A PHASE 1, RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, VEHICLE-CONTROLLED, FIRST-IN-HUMAN, MULTIPLE-DOSE STUDY, TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS, OF TOPICALLY ADMINISTERED PF-07295324 AND PF-07259955, IN HEALTHY ADULT PARTICIPANTS

Study Intervention Number:	[PF-07295324] [PF-07259955]
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	C4711001
Phase:	Phase 1

Brief Title: A Phase 1, FIH Study of Multiple Doses of Topically Administered PF-07295324 and PF-07259955, in Healthy Participants.

Document History

Document	Version Date
Amendment 1	21 April 2022
Original protocol	06 December 2021

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

Protocol Amendment Summary of Changes Table

Amendment 1 (21-April-2022)

Overall Rationale for the Amendment: Update the optional cohorts (cohorts 3 and 4) to clarify and allow these cohorts to repeat doses studied in previous cohorts.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design; Section 4.3 Justification for Dose; Section 1.1 Synopsis, Section 1.2 Schema and Section 1.3 SoA	Added language to allow to repeat doses studied in Cohort 1 and Cohort 2 in optional cohorts (ie, Cohort 3 and Cohort 4).	To clarify that doses tested in previous cohorts may be repeated to understand and/or further evaluate the safety/tolerability/PK observed in previous cohorts if the stopping criteriaare not met.
Section 4.1 Overall Design, Section 4.3 Justification for Dose, Section 1.2 Schema and Section 1.3 SoA, Section 6.5 Dose Modification	Added language to allow study of either PF-07295324 or PF-07259955 in Cohort 4 after review of data from Cohorts 1-3.	Cohort 4 may be used to further investigate PF-07295324 or PF-07259955 safety, tolerability and/or PK after review of Cohorts 1, 2 and 3.
Section 6.1.1.2 Calculation of Per Application Dose and throughout document (where applicable)	To clarify that that BSA administered in this study is less than or equal to 4000 cm^2.	In this study, the BSA administered is up to 20% or 4000 cm^2.
Section 1.1 Synopsis, Section 1.3 SoA, Section 4.1 Overall Design, Section 10.1.8 Source Documents, Section 10.1.11 Sponsor's Qualified Medical Personnel, Section 10.4.1 Male	Revisions outlined in the PACL dated 26 Jan 2022 have been incorporated.	Minor revisions were made to reconcile follow up contact/EOS to D41±3 days, to clarify the restriction on donating sperm would be 90 days, and since this is a PCRU study, wordings in

Section # and Name	Description of Change	Brief Rationale
Participant Reproductive Inclusion Criteria		Sections 10.1.8 and 10.1.11 were updated accordingly.
Section 10.9 Abbreviations	Added CTMS, PACL, PCRU and removed STOD.	Revised per changes specified in the protocol amendment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: A Phase 1, FIH Study of Multiple Doses of Topically Administered PF-07295324 and PF-07259955, in Healthy Participants.

Rationale: The purpose of the study is to evaluate the safety, (local and systemic) tolerability, and pharmacokinetics following multiple doses of topically applied, maximum feasible formulation of PF-07295324 (0.12% w/w) or PF-07259955 (2% w/w), on approximately 20% BSA in healthy adult participants.

The safety, local and systemic tolerability, and pharmacokinetics from this study will support the parallel clinical development of PF-07295324 and PF-07259955.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety, and local and systemic tolerability, of PF-07295324 and PF-07259955, following multiple doses of topically administered PF-07295324 or PF-07259955, on approximately 20% BSA in healthy adult participants.	• Incidence and severity of systemic AEs, safety laboratory tests, vital signs (including blood pressure and pulse rate), and heart rhythms as assessed via 12-lead electrocardiogram (ECG). • Incidence and severity of application site AEs as assessed by Draize score.
Secondary:	**Secondary:**
• To characterize plasma PK following multiple topical applications of PF-07295324 and PF-07259955.	• Plasma PK of multiple topical doses of PF-07295324 and PF-07259955, as data permits: Day 1: C_{max}, T_{max}, C_{avg}, C_{trough}, AUC_{tau} Day 10: C_{max}, T_{max}, C_{avg}, C_{trough}, AUC_{tau}, R_{ac} (C_{max}) , R_{ac}(AUC_{tau}), $t_{½}$, CL/F, and V_z/F
CCI [redacted]	[redacted]
[redacted]	[redacted]

Overall Design

Brief Summary

C4711001 is an investigator- and participant-blinded, interventional, randomized, vehicle-controlled, Phase 1 study to evaluate the safety, local and systemic tolerability, and pharmacokinetics of maximum feasible formulation of topical JAK inhibitors, PF-07295324 (0.12%) and PF-07259955 (2%) in healthy adult participants.

In minipigs, topical administration of an equivalent dose of PF-07295324 (0.12%) or PF-07259955 (2%), resulted in minimal non-adverse local skin irritation at maximal feasible formulation based on 6-week dermal toleration assessment (Section 2.2.3.1 and Section 2.2.3.2).

No dose escalation is planned for this study.

Due to similar pharmacology, same trial objectives, common study design elements, and identical safety monitoring plan, this FIH study will use a platform trial design. Under this platform design, the safety and tolerability of both the JAK inhibitors PF-07295324 and PF-07259955 will be investigated in healthy adult participants, under 1 single Phase 1 study protocol, C4711001.

