b]
Informed Consent	X										
Inclusion/Exclusion Criteria	X	X									
Medical, Drug, Tobacco and Alcohol History	X										
Complete Physical Examination[c]		X									
Demography, Height and Weigh	X										
Serum FSH (Postmenopausal Females Only)	X										
Serum Pregnancy Test (HCG) for WOCBP only	X	X							X	X	
Blood sampling for Pfizer Prep D1 banked sample(s)[d]			X								
Urine Drug Screen	X	X									
Single 12-Lead ECG	X		X[e]				X[e]		X	X	
Clinical Safety Labs (Blood and Urine)	X	X				X[f]			X	X	
Contraception check	X	X							X	X	X
Serology: HIV, HepBsAg, HepBcAb, HepBsAb, HCVAb testing	X										
QuantiFERON® - TB Gold Test	X										
Vital Signs and Oral Temperature	X		X[g]				X[g]		X	X	
Moderate Fat Meal consumed prior to dosing			X				X				
Metformin Dosing[h]			X				X				
PF-04965842 Dosing (Sequence 1)							X	X			
PF-04965842 Dosing (Sequence 2)			X	X							
Metformin PK Blood Sampling			X[i]	→	X[i]		X[i]	→	X[i]		
Metformin PK Urine Sampling			X[i]	→	X[i]		X[i]	→	X[i]		
NMN PK Blood Sampling			X[i]	X[i]			X[i]	X[i]			

Table 1. Schedule of Activities

Visit Identifier	Screening	Period 1					Period 2[a]			ET	Phone call
Days Relative to Day 1	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**1**	**2**	**3**		**28-35 days after last dose of metformin[b]**
NMN PK Urine Sampling			X[i]	X[i]			X[i]	X[i]			
CRU Confinement		X	→	→	→	→	→	→	X		
Serious and non-serious Adverse Event Monitoring	X	→	→	→	→	→	→	→	→	→	X
Prior/Concomitant Treatment Assessment	X	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HepBcAb = hepatitis B core antibody; HepBsAb = hepatitis B surface antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HCG = Human Chorionic Gonadotropin; HIV = human immunodeficiency virus; hr = hour; NMN = N^1-methylnicotinamide; PK = pharmacokinetic; TB = tuberculosis; WOCBP = women of childbearing potential.

a. Day 1 of Period 2 will be at least 4 days after Day 1 of Period 1.

b. Phone contact to capture any potential AEs and concomitant treatment(s) and to confirm appropriate contraception usage.

c. After the complete physical examination on Day -1, further examinations will be performed at the discretion of the investigator.

d. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

e. Perform single 12 lead ECG at pre-dose (before meal) and 2 hours post-dose.

f. Clinical safety labs will be collected before Period 2 Day 1.

g. Supine blood pressure, pulse rate and oral temperature pre dose and 2 hr post dose.

h. Participants will be dosed with metformin following a moderate-fat breakfast at approximately 08:00 AM (±2 hrs). On the day of co administration of metformin and PF-04965842, metformin will be administered with PF-04965842 concomitantly in no specific order, over no more than 5 minutes apart.

i. See pharmacokinetic sampling schema. (Table 2).

Table 2. Pharmacokinetic Sampling Schema

Visit Identifier	Periods 1 and 2											
	Day 1									Day 2		Day 3
Hours After Dose on Day 1	0[a]	0.5	1	2	4	6	8	12	16	24	36	48
Blood samples for												
PK blood sampling for metformin	X[a]	X	X	X	X	X	X	X	X	X	X	X
PK blood sampling for NMN	X[a]	X	X	X	X	X	X	X	X	X		
Urine samples for												
Predose PK spot urine blank	X[a]											
Start/Stop PK Urine collection for metformin concentrations[b,c]	X←	-------	-------	-------	-------	-------	------	→X←	-------	→X←	→X←	→X
Start/Stop PK Urine collection for NMN[b,d]	X←	-------	-------	-------	-------	-------	------	→X←	-------	→X		

Abbreviations: NMN = N1-methylnicotinamide; PK = pharmacokinetic.

a. Predose (metformin administration) sample collection.

b. Each subject will empty his or her bladder just prior to dosing. Then, all urine voids must be collected in appropriate urine collection containers. Each collection interval should have its own collection container(s). At the end of the urine collection interval, the total volume will be measured and recorded. The urine will then be mixed thoroughly. A 5 mL aliquot will be transferred to an appropriately labeled, screw capped polypropylene tube for NMN analysis. A second 5 mL aliquot will also be collected and analyzed for metformin PK concentrations.

c. PK urine collection interval for metformin concentration assessment: 0-12, 12-24, 24-36, and 36-48 hours postdose.

d. PK urine collection interval for NMN concentration assessment: 0-12 and 12-24 hours postdose.

2. INTRODUCTION

PF-04965842 is a Janus kinase (JAK) 1 inhibitor that is currently being developed for the treatment of moderate to severe atopic dermatitis (AD).

2.1. Study Rationale

With in vitro data indicating PF-04965842 may have the potential to inhibit multidrug and toxic compound extrusion transporter (MATE)1 and MATE2K, a clinical interaction study is needed to assess the effect of PF-04965842 on the activity of these transporters.

The primary purpose of this study is to assess the effect of PF-04965842 on the in vivo pharmacokinetics (PK) of metformin, a sensitive substrate for MATE1 and MATE2K.

2.2. Background

2.2.1. Mechanism of Action/Indication

The JAK family, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), is a group of cytoplasmic tyrosine kinases that mediates signal transduction via interactions with Type 1 and Type 2 cytokine receptors critical for leukocyte activation, proliferation, survival and function. Cytokine receptors demonstrate restricted association with JAKs such that different receptors or receptor classes preferentially utilize a given JAK dimer or trimer combination to transduce their signal. JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL) -4, -5, -6, -13, -21, -31, interferon gamma (IFN-γ), and interferon alpha (IFN-α). JAK2 homodimers are critical for the signaling of hematopoietic cytokines and hormones including erythropoietin (EPO), IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin. IL-12 and IL-23 are dependent on TYK2 and JAK2 for transmitting their signals.

Following cytokine activation, receptor-associated JAKs are phosphorylated, and in turn phosphorylate specific sites on the receptor intracellular domain. Phosphorylation of specific sites on the intracellular domain of the receptor allows for the recruitment of signal transducers and activators of transcription (STATs) that can subsequently be phosphorylated by JAKs.[7] Phosphorylated STAT molecules are released from the receptor, translocate to the nucleus where they bind to specific sites on the deoxyribonucleic acid (DNA) and regulate gene transcription.[12]

Key cytokines implicated in the pathophysiology of AD including IL-4, IL-5, IL-13, IL-22, IL-31, and IFN-γ, require JAK1 for signal transduction, suggesting that selective JAK1 inhibitors, that modulate the activity of these cytokines, represent a compelling approach to the treatment of inflammatory skin diseases such as AD.[13]

PF-04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. PF-04965842 has a high degree of selectivity against other kinases: 28-fold selectivity over JAK2, >340-fold over JAK3 and 43-fold over TYK2, as well as a good selectivity profile over the broader range of human kinases. The selective inhibition of JAK1 will lead to modulation of multiple cytokine

pathways involved in the pathophysiology of AD, including IL-4, IL-5, IL-13, IL-31 and IFN-γ. Data from a Phase 2b proof-of-concept (POC) study (B7451006) that evaluated participants with moderate to severe AD have shown positive efficacy, as well as an acceptable safety profile, sufficient to support further clinical development in a larger Phase 3 program.

2.2.2. Overview of Disease State

AD also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in the quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the United States (US).[1,2] Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves until late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7157 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study, comprising a total of 22,550 person-years,[3] it was concluded that symptoms associated with AD seem to persist well into the second decade of a child's life and likely longer. At every age, more than 80% of PEER study participants had symptoms of AD and/or were using medication to treat their AD.

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole was approved as a topical treatment in December 2016 by the Food and Drug Administration (FDA) for use in patients with mild to moderate AD. In addition, dupilumab, an injectable monoclonal antibody targeting IL-4 and IL-13 was recently approved for the treatment of AD. Additional treatments generally reserved for severe AD include phototherapy (eg, ultraviolet A light [UVA] with or without psoralen, ultraviolet B light [UVB] narrowband or broadband) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate [MTX], azathioprine, intravenous [IV] immunoglobulin).[4] Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.[5,6]

Other systemic agents to treat AD are under clinical development or recently approved. Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL) -4 and -13, was approved by the FDA in March 2017 and received marketing authorization in Europe in September 2017, and offers a novel mechanism of action for the treatment of moderate to severe AD. However, the approved dosing for Dupilumab as an initial dose of 2 × 300 mg subcutaneous injections followed by 300 mg every other week injections may limit the desirability of this route of treatment.

2.2.3. Rationale for Development of PF-04965842

PF-04965842 is being developed as an oral treatment for patients with moderate to severe AD based on its mechanism of action, and the clinical results obtained in Phase 1 and Phase 2 studies. The clinical development program for PF-04965842 includes healthy participants, participants with psoriasis and participants with AD.

2.2.4. Previous Human Experience with PF-04965842

PF-04965842 has been assessed in 5 completed clinical studies: 3 Phase 1 studies in healthy participants (B7451001, B7451004, and B7451008), 1 Phase 2 study in participants with psoriasis (B7451005) and 1 Phase 2 study in participants with AD (B7451006). A total of 423 participants received PF-04965842 or placebo in the 5 completed clinical studies with 335 participants having received at least 1 dose of PF-04965842 (n=61 in Study B7451001; n=12 in study B7451004; n=6 in study B7451008, n=45 in study B7451005; n=211 in Study B7451006).

2.2.4.1. Summary of Safety Data from Completed Studies

Based on the clinical experience with PF-04965842 and its mechanism of action, the potential risks of treatment with JAK inhibitors include: (1) viral reactivation; (2) serious infection and opportunistic infections; (3) malignancy and lymphoproliferative disorders; (4) decreased lymphocyte counts; (5) decreased neutrophil counts; (6) decreased platelets; and (7) alterations in the lipid profile.

In the completed Phase 1 and 2 studies in healthy participants, participants with psoriasis and participants with AD, PF-04965842 was generally safe and well tolerated.

In the completed Phase 1 studies in healthy participants receiving single doses of PF-04965842 up to 800 mg and multiple doses up to 200 mg twice daily (BID) or 400 mg once daily (QD), the most commonly reported adverse events (AEs) were diarrhea, nausea, vomiting, headache, acne, and dizziness. Following single or multiple dose of PF-04965842, most reported treatment emergent AEs (TEAEs) were mild or moderate in severity. In study B7451001, during the single-ascending dose phase, 1 participant in the placebo group had maximum QT interval calculated using Fridericia's correction factor (QTcF) interval of 450-<480 msec, and 1 participant in the PF-04965842 800 mg treatment group had maximum QTcF interval increase from baseline of 30 to <60 msec. In the multiple-ascending dose phase, 3 participants (1 each in the placebo, PF-04965842 30 mg QD, and 100 mg QD treatment groups) had maximum QTcF interval of 450-<480 msec, and 2 participants in the PF-04965842 200 mg BID treatment group had maximum QTcF interval increase from baseline of 30 to <60 msec.

In the completed Phase 2 study in participants with moderate to severe psoriasis (B7451005), the most frequently reported AEs across the PF-04965842 treatment groups (200 mg BID, 200 mg QD, and 400 mg QD) were nausea, followed by headache. Other commonly reported AEs include neutropenia and neutrophil counts decreased, thrombocytopenia and platelet count decreased. One of the participants in the 200 mg QD group with an AE categorized as infections and infestations was reported as having VIIth nerve paralysis

(Bell's palsy) and later developed herpes zoster (shingles). The incidence of normal and abnormal electrocardiogram (ECG) recordings were similar across all treatment groups at each time point. None of the abnormal ECG recordings were determined to be clinically significant by the investigator.

In the completed 12-week Phase 2b study (B7451006) in participants with AD, AEs and serious AEs (SAEs) were numerically higher in participants receiving PF-04965842 (10, 30, 100, and 200 mg QD) compared to placebo, but did not appear to increase with dose. The most common AEs were in the infections and infestations, skin and subcutaneous tissue disorders and gastrointestinal disorders system organ class (SOC), and the majority of the AEs were mild. The most commonly reported TEAE across all the treatment groups were dermatitis atopic (38 events), and viral upper respiratory tract infection (33 events). The most frequently reported treatment-related TEAE was nausea. There were 2 cases of non-serious herpes zoster, one in the 10 mg group (not treatment-related), and one in the 30 mg group (treatment-related). There were 2 participants (doses of ≥100 mg QD) with treatment related SAEs reported, the SAEs were Eczema herpeticum and Pneumonia. One participant randomized to the PF-04965842 10 mg group reported an SAE of malignant melanoma. Dose-dependent mean platelet count decreases from baseline were observed with a nadir at Week 4. At Week 4 the mean platelet count and the 90% confidence interval (CI) were within the normal reference range for both the 100 mg dose and 200 mg dose. In these treatment groups, the mean platelet count increased towards baseline after Week 4. There were no clinically significant findings in vital signs or physical examinations. Most of the ECG results were normal. The incidence of normal and abnormal ECG recordings was similar between PF-04965842 and placebo groups at each time point.

2.2.4.2. Summary of PF-04965842 Pharmacokinetics, Metabolism and In Vitro Enzymology

2.2.4.2.1. Single and Multiple Dose Pharmacokinetics

PF-04965842 was absorbed rapidly following single oral solution/suspension doses of 3 mg to 200 mg with median time to maximum concentration (T_{max}) observed less than 1 hour (ranging from 0.55 to 0.77 hours), and more slowly at the higher doses with median T_{max} of 1.5 and 4.0 hours for the 400 mg and 800 mg doses, respectively (Study B7451001). Following attainment of maximum observed concentration (C_{max}), the disposition of PF-04965842 generally showed a monophasic decline at the lower doses of 3 to 30 mg (mean apparent terminal half life [$t_{½}$] of 1.9 to 2.5 hours) while a biphasic decline was observed at doses of 100 to 800 mg with a mean $t_{½}$ of 3.6 to 4.9 hours. Plasma PF-04965842 C_{max} appeared to increase proportionally across the entire dose range from 3 mg to 800 mg, while increases in the plasma concentration-time area under the curve (AUC) from time 0 extrapolated to infinity (AUC_{inf}) were greater than proportional at doses of 400 and 800 mg. For the 2-fold doses increases between 200 to 400 mg and between 400 to 800 mg, the mean AUC_{inf} values in Western participants in this study appeared to increase approximately 3.5- and 2.7-fold, respectively.