Intervention Groups and Duration

This study will enroll healthy adult participants in ≤4 cohorts: 2 planned cohorts (Cohort 1 and Cohort 2) and 2 optional cohorts (Cohort 3 and Cohort 4) with approximately 6 participants/cohort, randomized as 4 active:2 vehicle.

In each cohort, participants confirming eligibility, will be admitted to the Clinical Research Unit (CRU), on Day -1. Participants enrolled in Cohort 1 and Cohort 2 will receive multiple topical applications of assigned study intervention, Q12H, from Day 1 to Day 9, with only morning (AM) application on Day 10. Participants will be discharged on Day 12, following the completion of all discharge procedures specified in the Schedule of Activities (SoA) of the protocol. Participants will be scheduled for a follow-up phone contact, approximately on Study Day 41±3 days.

Cohort 1 will be assigned to PF 07295324/vehicle, applied topically, as an ointment. Cohort 2 will be assigned to PF 07259955/vehicle, applied topically, as a cream.

Based on emerging data from Cohort 1 & Cohort 2, 1 optional cohorts (6 participants/cohort, 4:2 active:vehicle) for each intervention may be enrolled in this study. Optional Cohort 3 will be assigned to PF-07295324/vehicle and Optional Cohort 4 may be used to study either PF-07295324 or PF-07259955.

- The optional cohorts may be used to repeat doses studied in previous cohorts, explore lower strength formulation on approximately 20% BSA, or to investigate the safety of

maximum feasible formulation on lower body surface area, or at a less frequent dosing regimen on approximately 20% BSA. Participants enrolled in the optional cohorts will be randomized 4:2 active: vehicle and will be guided by the same stopping criteria as planned cohorts.

- Participants in optional cohort will be dosed only after review of available safety data from a minimum of 4 participants (3 active:1 vehicle), dosed in planned cohort up to day 10.

Dosing will be terminated based on protocol specified individual discontinuation criteria (Section 6.5.1, Section 6.5.2).

Planned cohorts assigned to different interventions may progress simultaneously. Similarly, optional cohorts assigned to different interventions may progress simultaneously (Section 1.2).

The planned duration of participation from screening to follow-up is approximately 10 weeks.

Data Monitoring Committee or Other Independent Oversight Committee: No

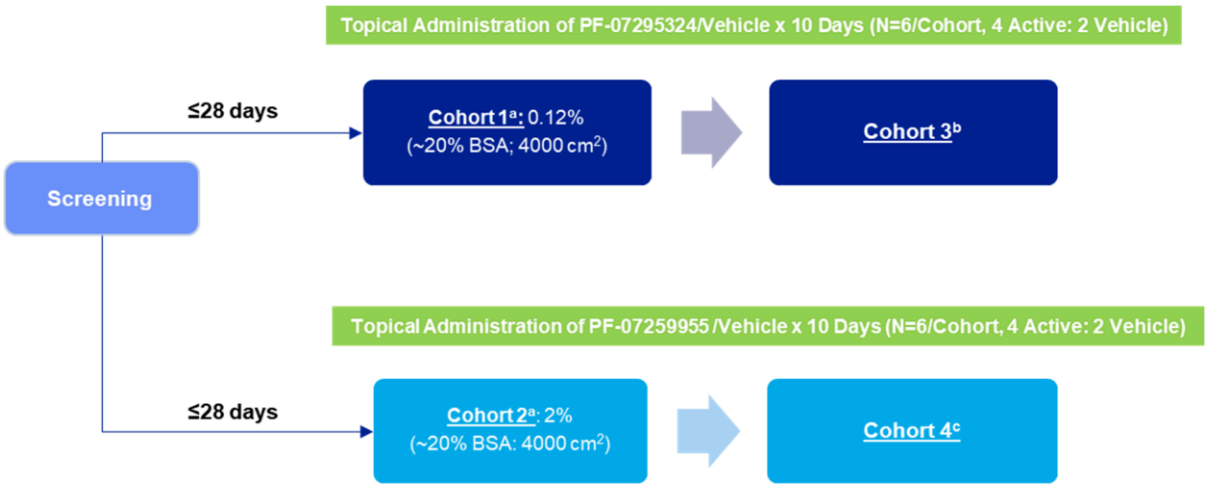
Statistical Methods:

No formal hypothesis testing will be applied to the safety and PK data. The cohort sample size has been chosen based on the need to minimize first exposure to humans of a new chemical entity and the requirement to provide adequate safety and tolerability assessment for each asset.

The safety data and plasma PK parameters will be tabulated and summarized descriptively by study intervention, by treatment group and by day, in accordance with Pfizer data standards, as data permit. Detailed methodology for descriptive statistical summary will be described in statistical analysis plan (SAP).

1.2. Schema

Figure 1. Study Schema



a. PF-07295324 (0.12%)/vehicle in Cohort 1 or PF-07259955 (2%)/vehicle in Cohort 2, will be topically applied on approximately 20% body surface area or less than or equal to 4000 cm^2, Q12H from D1 to D9; only morning (AM) dose will be applied on D10.

b. Based on review of emerging safety from Cohort 1, optional Cohort 3 may be enrolled to repeat the PF-07295324 dose studied in Cohort 1, explore lower formulation strength of PF-07295324, topically applied on approximately 20% BSA or PF-07295324 (0.12%) on lower body surface area or at a less frequent dosing regimen on approximately 20% BSA or less than or equal to 4000 cm^2.

c. Based on review of emerging safety assessments from Cohort 1, Cohort 2 and Cohort 3, optional Cohort 4 may be enrolled to study either PF-07295324 or PF-07259955 by repeating doses studied in previous cohort(s), exploring lower formulation strength topically applied on approximately 20% BSA or investigating the safety of maximum feasible formulation on lower body surface area or at a less frequent dosing regimen on approximately 20% BSA or less than or equal to 4000 cm^2.