On Day 10 of multiple-dose administration, PF-04965842 was absorbed rapidly with median T_{max} of about 1 hour or less (ranging from 0.50-1.05 hours) across the entire range of doses, from a total daily dose of 30 mg (30 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, the disposition of PF-04965842 was consistent with that observed following single-dose administration, showing a biphasic decline following all but the lowest dose and a mean terminal $t_{½}$ of about 2.8 to 5.0 hours. Plasma C_{max} and AUC from time 0 to time tau, the dosing interval (AUC_{tau}) both appeared to show a trend towards greater than proportional increases at doses higher than 200 mg given once-daily. Geometric mean values for the observed accumulation ratio (R_{ac}), that compares AUC_{tau} for multiple-dose administration to AUC_{tau} for single-dose administration, ranged from 1.3 to 1.5 for QD dosing and 1.3 to 2.3 for BID dosing. Similar ratios for C_{max} comparison (R_{ac}, C_{max}) ranged from 1.1 to 1.3 for QD dosing and from 1.3 to 2.8 for BID dosing. These results showed that drug concentration accumulation after repeated oral QD or BID administration is less than about 1.5- and 2.3-fold, respectively; at doses up to 200 mg QD, the accumulation was minimal and generally consistent with the prediction from $t_{½}$.

At a single 800-mg dose, the geometric mean C_{max} was similar in Western and Japanese participants. However, geometric mean AUC_{inf} was 26% higher in Western participants than that observed in Japanese participants. Geometric mean C_{max} and AUC_{tau} following multiple-dose administration of 200 mg BID were 17% and 56% higher, respectively, in the Western participants than in Japanese participants.

The urinary recovery of PF-04965842 was low, with <4% of the dose recovered unchanged in urine across all doses and regimens in all cohorts in study B7451001.

The bioavailability (BA) of a solid dose formulation of PF-04965842 relative to a suspension formulation was evaluated in an open label, single-dose, 3-way crossover study in 12 healthy participants under fasting and fed conditions (Study B7451004). Following single oral 400 mg doses under fasted conditions, C_{max} was reached rapidly for the oral suspension (median T_{max} 0.52 hours) and more slowly for the tablet formulation (4 × 100 mg, median T_{max} 2.0 hours). When the tablet was administered under fed conditions, T_{max} was further delayed with a median value of 4.0 hours. Mean terminal $t_{½}$ was 4.9 hours for the oral suspension fasted, 5.3 hours for the tablet fasted, and 3.2 hours for the tablet under fed conditions. Relative BA of 4 × 100 mg PF-04965842 tablets compared to 400 mg oral suspension under fasted condition was 96.54% and the 90% CI for the ratio (tablet/suspension) of adjusted geometric mean AUC_{inf} values was (90.31%, 103.21%), within the 80% to 125% interval demonstrating equivalence of total exposure. The ratio (90% CI) for C_{max} was 79.48% (62.88%, 100.46%). Administration of 4 × 100 mg PF-04965842 tablets with food did not change AUC_{inf}, and appeared to result in slightly lower C_{max} with reduced variability compared to fasted conditions. The ratio (90% CI) of adjusted geometric means for fed/fasted administration was 100.70% (94.42%, 107.40%) for AUC_{inf} and 95.56% (76.22%, 119.82%) for C_{max}. The magnitude of decrease in C_{max} (<5%) was not considered to be clinically important. Therefore, PF-04965842 can be administered with or without food. There were no clinically significant changes in ECG findings during the study.

2.2.4.2.2. Metabolism and In Vitro Enzymology

In vitro and in vivo metabolite profiling in rat, monkey, and human indicated that the primary clearance mechanism for PF-04965842 was cytochrome P450 (CYP450)-mediated oxidative metabolism. No unique human metabolites were observed clinically compared to metabolite profiling in rat and monkey. There was no evidence of chiral inversion in human plasma samples. Plasma profiling from the [^{14}C]PF-04965842 human mass balance study indicated parent as the most prevalent circulating species (26%), with 3 major and more polar mono-hydroxylated metabolites identified: 340-1 (3-hydroxypropyl, 11%), 340-2a (2-hydroxypropyl, 12%), and 340-4 (pyrrolidinone pyrimidine, 14%).

In vitro human CYP450 phenotyping studies indicated that CYP2C19 (fraction metabolized [fm] ~0.5), CYP2C9 (fm ~0.3), CYP3A4 (fm ~0.1), and CYP2B6 (~0.1) were involved in the metabolism of PF-04965842. Early assessment of clinical genotypes from first-in-human (FIH) participants indicated PK variability of all available non-wild-type genotypes (CYP2C19*1/*2, *2/*3, *2/*2, *1/*17, and *17/*17; CYP2C9*1/*2, *1/*3) were within the variability seen in wild-type CYP2C9*1/*1 and CYP2C19*1/*1 participants.

PF-04965842 did not inhibit the major CYP enzymes (50% inhibitory concentration [IC$_{50}$] values >100 μM) by competitive inhibition and did not cause time-dependent inhibition without the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). In the presence of NADPH, PF-04965842 caused relatively weak time-dependent inhibition of CYP2C19 (IC$_{50}$, 42 μM), CYP2D6 (IC$_{50}$, 92 μM), and CYP3A4/5 (IC$_{50}$, 40 to 81 μM).

PF-04965842 concentration dependently induced CYP3A4 messenger ribonucleic acid (mRNA) in 2/3 hepatocyte lots at ≥10 μM and CYP2B6 mRNA in 3/3 hepatocyte lots at ≥10 μM. Enzyme activity of CYP2B6 increased >2-fold at ≥30 μM in 1 of 3 lots of hepatocytes. Conversely, PF-04965842 caused a concentration-dependent decrease in CYP3A4 and CYP1A2 enzyme activities in 3/3 hepatocyte lots. Clinically, PF-04965842 PK showed apparent dose proportionality of single and multiple daily doses up to 200 mg, with no significant changes (~ <20%) in the CYP3A plasma biomarker 4β-hydroxycholesterol/cholesterol ratio following 10 days of dosing (Study B7451001). Preliminary SimCYP® modelling of PF-04965842 dosed 200 mg QD for 10 days indicated a low risk of precipitating a significant drug interaction with midazolam (CYP3A), buproprion (CYP2B6), or mephenytoin (CYP2C19).

PF-04965842 did not inhibit the major uridine diphospho-glucuronosyltransferase (UGT) enzymes; all IC$_{50}$ values >100 μM. PF-04965842 was not a substrate for organic anion transporting polypeptide (OATP) 1B1 or OATP1B3, nor inhibited these transporters (IC$_{50}$ values >300 μM). PF-04965842 did not inhibit organic anion transporter (OAT) 1 (IC$_{50}$ >300 μM) or organic cation transporter (OCT) 2 (IC$_{50}$ >300 μM), but weekly inhibited OAT3 (IC$_{50}$ = 26 μM), multi-drug resistance 1 (MDR1) (IC$_{50}$ = 100 μM), OCT1 (IC$_{50}$ = 44 μM), and showed some inhibitory activity of breast cancer resistance protein (BCRP) (IC$_{50}$ = 9.8 μM), MATE1 (IC$_{50}$ = 5.5 μM), and MATE2K (IC$_{50}$ = 10.7 μM). Clinically, PF-04965842 did not significantly affect 24 hour (hr) urinary creatinine (OCT2 and MATE1/2K substrate) up to doses of 800 mg (Study B7451001). Preliminary SimCYP®

modelling of PF-04965842 dosed at 200 mg QD indicated a low risk of precipitating a significant drug interaction with metformin (OCT2/MATE substrate) or digoxin (MDR1 substrate).

2.2.4.2.3. Population Pharmacokinetics

Population PK analysis was conducted by pooling data from 2 Phase 1 studies (B7451001, and B7451004) in healthy participants and the POC study (B7451006) in AD patients. A total of 2465 PK observations from 354 participants were included in the analysis and the data were described using a 2 compartment model with first-order absorption. The estimates of apparent clearance (CL/F), apparent central volume of distribution (Vc/F) and apparent peripheral volume of distribution (Vp/F) were 44.8 L/hr, 147 L and 20.8 L, respectively. The apparent clearance of PF-04965842 in AD patients was estimated to be ~38% lower than that in healthy participants. Baseline body weight, race, age and sex were tested as covariates on clearance and did not appear to impact the PK of PF-04965842.

2.3. Benefit/Risk Assessment

PF-04965842 and metformin are not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, and PK data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-04965842 may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study. The SRSD for metformin is the GLUCOPHAGE® Belgian summary of product characteristics (SmPC).[14]

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the effect of PF-04965842 on MATE1/2K activity via the pharmacokinetic assessment of a single, oral dose of metformin in healthy participants.	• Metformin CL_r.
Secondary:	**Secondary:**
• To evaluate the PK, safety and tolerability of a single oral dose of metformin when co-administered with PF-04965842.	• Metformin AUC_{inf}, C_{max}, T_{max}, AUC_{last}, CL/F, Vz/F, t½, Ae, and Ae%. • Vital signs, laboratory tests and adverse events.

Tertiary/Exploratory:	Tertiary/Exploratory:
• To evaluate the effects of PF-04965842 on N^1-methylnicotinamide. • To correlate the effects of PF-04965842 on N^1-methylnicotinamide versus metformin. • To enable exploratory research through the collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.	• N^1-methylnicotinamide AUC_{24}, C_{max}, Ae and CL_r. • Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, 2-way crossover, open label study of the effect of PF-04965842 on metformin PK in healthy adult participants. The effect of PF-04965842 on N^1-methylnicotinamide (NMN) PK and its correlation to the effect on metformin PK will also be assessed.

A total of approximately 12 healthy male and/or female participants will be enrolled in the study so that approximately 6 participants will be enrolled in each treatment sequence. Each treatment sequence will consist of 2 periods. Participants who discontinue from the study may be replaced at the sponsor's discretion. The replacement participant will receive the same treatment sequence as the participant who discontinued.

Participants will be screened within 28 days of the first dose of investigational product. Participants will report to the clinical research unit (CRU) the day prior to Day 1 (ie Day -1) dosing in Period 1 for both treatment sequences. In both sequences, participants will remain in the CRU for a total of 8 days and 7 nights (including Period 1 and Period 2). To adequately remove any drug effects of metformin (plasma half-life ~ 6 hours/whole blood half-life ~ 18 hours) from Period 1 to Period 2, there will be a minimum 4-day washout period between 2 dosing events. The minimum 3-day washout for PF-04965842 in Sequence 2 is sufficient as the half-life of PF-04965842 is ~3-5 hours. The metformin PK will be assessed over 48 hours. Participants will be assigned to one of the following 2 treatment sequences (Table 3):

Table 3. Treatment Sequences

Sequence	Period 1	Washout	Period 2
Sequence 1 (N = 6)	Treatment A	At least 4 days from metformin administration	Treatment B
Sequence 2 (N = 6)	Treatment B	At least 4 days from metformin + PF-04965842 administration[a]	Treatment A

Abbreiviation: N = number of enrolled participants; QD = once daily.

Treatment A (Reference): Single oral administration of metformin 500 mg on Day 1.

Treatment B (Test): Concomitantly single oral administration of metformin 500 mg on Day 1 and oral administration of PF-04965842 200 mg QD for 2 days on Days 1-2.

a. At least a 3 day washout is required from the last dose of PF-04965842.

- All treatments administered on Day 1 will be administered following a moderate-fat meal. PF-04965842 can be dosed with or without food on Day 2 in Treatment B.

4.2. Scientific Rationale for Study Design

In preclinical in vitro inhibition studies, the potential for PF-04965842 to inhibit MATE1 and MATE2K was assessed. A steady-state total C_{max} of PF-04965842 was 3.7 μM (1199 ng/mL) at a maximum clinical dose of 200 mg daily and unbound C_{max}/IC_{50} ratio is 0.24 and 0.13 for MATE1 and MATE2K, respectively, suggesting that PF-04965842 has a potential to inhibit these drug transporters in vivo as ratios exceed the in vitro regulatory threshold unbound C_{max}/IC_{50} ratio of 0.02.[8]

Therefore, a clinical interaction study with a sensitive MATE1 and MATE2K substrate is needed to assess the effect of PF-04965842 on the activity of these transporters. The primary purpose of this study is to assess the effect of PF-04965842 on the in vivo pharmacokinetics (PK) of metformin, a sensitive substrate for MATE1 and MATE2K.[8] Metformin is also a substrate for organic cation transporter (OCT)1 and OCT2 however PF-04965842 is not an inhibitor of OCT2 (C_{max}/IC_{50} ratio is >300) and despite the unbound PF-04965842 C_{max}/IC_{50} ratio for OCT1 is just above 0.02 (0.03), inhibition of OCT1, a hepatic uptake transporter, is not expected to increase plasma metformin exposures as OCT1 does not modulate metformin clearance as it is primarily excreted unchanged in urine. Both MATE1 and MATE2K are renal transporters that are expressed in the apical membrane of the renal proximal tubules thus play an important role in tubular secretion and reabsorption of drug molecules in the kidney. Therefore, significant MATE1/2K inhibition would primarily impact the renal clearance of substrates for these transporters with having minimal effects, if any, on plasma exposures.