1.3. Schedule of Activities

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

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

1.3.1. Schedule of Activities from Screening to End of Study (EOS): Multiple doses of topical application for 10 days

Table 1. Schedule of Activities from Screening to End of Study

Visit Identifier[a]	Screening	In patient											Follow-Up Contact/EOS	Early Termination/ Discontinuation
Days Relative to Day 1	≤-28	Day -1	1	2	3-4	5	6	7	8-9	10	11	12[b]	41±3[c]	
Informed consent	X													
Outpatient visit to CRU	X													
Inclusion/exclusion criteria	X	X												
CRU confinement[d]		X	→	→	→	→	→	→	→	→	→	X		
Medical/medication history (update)[e]	X	X												
Physical exam[f]	X	X										X		X
Demography (including height and weight)	X													
Contraception check	X	X										X	X	X
Urine drug testing	X	X												
COVID-19 testing[g]	X	X												
COVID-19 temperature check	X	X												
Triplicate supine 12-Lead ECG[h] (single at screening and ET)	X		X	X		X		X		X	X	X		X
Supine Vital signs[i] (Blood pressure and pulse rate)	X		X	X		X		X		X	X	X		X
Topical administration of study intervention, Q12H[j]			X	X	X	X	X	X	X	X				
Serious and non-serious adverse event monitoring	X	X	→	→	→	→	→	→	→	→	→	X	X	X

Table 1. Schedule of Activities from Screening to End of Study

Visit Identifier[a]	Screening	In patient											Follow-Up Contact/EOS	Early Termination/ Discontinuation
Days Relative to Day 1	**≤-28**	**Day -1**	**1**	**2**	**3-4**	**5**	**6**	**7**	**8-9**	**10**	**11**	**12[b]**	**41±3[c]**	
Application site monitoring[k]	X	X	→	→	→	→	→	→	→	→	→	X		X
Serum FSH[l]	X													
QuantiFERON TB Gold Test or equivalent	X													
HIV, HCVAb, HBcAb, HBsAg	X													
Safety Laboratory[m]	X	X				X		X		X		X		X
Pharmacokinetic blood sampling[n]			X	X		X		X		X	X	X		X
[redacted]														

a. Day relative to start of study intervention (D1). Abbreviations used in this table may be found in Appendix 9.

b. Participants will be discharged on D12, following completion of all scheduled procedures. Participants who may experience AEs or dermatological observations on D12 may be confined to the CRU at the discretion of the PI until AEs or dermatological observations are resolved and may be asked to return to the CRU at the discretion of the investigator, for follow-up contact. If unexpected reactions (eg, rash, hives) other than irritation reactions outlined in, Section 8.2.5 occur, the body surface area location must be recorded. Appearance of the reactions should be described.

c. Participants will be scheduled for a follow-up phone call on D41±3 days . Additional follow-up contacts may be scheduled at investigator's discretion, including follow-ups to monitor open AEs based on emerging safety data.

d. Participants will be admitted at least 12 hours prior to dosing.

e. Medical history will be collected at screening and updated on D-1 only.

f. Complete physical examination will be conducted at screening or on D-1 only; otherwise brief physical examination is envisioned for findings during previous or new/open AEs, at the discretion of the PI.

g. Check for exposure to COVID-19 positive participants as per standard CRU protocol.

h. Singlet measure at screening and early termination only. Triplicate measures at all other times approximately 2-4 minutes apart; ECGs will be measured on D1 and D10 as specified in Table 2; ECGs will be measured at pre-AM application on D2, D5 and D7, on D11 at approximately 24H post last application and on D12 prior to discharge.

i. Vitals will be collected at screening and early termination; vitals should be measured on D1 and D10 as specified in Table 2; vitals should be collected at pre- AM application on D2, D5 and D7; vital signs will be collected on D11 at approximately 24H post last application and D12 prior to discharge.

Table 1. Schedule of Activities from Screening to End of Study

Visit Identifier[a]	Screening	In patient											Follow-Up Contact/EOS	Early Termination/ Discontinuation
Days Relative to Day 1	≤-28	Day -1	1	2	3-4	5	6	7	8-9	10	11	12[b]	41±3[c]	

j. In Cohorts 1 and 2, study intervention/vehicle will be applied, on D1 to D9, Q12H. PM dose will be applied approximately 12±1 hours post-AM dose. On D10, study intervention/vehicle will be applied, at AM only. No PM dose will be applied on D10. PF-07295324/vehicle ointment will be applied to participants enrolled in Cohort 1 and in optional Cohort 3. PF-07259955/vehicle cream, will be applied to participants enrolled in Cohort 2. PF-07295324 or PF-0725995 may be studied in optional Cohort 4.

k. Application sites will be identified at screening. Examination of application sites will be conducted at screening and on D-1. On D1 to D10, skin irritation assessment using Draize's scoring (Table 5) will be performed prior to each application of the investigational product. On D11 (approximately 24H post last dose) and on D12 prior to discharge, skin irritation assessment using Draize's scoring will be performed. Refer to Section 8.2.5.

l. At screening, FSH test will be performed in females only, to confirm postmenopausal status.

m. Safety labs will be collected at screening, admission (D-1), during in-patient dosing as specified in Table 1, at discharge, and at early termination.

n. See Table 2 for detailed blood sampling schedule for PK on D1 and D10. Samples will be collected at pre-AM application on D2, D5 and D7. PK sample will be collected on D12, prior to discharge.