NMN, a metabolite of niacin, has been reported to be an endogenous biomarker for assessing MATE/OCT2 inhibition. Renal clearance of NMN was shown to be reduced by ~70% by pyrimethamine, a potent MATE/OCT2 inhibitor.[9] As such, NMN is being assessed in this study to further investigate the utility of this endogenous substance as a biomarker for MATE

activity in comparison to metformin, the gold standard for assessing MATE activity in DDI studies.[8]

Preliminary SimCYP® modelling of PF-04965842 dosed at 200 mg QD indicated a low risk of precipitating a significant drug interaction with metformin, a MATE1 and MATE2K substrate. Additionally, PF-04965842 did not significantly affect 24 hour urinary creatinine (a MATE1/2K and OCT2 substrate) up to doses of 800 mg in clinical studies.

Banked biospecimens will be collected for exploratory pharmacogenomic/genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

4.3. Justification for Dose

An oral dose of 200 mg QD PF-04965842 and a single oral dose of metformin 500 mg will be used in this study.

An oral dose of 200 mg QD PF-04965842 for 2 days will be used as it is the highest dose and administration frequency being evaluated in the Phase 3 AD program. Drug concentration accumulation of PF-04965842 is minimal after repeated oral administration at doses lower than 200 mg BID, consistent with the prediction from the short half-life. PF-04965842 also displays linear PK at the 200 mg dose with no evidence of mechanism-based inhibition. Oral doses of PF-04965842 as high as 800 mg (single dose), 400 mg QD and 200 mg BID (up to 10 days) have been found to be safe and well tolerated. Based on the safety data of PF-04965842 and prior clinical experience as described above, administration of PF-04965842 200 mg QD for 2 days is expected to pose little risk to healthy adult participants.

Metformin is approved to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus. An oral dose of 500 mg of metformin will be used in this study as this is the lowest approved single dose used in clinical practice and will provide metformin exposures at the lower end of clinically-relevant metformin doses in the even that metformin exposures are increased in the presence of PF-04965842. The most common adverse reactions (>5.0%) in clinical studies following multiple dose administration of metformin were diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache with the risk of adverse events likely to be lower with a single dose administration. Thus, a single 500 mg dose of metformin is anticipated to be safe and generally well-tolerated in healthy participants.

The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50% to 60%. After oral administration of a single 500 mg dose of metformin in healthy participants, C_{max} occurs at approximately 3 hour post administration in the fasted state. Studies using single oral doses of metformin 500 to 1500 mg and 850 to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Intravenous single-dose studies

in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.[14, 15]

Metformin will be administered following consumption of a moderate fat meal as metformin is administered with food, in standard clinical practice, to improve its tolerability. Food decreases the extent of absorption of metformin and slightly delays its absorption, as shown by an approximate 40% lower mean C_{max}, 25% lower AUC, and a 35-minute prolongation of T_{max} following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting.[14, 15] Administration of 4 × 100 mg PF-04965842 tablets (400 mg) with food did not change AUC_{inf}, and appeared to result in slightly lower C_{max} with reduced variability compared to fasted conditions. As such, PF-04965842 will also be administered with a moderate fat meal during co-administration with metformin and can be administered with or without food when dosed on Day 2.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last contact phone call.

The end of the study is defined as the date of the last scheduled procedure shown in the schedule of activities of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. 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. Male and female participants must be 18 to 55 years of age, inclusive, at the time of signing the informed consent document (ICD).

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

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including a detailed medical history, complete physical examination, laboratory tests, and cardiovascular tests.

3. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

4. Female participants who are of child-bearing potential must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply:

   a. Female participants of childbearing potential must have a confirmed negative pregnancy test prior to treatment with investigational product;

   b. Female participants of childbearing potential must agree to use a highly effective method of contraception (as per Appendix 4 Section 10.4.4) for the duration of the active treatment period and for at least 28 days after the last dose of investigational product.

5. Female participants of non-childbearing potential (as defined per Section 10.4.3).

Weight:

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

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic (including alcoholic liver disease, nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, and hereditary liver diseases), psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy).

3. History of human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C virus antibody (HCVAb).

   As an exception, a positive hepatitis B surface antibody (HepBsAb) as a result of participant vaccination is permissible.

4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

5. Evidence or history of clinically significant dermatological condition (eg, atopic dermatitis or psoriasis) or visible rash present during physical examination.

6. Clinically relevant history of lactic acidosis.

Prior/Concomitant Therapy:

7. 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 investigational product. (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

9. A positive urine drug test.

10. Screening supine systolic blood pressure (BP) <90 mm Hg or ≥140 mm Hg following at least 5 minutes of supine rest OR

    Screening supine diastolic BP <50 mm Hg or ≥90 mm Hg following at least 5 minutes of supine rest.

    If a participant meets **any** of these criteria, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

11. Screening supine 12-lead ECG demonstrating:

    - QTcF >450 msec **OR**
    - QRS interval >120 msec.

12. 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.

13. 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:

    - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) **or** alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) level ≥1.5 × upper limit of normal (ULN).
    - Total bilirubin level >1.0 × 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 ≤1.0 × ULN.
    - Prothrombin Time (PT)/International Normalized Ratio (INR) or partial thromboplastin time (PTT)/activated partial thromboplastin time (aPTT) >1.0 × ULN.
    - Estimated creatinine clearance <90 mL/min (see Appendix 2 for Cockcroft-Gault formula).

Other Exclusions:

14. History of regular alcohol consumption exceeding 14 drinks/week for female participants or 21 drinks/week for male participants (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.

15. Known relevant history of elevated liver function tests (LFTs).

16. History of tuberculosis (TB) (active or latent) or inadequately treated TB infection. Positive QuantiFERON® – TB Gold test.

17. Any history of chronic infections, any history of recurrent infections, any history of latent infections, or any acute infection within 2 weeks of baseline.

18. History of disseminated herpes zoster, or disseminated herpes simplex, or recurrent localized dermatomal herpes zoster.

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

20. Use of tobacco- or nicotine- containing products in excess of the equivalent of 5 cigarettes per day.

21. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to first dose of investigational product.

22. History of hypersensitivity to metformin.

23. Unwilling or unable to comply with the criteria in the Section 5.3 of this protocol.

24. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.

25. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.

- Water is permitted until 1 hour prior to investigational product administration (with exception of water served during breakfast). Water may be consumed without restriction beginning 1 hour after metformin or PF-04965842 dosing on Day 1. Noncaffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices—see below) may be consumed with meals and the evening snack.

- A moderate fat meal (breakfast) will be provided 30 minutes before dosing and will be consumed up to at least 10 minutes prior to administration of metformin and/or PF-04965842 on Day 1. The caloric intake of a moderate fat breakfast should be approximately 840 kcal of which approximately 50% of its composition (400-440 kcal) should come from fat.

- On Day 2 (Treatment B), PF-04965842 can be dosed with or without food.

- Food may be consumed without restriction beginning 4 hours after dosing on Day 1 of each Period. No restriction to breakfast on the other days provided other restrictions are followed.

- 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.
- 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 investigational product until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. 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 to admission to the clinical research unit (CRU) and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.
- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. 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.

5.3.4. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and her/his partner from the permitted list of contraception methods (see Appendix 4 Section 10.4.4 will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct

use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to investigational product/entered in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the investigational products are PF-04965842 (provided as 100 mg tablets) and metformin (provided as 500 mg tablets).