CCI [redacted]

1.3.2. Vitals, ECGs, PK, and PD Sampling Schedule on D1 and D10

Table 2. Schedule of Activities for Vitals, ECGs,, PK, and PD on Day 1 and Day 10

Abbreviations used in this table may be found in Appendix 9.	**Inpatient**									
Days Relative to Day 1	**Day 1 and Day 10**									
Hours After topical AM application of PF-07295324 or PF-07259955	**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**24**
Triplicate Supine 12-lead ECG	X		X		X		X		X	X
Supine Vitals (BP and -pulse rate)	X		X		X		X		X	X
Study intervention application	X								X[a]	
Plasma PK collected for the dosed compound	X		X	X	X	X	X		X	X
CCI										

a. In Cohort 1 and Cohort 2, study intervention/vehicle will be applied topically, on D1 to D9, Q12H. PM dose will be applied approximately 12±1 hours post-AM application. On D10, study intervention/vehicle will be applied topically at AM only. No PM application on D10. PF-07295324/vehicle ointment will be topically applied to healthy participants enrolled in Cohort 1 and in optional Cohort 3. PF-07259955/vehicle cream will be topically applied to healthy participants enrolled in Cohort 2. PF-07295324 or PF-0725995 may be studied in optional Cohort 4.

CCI

2. INTRODUCTION

PF-07295324 and PF-07259955 are JAK inhibitors, and are proposed for topical treatment of mild to moderate AD.

2.1. Study Rationale

The purpose of the study is to evaluate the safety, local and systemic tolerability, and pharmacokinetics following multiple doses of topically applied, maximum feasible formulation of PF-07295324 (0.12% w/w) and PF-07259955 (2% w/w), on approximately 20% BSA in healthy adult participants.

As is typical for first-in-human (FIH) studies, the population envisioned for this study will be healthy, adult, male and female participants. Female participants will be confirmed to be categorized as women of non-childbearing potential (WONCBP) as, at the present time, embryo-fetal developmental toxicology studies with PF-07295324 and PF-07259955 have not been conducted. In male participants, appropriate measures to minimize potential transfer of PF-07295324 and PF-07259955 via semen to partners are expected to be followed (refer to Section 10.4).

As this is the first time PF-07295324 and PF-07259955 will be topically administered in humans, safety risks to participants will be minimized by conducting the study in in-patient settings, with adequate monitoring of local and systemic AEs, safety laboratory parameters, 12-lead ECGs, and vital signs. Cumulative safety data will be reviewed after the completion of each cohort.

The safety, local and systemic tolerability, and PK from this study will support the parallel clinical development of PF-07295324 and PF-07259955.

2.2. Background

Signal Transduction Through The JAK Family Proteins

The JAK family, including JAK1, JAK2, JAK3 and TYK 2, is a group of cytoplasmic tyrosine kinases that mediate 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. 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.[1] Phosphorylated STAT molecules are released from the receptor, dimerize and translocate to the nucleus where they bind to specific sites on the DNA and regulate gene transcription.[2] JAK1 pairs with JAK3 to mediate γ-common cytokine signaling and also with JAK2 and/or TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses including interleukin (IL)-6, interferon (IFN)γ, and IFNα. 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 signal.

Disease Overview

Atopic Dermatitis (AD): Multiple pathogenic cytokines are implicated in AD including IL-4, IL-13, IL-22, IL-31 and TSLP, which all signal via JAK1. These cytokines prevent apoptosis of inflammatory T cell infiltrates in the skin, promote Th2 cell differentiation and IgE class switching in B cells, induce epidermal hyperplasia, impair barrier function and anti-microbial protein production and act on neurons to promote pruritus .[3,4]JAK1 inhibition by JAK inhibitors is expected to block or attenuate the signaling of these pathogenic cytokines. Together with Th2 cells, Th1 and Th17 cells promote inflammation in lesional skin in AD patients , and as noted above, differentiation of Th1 and Th17 cells in this disorder as well as other diseases, should be reduced by treatment with JAK inhibitors.[3,4]

Available Treatments and Rationale for the Development of PF-07295324 and PF-07259955

There are several small and large molecule therapeutics proposed for the treatment of AD (corticosteroids, triamcinolone, calcineurin inhibitors, dupilumab etc.). However, there remains a medical need for additional safe and effective therapeutic intervention which improve the clinical symptoms of AD. PF-07295324 and PF-07259955 are potent and selective JAK inhibitors. Both are novel compounds proposed to be administered as topical treatments in healthy participants in this study to prepare for future evaluations in AD patients.

2.2.1. Nonclinical Pharmacology

2.2.1.1. Nonclinical Pharmacology for PF-07295324

PF-07295324, a JAK1, JAK2, and TYK2 inhibitor with selectivity over JAK3, is proposed for the dermal treatment of AD. PF-07295324 is expected to block or attenuate the signaling of multiple pathogenic cytokines implicated in AD such as IL-4, IL-13, IL-22, IL-31 and TSLP. These cytokines prevent apoptosis of inflammatory T cell infiltrates in the skin, promote Th2 cell differentiation and IgE class switching in B cells, induce epidermal hyperplasia, impair barrier function and anti-microbial protein production and act on neurons to promote pruritus.[3,4] Pharmacology studies were conducted with the free base of PF-07295324.

Topical application of PF-07295324 results in diminished expression of pro-inflammatory molecules and enhanced expression of the protective skin barrier protein filaggrin in freshly excised human skin. Therefore, PF-07295324 is expected to demonstrate beneficial effects in the treatment of AD.

In vitro kinase studies showed that PF-07295324 potently inhibits JAK1, JAK2, and TYK2 with less activity against JAK3, as well as a good specificity profile over the broader kinome. JAK enzymes are critical signaling kinases that regulate the signal

transduction pathways triggered by cytokines. In a cellular setting, PF-07295324 potently inhibits signaling pathways induced by aforementioned pathogenic cytokines, which are mainly responsible for inflammation and pruritus in AD.

Upon ex vivo topical application to intact human skin that was stimulated with cytokines, PF-07295324 inhibited the expression of inflammatory genes and stimulated the expression of a skin barrier protein.

2.2.1.2. Nonclinical Pharmacology for PF-07259955

PF-07259955, a JAK1/TYK2 inhibitor, is being developed for the dermal treatment of AD. JAK1 is a critical signaling component which regulates the signal transduction pathways triggered by several pathogenic cytokines implicated in the pathogenesis of AD, including IL-4, IL-13, IL-22, IL-31 and TSLP. PF-07259955 potently inhibits the signaling of the cytokines noted above and blocks the IL-12/Th1 and IL-23/Th17 axes that potentiate the pathogenesis of AD.

Topical application of PF-07259955 results in diminished expression of pro-inflammatory molecules and enhanced expression of the protective skin barrier protein filaggrin in freshly excised human skin. Therefore, PF-07259955 is expected to demonstrate beneficial effects in the treatment of AD.

In vitro kinase studies showed that PF-07259955 inhibits JAK1 and TYK2 with lower activity against JAK2 and selectivity over JAK3 and the broader kinome. JAK enzymes are critical signaling kinases that regulate the signal transduction pathways triggered by cytokines. In a cellular setting, PF-07259955 potently inhibits signaling pathways induced by aforementioned pathogenic cytokines, which are mainly responsible for inflammation and pruritus in AD.

Upon ex vivo topical application to intact human skin that was stimulated with cytokines, PF-07259955 inhibited the expression of inflammatory genes and stimulated the expression of a skin barrier protein.

2.2.2. Nonclinical Pharmacokinetics and Metabolism

2.2.2.1. Brief Summary for PF-07295324

Single-dose PK studies in rats and minipigs indicated a moderate to high systemic clearance of PF-07295324 with a moderate V_{ss}, resulting in short $t_{½}$ (<1 hour). PF-07295324 had an oral bioavailability of 32% in rats. Following repeat oral doses in rats or dermal doses in minipigs, mean systemic exposure (as assessed by C_{max}, AUC_{24}, or C_{av}) increased with increasing dose. In both species, systemic exposures were higher in females as compared with males and accumulation was observed after repeat dosing, with accumulation ratios up to 89 in male minipigs. The average dermal bioavailability after repeat dose in minipigs was 10%.

PF-07295324 was moderately bound to plasma proteins with mean fraction unbound values of 0.162 (rat), 0.361 (minipig), 0.264 (dog), and 0.148 (human) and preferentially distributed

into plasma relative to blood cells in rat, dog and human, with a slight preferential partition into blood cells in minipig.

The primary metabolic pathway for PF-07295324 is through oxygenation and glucuronidation. The in vitro metabolic profiles of PF-07295324 were generally similar across all species and there were no human unique metabolites. Investigation of the metabolism of PF-07295324 in rat, minipig, and dog plasma following oral or dermal dose indicated qualitative agreement between in vitro and in vivo metabolism of PF-07295324. In minipig plasma, only trace amounts of PF-07295324 and metabolites were detected after dermal dosing due to low systemic exposures.

The total CYP and UGT f_m were 0.81 and 0.19, respectively. The overall assignment of CYP f_m was 0.41 by CYP2C9, 0.25 by CYP3A4, and 0.15 remained unassigned. The overall assignment of UGT f_m was >0.053 by UGT1A4, 0.032 for UGT2B4, 0.027 by UGT2B7, and 0.078 remained unassigned.

Human clearance of PF-07295324 was predicted to be 7.4 mL/min/kg. Dermal bioavailability in humans is predicted to be 10% based on an assumed equivalent bioavailability to minipigs. Based on these human predictions, a BID dose of 0.12% (MFD) PF-07295324 applied to approximately 20% body surface area is projected to result in an unbound plasma C_{av} of 0.48 ng/mL (1.0 nM). Activity of PF-07295324 was demonstrated ex vivo in human skin. Compound was topically applied in vitro on freshly excised human skin which was subsequently stimulated with an antibody-cytokine cocktail to induce pro-inflammatory molecules. Compound caused a dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 and a dose-dependent stimulation of gene expression of filaggrin, a protective skin barrier protein. Maximum effects were observed at the PF-07295324 (0.12%) formulation proposed in this study. The topical efficacious dose is defined as the maximum feasible, safe and well tolerated formulation (IB Section 5.1.2.1.4).