PF-04965842 100 mg tablets will be supplied to the CRU in bulk along with individual dosing containers for unit dosing.

Commercially available metformin (GLUCOPHAGE®) will be acquired from an external/local supplier as 500 mg tablets. The CRU will ensure that all containers of metformin tablets to be used in the study are from the same lot.

6.1.1. Administration

Administration of investigational product will be carried out according to the conditions described in the Section 1.3 and Section 5.3.1 of this protocol.

For Treatment A, following consumption of a moderate fat meal (provided 30 minutes prior to administration), participants will receive metformin at approximately 08:00 AM (±2 hours), followed by intake of approximately 240 mL of ambient temperature water.

For Treatment B, following consumption of a moderate fat meal (provided 30 minutes prior to administration), the PF-04965842 200 mg dose and metformin 500 mg dose will be concomitantly administered, in no specific order, over no more than 5 minutes at 08:00 AM ± 2 hours with ambient temperature water to a total volume of approximately 240 mL. The second dose of PF-04965842 200 mg administered approximately 24 hours after the administration of the first dose will be administered with or without food.

Participants will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing.

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.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention, as applicable for temperature-monitored shipments.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. 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 temperature since previously documented for all site storage locations upon return to business.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions (PF-04965842 oral tablets and metformin oral tablets) will be accounted for using an investigational product accountability form/record.

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

5. Study interventions should be stored in their original containers and in accordance with the labels. PF-04965842 investigational product and metformin 500 mg tablets should be stored in its original container and in accordance with the label. See the Belgian SmPC for GLUCOPHAGE® for storage conditions of metformin.

6. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, 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. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site by the sponsor or designee.

7. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). 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, and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

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

PF-04965842 tablets will be prepared at the CRU in the individual dosing containers by 2 operators, one 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 will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Metformin tablets will be packaged at the CRU in the individual dosing containers by 2 operators, one 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) as allowed by local, state, and institutional guidance.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Investigational Product

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.

6.4. Study Intervention Compliance

Investigational product will be administered under the supervision of qualified investigator site personnel. The oral cavity of each participant will be examined following dosing to ensure the investigational product was taken.

6.5. Concomitant Therapy

Participants will abstain from all concomitant treatments, except for the treatment of AEs. Limited use of non-prescription medications that are not believed to affect participant's 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.

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 investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments, while hormonal contraception will not be allowed.

Females using hormonal contraceptives 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. (see Appendix 4).

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the adverse events (AEs) observed with PF-04965842 and/or metformin; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Dose modification is not allowed in this study.

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue investigational product. If investigational product is permanently discontinued, the participant will not remain in the study. See the Table 1 for data to be collected at the time of discontinuation of investigational product.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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 randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples, but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

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

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the case report form (CRF) and reported on the Clinical Trial (CT) SAE Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment 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 him or her 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 investigational product 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 he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Participants will be screened within 28 days prior to administration of the investigational product to confirm that they meet the study population criteria for the study. The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

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

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

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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.

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 may 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 he or she has 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.

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 participant in this study is approximately 185 mL for both Sequence 1 and Sequence 2. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Section 5.3 and Section 6.5 of the protocol.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

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

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

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

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

8.2.2. Vital Signs

Supine BP and pulse rate will be measured at times specified in the Table 1 of this protocol. 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.

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

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

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

Single 12-Lead ECGs should be collected at times specified in the Table 1 of this protocol.

All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position. Supine body position with fully lowered headrest should be consistently maintained for each ECG performed. Environmental distractions in the clinic (TV, radio, conversation) and other study procedures (eg, BP measurement, PK sampling) during both the pre-ECG rest and the ECG recording period must be minimized. In particular, changes in heart rate should be avoided. Whenever the nominal time points for different procedures coincide, the ECGs should always be collected prior to any other procedures (including vital signs and blood collection). ECGs should not be collected approximately within 2 hours of a meal in order to avoid the effect of food intake on the ECG. The time of meals must be standardized (±15 minutes) between study days and study periods (see also the Section 5.3).

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements from the current period. Additional ECG monitoring will occur if a) a postdose corrected QT interval (QTc) interval is increased by ≥30 msec from the baseline and is >450 msec; or b) an absolute QTc value is ≥500 msec 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 QTc 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 postdose QTc interval remains ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

Special attention should be given to ensure identical ECG lead placement during every measurement. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to an observed ECG abnormality. The lead to be used for interval measurements should be pre-specified; baseline and on-treatment measurements should be using the same lead.

In this study, a semi-automated approach to ECG acquisition will be used. This technique uses a computer algorithm for the initial placement of reference marks on the waveforms to note where on the tracing the computer is making its measurements. A standard semi-automated algorithm will be used so that a limited number of CRU staff will review program-determined interval onsets and offsets and modify using digital calipers on the rare occasion when this is necessary. This review must be performed by an appropriately qualified member of CRU staff. Use of this semi-automated algorithm is designed to further improve the validity of the automated ECG readout by reducing the variability associated with interpretation of the ECG waveform. This approach can have the advantage of greater consistency and reproducibility than fully manual readings, while providing an opportunity to correct any mistakes made by the algorithmic methods. Recent evidence suggests that

automated techniques are capable of detecting small changes in the QTc similar to those with manual readings and with the same conclusion.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. 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.

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. Clinically significant abnormal laboratory findings are those which 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 significantly abnormal during participation in the study or within 28 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 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.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

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 investigational product.

8.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (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 the participant's receiving the investigational product. 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 institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 it meets the criteria for classification as an SAE or that caused the participant to discontinue the study intervention (see Section 7).

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

8.3.1. 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 the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF), not the AE section.

Follow-up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately 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 it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.

8.3.2. 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.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/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 given in Appendix 3.

8.3.4. 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 towards 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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 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 is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

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

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

In the event of a medication dosing error, the sponsor should be notified immediately.

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 an AE page of the CRF.

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

8.4. Treatment of Overdose

For this study, any dose of PF-04965842 greater than 8 × 100 mg tablets within a 24-hour time period [±12 hours] or administering ≥4 tablets per day for 4 consecutive days will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose for PF-04965842. Observation and if required, supportive care would be expected.

Any dose of metformin greater than 5 × 500 mg capsules within a 24-hour time period [±12 hours] will be considered an overdose.

Hemodialysis may be considered for removal of accumulated metformin from participants and may be used in case of overdose. Please see the GLUCOPHAGE® Belgian SmPC for further information.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities until PF-04965842 or metformin can no longer be detected systemically (at least 3 days).

3. Obtain a blood sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

8.5.1. Plasma for Metformin Analysis

Blood samples of approximately 3 mL, to provide approximately 1 mL plasma, will be collected into appropriately labeled tubes containing tripotassium ethylenediaminetetraacetic acid (K_3EDTA) for measurement of plasma concentrations of metformin as specified in the Table 1 and Table 2.

The actual date and time (24-hour clock time) of each sample will be recorded. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) 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 data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT).