Based on the projected unbound C_{av} of 0.48 ng/mL (1.0 nM) at the highest planned clinical dose, the overall risk of PF-07295324 perpetrating a pharmacokinetic DDI is low. Using a static mechanistic model, the risk of PF-07295324 to time-dependently inhibit CYP3A is low.

Refer to the PF-07295324 investigator's brochure (IB) for further details.

2.2.2.2. Brief Summary for PF-07259955

Following single IV dose, PF-07259955 exhibited moderate to high CL, moderate V_{ss} and short $t_{½}$ (≤ 1 hour) in rats and minipigs. PF-07259955 had an oral bioavailability of 55% in rats. Following repeat oral doses in rats or dermal doses in minipigs, mean systemic exposures increased with increasing dose and there were no consistent sex related differences. Accumulation was only observed in minipigs after repeat dermal doses.

PF-07259955 was moderately bound to plasma proteins with mean fraction unbound values of 0.317 (rat), 0.373 (minipig), 0.450 (dog), and 0.345 (human) and preferentially distributed

into plasma relative to blood cells in rat, dog and human, with a slight preferential partition into blood cells in minipig.

The primary metabolic pathway for PF-07259955 is through monooxygenation. The in vitro metabolic profiles of PF-07259955 were generally similar across all species and there were no human-unique metabolites. CYP3A4 is predicted to be the major contributor to in vitro metabolism of PF-07259955 with a f_m value of ≥0.88. Investigation of the metabolism of PF-07259955 in rat and minipig plasma following oral or dermal doses indicated qualitative agreement between in vitro and in vivo metabolism of PF-07259955. In minipig plasma, only trace amounts of PF-07259955 and metabolites were detected after dermal dosing.

Human clearance of PF-07259955 was predicted to be 6.1 mL/min/kg. Dermal bioavailability in humans was estimated to be 8.7% based on an assumed equivalent bioavailability to minipigs. Based on these human predictions, a BID dose of 2% (MFD) PF-07259955 to 20% body surface area is projected to result in a total plasma C_{av} of 45 ng/mL.

Activity of PF-07259955 was demonstrated ex vivo in human skin. Compound was topically applied in vitro on freshly excised human skin which was subsequently stimulated with an antibody-cytokine cocktail to induce pro-inflammatory molecules. Compound caused a dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 and a dose-dependent stimulation of gene expression of filaggrin, a protective skin barrier protein. Maximum effects were observed at the PF-07259955 (2%) formulation proposed in this study. The topical efficacious dose is defined as the maximum feasible, safe and well tolerated formulation (IB Section 5.1.2.1.4).

Based on the projected total plasma C_{av} of 45 ng/mL, the overall risk of PF-07259955 perpetrating a pharmacokinetic DDI is low. Using a static mechanistic model, there is a potential for PF-07259955 to inhibit OCT2.

Refer to the PF-07259955 IB for further details.

2.2.3. Nonclinical Safety

2.2.3.1. Nonclinical Safety for PF-07295324

The immune and hematolymphopoietic systems were identified as the target organs in the rat 6-week GLP oral toxicity study with an NOAEL representing 183× exposure margin over the predicted human C_{av} (unbound) of 0.48 ng/mL at the highest planned clinical dose (0.12% ointment applied to 20% BSA). Local effects in the skin included exacerbation of a vehicle-related dermal findings in the 6-week GLP dermal minipig toxicity study with the NOAEL dose of 0.0528 mg/cm²/day representing 8.8× the planned clinical local dose (0.12% ointment applied at 2.5 mg/cm^2, or 0.006 mg/cm²/day). No adverse findings were observed, either systemically or locally, at any dose and, therefore, the 0.12% ointment (0.0528 [0.0264 BID] mg/cm²/day dose) was the NOAEL. PF-07295324 has no potential for genotoxicity or phototoxicity at the intended clinical doses.

The nonclinical safety profile of this test article has been adequately characterized to support progression into clinical trials in adults and adolescents of up to 6 weeks duration.

Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

2.2.3.2. Nonclinical Safety for PF-07259955

The immune and hematolymphopoietic systems were identified as the target organs in the rat 6-week GLP oral toxicity study with an NOAEL representing 107× exposure margin over the projected human C_{av} of 45 ng/mL at the highest planned clinical dose (2% cream applied to 20% BSA). Local effects on the skin were observed at the administration site in the 6-week GLP dermal minipig toxicity study with the NOAEL of 0.74 (0.37 BID) mg/cm^2/day (2% cream), representing 9.3× margin over the highest planned clinical dose (2% cream applied at ~2 mg/cm^2 formulation per dose, or 0.08 [0.04 BID] mg/cm^2/day). No test article related adverse systemic or local effects were observed in any of the study parameters or endpoints evaluated and, therefore, the 2% concentration (0.74 [0.37 BID] mg/cm^2/day) was the NOAEL. PF-07259955 has no potential for genotoxicity or phototoxicity at the intended clinical doses. PF-07259955 has a low-risk potential to induce skin sensitization at proposed clinical doses.

The nonclinical safety profile of PF-07259955 has been adequately characterized to support progression into clinical trials in adults and adolescents of up to 6 weeks duration.

Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

2.2.4. Clinical Overview

As this is a first experience of administration of PF-07295324 and PF-07259955 in humans, no clinical data is available to date.

2.3. Benefit/Risk Assessment

PF-07295324 and PF-07259955 are not expected to provide any clinical benefit to healthy participants. This study is primarily designed to investigate safety and local and systemic tolerability following topical administration of PF-07295324 (0.12% ointment) or PF-07259955 (2% cream), on approximately 20% body surface area, in healthy participants.

Study C4711001 is the first time that PF-07295324 or PF-07259955 will be administered to humans. The purpose of the study is to provide the basis for further clinical development of PF-07295324 and PF-07259955 as potential new, pharmacological, topical agents for the treatment of participants with mild to moderate AD. As of December 2021, no specific human risks have been identified; postulated risks based on nonclinical studies are summarized in Section 2.2.3. The clinical impact of these potential risks will be minimized by conducting the study in in-patient settings, and through adequate safety monitoring of the participants following administration of multiple, topical doses of the assigned study intervention, PF-07295324 and PF-07259955, as outlined in the Section 1.3 SoA.

Due to similarities in the mechanism of action of both PF-07295324 and PF-07259955 and common study design elements, a platform FIH trial design has been implemented. This platform design will lead to increased efficiency of trial conduct, with no increased safety risks to participants enrolled in the study.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07295324 and PF-07259955 may be found in the respective investigator's brochure, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) PF-07295324 and PF-07259955		
Skin irritation	Based on local effects in the skin noted in the nonclinical studies	Local tolerability following topical application will be assessed throughout the study by evaluation of skin irritation potential using Draize's scoring criteria at frequencies specified in the Section 1.3 SoA
Skin Sensitization	A low risk for skin sensitization was identified in nonclinical studies with PF-07259955	Participants will be assessed for safety at regular intervals throughout the study, including assessment of the administration site. Participants with any history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products will be excluded from the study.
Study Procedures		
Adverse events (AEs) related with study procedures	Study procedures may cause AEs from blood draws or electrocardiograms monitoring, although the potential risks (eg infection, bleeding, inflammation of the vein or skin, blood clots, or local nerve damage) might be low.	The protocol is designed to minimize the burden on participants while maintaining the integrity of the study design to support the objectives/endpoints. All of the study procedures are only performed by qualified medical personnel. Participants will be informed of the potential risks.
Other		
Risks due to COVID-19	Potential cross-contamination; results could potentially be confounded by COVID-19 related AEs	COVID-19 testing according to SoA

2.3.2. Benefit Assessment

PF-07295324 and PF-07259955 are not expected to provide any clinical benefit to healthy participants, although clinical assessments including vital signs, ECGs, and laboratory tests may be beneficial if they have underlying basic diseases that are measured while reviewing the inclusion/exclusion criteria.

2.3.3. Overall Benefit/Risk Conclusion

At the issuance of this protocol, no human data is available. The study incorporates an adequate safety monitoring plan and includes inpatient monitoring of the participants following topical administration of the investigational products. The clinical impact of potential risks will be minimized through cumulative review of emerging safety and tolerability, as the study progresses.

Taking into account the measures to minimize risk to study participants, the potential risks identified in association with PF-07295324 and PF-07259955 are justified by the anticipated therapeutic benefits that may be afforded to future trial participants with mild to moderate atopic dermatitis.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety, and local and systemic tolerability, of PF-07295324 and PF-07259955, following multiple doses of topically administered PF-07295324 or PF-07259955, on approximately 20% BSA in healthy adult participants.	• Incidence and severity of systemic AEs, safety laboratory tests, vital signs (including blood pressure and pulse rate), and heart rhythms as assessed via 12-lead electrocardiogram (ECG). • Incidence and severity of application site AEs as assessed by Draize score.
Secondary:	**Secondary:**
• To characterize plasma PK following multiple topical applications of PF-07295324 and PF-07259955.	• Plasma PK of multiple topical doses of PF-07295324 and PF-07259955, as data permits: Day 1: C_{max}, T_{max}, C_{avg}, C_{trough}, AUC_{tau} Day 10: C_{max}, T_{max}, C_{avg}, C_{trough}, AUC_{tau}, R_{ac} (C_{max}), R_{ac}(AUC_{tau}), $t_{½}$, CL/F, and V_z/F
CCI	

4. STUDY DESIGN

4.1. Overall Design

C4711001 is an investigator- and participant-blinded, interventional, randomized, vehicle-controlled, Phase 1 study to evaluate the safety, and local and systemic tolerability and pharmacokinetics of maximum feasible formulation of topical JAK inhibitors, PF-07295324 (0.12%) and PF-07259955 (2%) in healthy adult participants.

This study will enroll healthy adult participants in ≤4 cohorts: 2 planned cohorts and 2 optional cohorts. Approximately 6 participants will be enrolled in each cohort, randomized as 4 active:2 vehicle. Cohort 1 and the optional Cohort 3 will be assigned to PF-07295324/vehicle, administered topically as an ointment. Cohort 2 will be assigned to PF-07259955/vehicle administered topically as a cream. PF-07295324 or PF-0725995 may be studied in optional Cohort 4.

Participants will be enrolled in the optional cohorts in a sequential design to the respective planned cohort, as shown in Section 1.2. Planned cohorts assigned to different interventions may progress simultaneously. Similarly, optional cohorts assigned to different interventions may progress simultaneously (Section 1.2).