8.5.2. Urine for Metformin Analysis

Urine samples will be collected at times specified in the Table 1 and Table 2. Each subject will empty his or her bladder just prior to dosing. All urine voids must be collected in appropriate urine collection containers. Each collection interval should have its own collection container(s). At the end of the urine collection interval, the total volume will be measured and recorded. The urine will then be mixed thoroughly and a 5 mL aliquot will be collected for measurement of metformin PK.

The actual date and time (24-hour clock time) of each sample will be recorded. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing.

Further detail instructions for the collection,handling, aliquoting, storage, and shipping of PK plasma and urine samples will be provided in the laboratory manual or by the sponsor.

Samples collected for measurement of plasma and urine concentrations of metformin will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (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.

The plasma and urine samples may be used for exploratory analysis and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report (CSR).

8.6. Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimens will be collected for exploratory pharmacogenomic/genomic/biomarker analyses and retained in the Biospecimen Banking System (BBS), which makes it possible to better understand the investigational product's mechanism of action and to seek explanations for differences in, for example, exposure, tolerability, safety, and/or efficacy not anticipated prior to the beginning of the study.

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

Banked biospecimens may be used for research related to drug response. Genes and other analytes (eg, proteins, ribonucleic acid (RNA), nondrug metabolites) may be studied using the banked samples.

Unless prohibited by local regulations or IRB/EC decision, participants will be asked to indicate on the consent document whether they will allow their banked biospecimens to also be used to design and conduct research in order to gain a further understanding of other diseases and to advance science, including development of other medicines for patients. This component of the sampling banking is optional for participants; they may still participate in

the study even if they do not agree to the additional research on their banked biospecimens. The optional additional research does not require the collection of any further samples.

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

8.8. Biomarkers

8.8.1. Plasma for NMN Analysis

Blood samples of approximately 3 mL, to provide approximately 1 mL plasma, will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) for measurement of plasma concentrations of NMN as specified in the Table 1 and Table 2.

The actual date and time (24-hour clock time) of each sample will be recorded. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) 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 data collection tool (eg, CRF/DCT). 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 data collection tool (eg, CRF/DCT).

8.8.2. Urine for NMN Analysis

Urine samples will be collected at times specified in the Table 1 and Table 2. Each subject will empty his or her bladder just prior to dosing. All urine voids must be collected in appropriate urine collection containers. Each collection interval should have its own collection container(s). At the end of the urine collection interval, the total volume will be measured and recorded. The urine will then be mixed thoroughly and a 5 mL aliquot will be collected for measurement of NMN PK.

The actual date and time (24-hour clock time) of each sample will be recorded. The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing.

Further detail instructions for the collection, handling, aliquoting, storage, and shipping of PK plasma and urine samples will be provided in the laboratory manual or by the sponsor.

Samples collected for measurement of plasma and urine concentrations of NMN will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (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.

The plasma and urine samples may be used for exploratory analysis and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report (CSR). The plasma and urine samples may be stored at a facility selected by the sponsor for a maximum of 3 years (or according to local regulations) following the last participant's last visit for the study.

8.8.3. Other Biomarkers

Leftover plasma and urine samples could be used to assess concentrations of endogenous biomarkers for OCT1, OCT2, MATE1, and/or MATE2K.

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 a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

No formal inferential statistics will be applied to the safety or PK data.

9.2. Sample Size Determination

A sample size of 12 participants will provide 90% confidence intervals for the difference between treatments of ±0.134, ±0.161 and ±0.148 on the natural log scale for metformin AUC_{inf}, C_{max} and CL_r, respectively, with 80% coverage probability. The following table presents the width of 90% confidence interval for different estimated effects (Table 4):

Table 4. Sample Size Determination

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
CLr	60%	51.73, 69.60	17.88
	70%	60.35, 81.20	20.85
	80%	68.97, 92.80	23.83
	90%	77.59, 104.40	26.81

	100%	86.21, 115.99	29.79
AUCinf	100%	87.47, 114.32	26.84
	120%	104.97, 137.18	32.22
	160%	139.96, 182.91	42.95
	200%	174.94, 228.63	53.69
Cmax	100%	85.10, 117.50	32.39
	120%	102.13, 141.00	38.88
	160%	136.17, 188.00	51.83
	200%	170.21, 235.00	64.79

Abbreviation: CI = confidence interval

These calculations are based on estimates of within participant standard deviations of 0.156, 0.188 and 0.173 for $\log_e AUC_{inf}$, $\log_e C_{max}$ and $\log_e CL_r$ of metformin, respectively, as obtained from internal and/or external data in previous clinical studies with metformin.[10, 11]

Participants who discontinued from the study may be replaced at the sponsor's discretion.

9.3. Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	Participants will be randomized to 1 of 2 treatment sequences in a 2-way crossover design. A total of 12 healthy participants will be enrolled in the study so that 6 participants will be enrolled in each treatment sequence.
PK Population	The pharmacokinetic (PK) concentration population is defined as all enrolled subjects who received at least 1 dose of metformin and in whom at least 1 plasma concentration value is reported.
Safety Population	All participants randomly assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in 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.

9.4.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.4.2. Safety Analyses

All safety analyses will be performed on the safety population.

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

Medical history and 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.

9.4.2.1. Electrocardiogram Analyses

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

The number (%) of participants with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment (Table 5):

Table 5. Safety QTc Assessment

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

Abbreviation: msec = millisecond

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

9.4.3. Other Analyses

Pharmacogenomic (PGx) and endogenous biomarker PK data, other than NMN, will be collected and retained for potential future analyses, but will not be analyzed, specifically, for this study.

9.4.4. Pharmacokinetic Analyses

9.4.4.1. Analysis of Population

The PK concentration population is defined as all participants randomized and treated who have at least 1 concentration in at least 1 treatment period.

The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

9.4.4.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

PK parameters for metformin and NMN will be derived from the plasma concentration-time profiles and urine concentrations as shown below in Table 6.

Table 6. Derivation of PK Parameters

Parameter	Definition	Method of Determination	Analyte
AUC_{24}	Area under the plasma concentration-time profile from time zero to 24 hours	Linear/Log trapezoidal method.	N
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.	N, M
AUC_{inf} [a]	Area under the plasma concentration-time profile from time zero extrapolated to infinity	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.	M
C_{max}	Maximum plasma concentration	Observed directly from data.	N, M
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence.	N, M
$t_{½}$ [a]	Terminal elimination 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.	M
CL/F	Apparent clearance for extravascular dosing	$Dose/AUC_{inf.}$	M
V/F	Apparent volume of distribution for extravascular dosing	Apparent volume of distribution, estimated from terminal phase, for extravascular dosing.	M
Ae	Cumulative amount of drug recovered unchanged in urine	Sum of amount excreted for each collection period (Urine Concentration * Volume of Urine).	N, M
Ae%	Cumulative amount of drug recovered unchanged in urine, expressed as percent of dose	100 × (Ae/Dose).	M
CL_r	Renal clearance	Ae/AUC.	N, M

Abbreviations: N = N^1-methylnicotinamide; M = metformin; PK = pharmacokinetic.
a. If data permit.

Actual PK sampling times will be used in the derivation of PK parameters.

PK parameters in Table 6 will be summarized descriptively by analyte and by treatment, as applicable, in accordance with Pfizer Data Standards. Concentrations will be listed and summarized descriptively by analyte, nominal PK sampling time and treatment. Individual subject and median profiles of the plasma concentration-time data will be plotted by treatment using actual and nominal times, respectively. Median profiles will be presented on both linear-linear and log-linear scales. Individual changes from baseline for metformin CL_r versus NMN CL_r will be plotted and a Pearson correlation coefficient (r) will be presented.

Natural log transformed AUC_{inf}, AUC_{last}, C_{max} and CL_r of metformin will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Additionally, AUC_{24}, C_{max} and CL_r of NMN will also be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios. Metformin alone will be the Reference treatment, while the metformin co-administered with PF-04965842 will be the Test treatment.

9.5. Interim Analyses

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

9.5.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and 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.

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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), 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 investigational product, 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 ICH GCP 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 his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study 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 his/her 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 his/her 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 his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her 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 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 ICD(s) during their participation in the study.

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

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

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 shall 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 natural persons 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 his or her actual identity. 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.

10.1.5. 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 European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (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 US Basic 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. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

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

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.

10.1.6. 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.

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

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

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

Monitoring details describing strategy (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, remote, or on-site monitoring), are provided in the monitoring plan/contracts.

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

Study monitors will perform ongoing source data verification 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, and all applicable regulatory requirements.

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.

10.1.7. 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 electronic CRF (eCRF) that are transcribed 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 can be found in investigator site file.

10.1.8. Study and Site Closure

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. 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 contract research organization (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 GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

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.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer-intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigators Site Master File.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than

a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The safety laboratory tests listed in Table 7 below 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 concerns. Creatinine clearance is estimated using the Cockcroft-Gault formula to estimate glomerular filtration rate at screening:

Creatinine Clearance (estimated) / Conventional mL/min =

((140 - Age (years)) X Weight (kg) X Factor[a]) / (72 X Serum Creatinine (mg/dL))

[a] Factor is equal to 0.85 in females and 1.00 in males.

Table 7. Safety Laboratory Tests

Hematology &Coagulation	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) PT/INR PTT/aPTT	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	QuantiFERON®-TB Gold Test[e] FSH[c,e] Urine drug screening[f] Serum Pregnancy Test (HCG)[f] **Serology[b]** panel to include: • Hepatitis B surface antigen; • Hepatitis B surface Ab; • Hepatitis B core antibody; • Hepatitis C antibody; • Human immunodeficiency virus.
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels		

Abbreviations: Abs = absolute, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CO2 = carbon dioxide (bicarbonate), FSH = follicle-stimulating hormone, GGT = gamma-glutamyl transferase, HCG = Human Chorionic Gonadotropin, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, pH = measure of acidity, PT/INR = prothrombin time/international normalized ratio, qual = qualitative, RBC = red blood cell, TB = tuberculosis, WBC = white blood cell.

a. Only if urine dipstick is positive for blood, protein, nitrites, glucose or leukocyte esterase.
b. Serology at Screening only, additional 5 mL blood sample required.
c. For confirmation of postmenopausal status only.
d. Serum HCG for female participants of childbearing potential at screening, admission and discharge.
e. Screening only.
f. Screening and admission only.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

Investigators must document their review of each laboratory safety report.

Any remaining serum 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 clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer-approved Biospecimen Banking System (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 (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions 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/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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 SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

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 detained (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 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) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or 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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product 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 investigational product under study during pregnancy or breastfeeding, and occupational exposure.	**None**	All (and exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/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/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/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/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: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  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/SAE.
- 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.

- The investigator will use clinical judgment to determine the relationship.
- 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 investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has 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 his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" 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 professionals.
- 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 completed CRF.
- 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 Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool 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 data collection tool 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 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, 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 Guidance and Collection of Pregnancy Information

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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 definitions below in Section 10.4.3);

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). 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 (WOCBP)

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 an alternate 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 age 60 years or older or no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Females of childbearing potential participating in this study cannot use oral, transdermal, intrauterine, injected or implanted hormonal methods of contraception and must use one of the below options:

1. Copper-containing intrauterine device (IUD).
2. Bilateral tubal occlusion.

3. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential 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.

4. 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.

Collection of Pregnancy Information.

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, 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. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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).

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 includes miscarriage and missed abortion;
- 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 investigational product.

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.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Samples for banking (see Section 8.7.2) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their banked biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

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 drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili 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 TBili 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 TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili 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** TBili 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 TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili 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 TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (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 (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, 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 and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (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: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec 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 premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• 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 (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >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 Serious Adverse Events
• 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.

Appendix 8: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	Atopic dermatitis
Ae	cumulative amount of drug recovered unchanged in urine
Ae%	cumulative amount of drug recovered unchanged in urine, expressed as percent of dose
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{24}	area under the curve from zero to 24 hours
AUC_{inf}	area under the curve from zero to infinity
AUC_{last}	area under the plasma concentration-time curve from 0 to the time of last measurement
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
BA	bioavailability
BBS	Biospecimen Banking System
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CL_r	renal clearance
CL/F	clearance for extravascular dosing
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CYP450	cytochrome P450

Abbreviation	Term
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EMA	European Medicines Agency
EPO	erythropoietin
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte-macrophage colony-stimulating factor
HepBcAb	hepatitis B core antibody
HepBsAb	hepatitis B surface antibody
HepBsAg	hepatitis B surface antigen
HCG	serum pregnancy test
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hr	hour
IB	Investigator's brochure
ICD	informed consent document
ICH	International Conference on Harmonisation
IC_{50}	50% inhibitory concentration
IFN	interferon
IFN-α	interferon alpha
IFN-γ	interferon gamma
IL	interleukin
IND	Investigational New Drug
INR	international normalized ratio
IGA	Investigator's Global Assessment
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
JAK	Janus kinase

Abbreviation	Term
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
$\log_e$	logarithm
MATE	multidrug and toxin extrusion transporter
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDR	multi-drug resistance
mRNA	messenger ribonucleic acid
msec	millisecond
MTX	methotrexate
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NASH	nonalcoholic steatohepatitis
NMN	N^1-methylnicotinamide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PCD	primary completion date
PD	pharmacodynamic(s)
PEER	Pediatric Eczema Elective Registry
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
POC	proof of concept
PT	prothrombin time
PTT	partial thromboplastin time
PVCs	premature ventricular complexes
QD	once daily
QTc	corrected QT interval
QTcF	QT interval calculated using Fridericia's correction factor
qual	qualitative
R_{ac}	accumulation ratio
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	summary of product characteristics
SOC	system organ class
SOP	standard operating procedure

Abbreviation	Term
SRSD	single reference safety document
STAT	signal transducers and activators of transcription
SUSARs	suspected unexpected serious adverse reactions
$t_{½}$	apparent terminal half-life
TB	Tuberculosis
TBili	total bilirubin
TEAEs	treatment emergent adverse events
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
TYK	Tyrosine kinase
UGT	uridine diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UVA	ultraviolet A light
UVB	ultraviolet B light
V/F	apparent volume of distribution
Vc/F	apparent central volume of distribution
Vp/F	apparent peripheral volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential

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