Healthy adult participants will be screened for eligibility criteria within 28 days prior to the administration of the first dose in each part of the study. Participants enrolled in 1 cohort of this study will not be allowed to enroll in any other cohorts of the study. Participants enrolled in each of the cohorts will be discharged following completion of all scheduled assessments as specified in the SoA.

Participants confirming eligibility according to Section 5 will be admitted to the CRU on Day -1. On Day 1, application sites of all participants will be assessed, prior to the administration of study intervention/vehicle. Dermal reactions at the application site will be assessed clinically using a visual grade that rates the degree of erythema, edema, and other signs of skin irritation. Participants enrolled in Cohort 1 and Cohort 2, with no dermal site reactions at pre-dose on Day 1, will receive multiple topical doses of study intervention or vehicle, Q12H from Day 1 to Day 9, and only AM application on Day 10. All AM doses will be administered approximately 60 minutes following shower, if participants choose to shower; all PM doses will be administered approximately 12±1 hour post-AM dose. Participants will be discharged on Day 12 following the completion of all scheduled procedures as per SoA. Participants will be scheduled for a follow-up phone contact on Study Day 41±3 days.

Up to 2 optional cohorts (Cohort 3 and Cohort 4) of up to 6 participants/cohort may be enrolled in this study. Participants enrolled in the optional cohort will be randomized to either active or vehicle (4:2). The optional cohorts may be used to repeat the doses studied in previous cohorts, explore lower strength formulations on approximately 20% BSA, or to repeat the maximum feasible formulation on lower body surface area, or to administer maximum feasible formulation at a less frequent dosing regimen on approximately 20%

BSA. Participants enrolled in the optional cohorts will be guided by the same stopping criteria as the planned cohorts.

If a participant has any clinically significant, study related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the participant may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. Participants who experience a treatment-related AE will continue to be followed to resolution or stabilization of the event as agreed upon by the investigator and sponsor. Participants who discontinue for non-safety related reasons prior to end of the study may be replaced, at the discretion of the principal investigator (PI) and the sponsor.

The planned duration of participation from screening to follow-up is approximately 10 weeks.

4.2. Scientific Rationale for Study Design

C4711001 is a Phase 1, First-in-Human (FIH) study. The purpose of this study is to investigate the local and systemic tolerability of multiple topical applications of PF-07295324 and PF-07259955 on approximately 20% body surface area, in healthy adult participants.

The intended route of administration for future clinical development of PF-07295324 and PF-07259955 is topical, which is the same route that will be tested in this study.

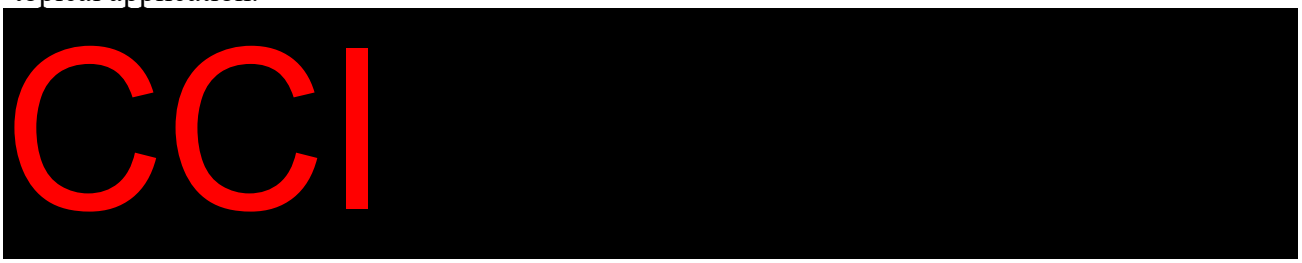
As is typical for FIH studies, the population envisioned for this study will be healthy male and female participants. Female participants will be confirmed to be categorized as women of non-childbearing potential as, at the present time, embryo-fetal developmental toxicology studies with PF-07295324 and PF-07259955 have not been conducted. Appropriate measures to minimize potential transfer of PF-07295324 and PF-07259955 via semen to partners are expected to be followed by male participants (refer to Section 10.4.1).

PF-07295324 and PF-07259955 are both potent JAK inhibitors demonstrating similar non-clinical pharmacology. The objective of the FIH study is to evaluate the safety and tolerability of the two topical JAK inhibitors. As the FIH study of the two topical JAK inhibitors will use common study design elements including study population, inclusion/exclusion criteria, sample size, randomization ratio, route of administration and frequency of dosing. Due to similar non-clinical safety outcomes, both JAK inhibitors will be monitored using identical safety monitoring plan and individual discontinuation criteria in FIH study.

Due to a common framework described above, this FIH study of both the JAK inhibitors PF-07295324 and PF-07259955, has been designed under 1 single Phase 1 study protocol, C4711001. This design will lead to increased efficiencies by optimizing the use of operational resources leading to simultaneous characterization of the two topical JAK inhibitors, and with no increased safety risks to participants enrolled in the trial.

To permit an unbiased assessment of safety, participants will be randomized to active or vehicle in a ratio of 4 active: 2 vehicle. The participants and clinical research unit (CRU) staff (except specific personnel involved in the preparation of doses) will be blinded to treatment assignment in each cohort, to permit an unbiased assessment of safety and tolerability. A limited number of team members will be unblinded to permit real time monitoring of emerging safety.

As this is a first experience of PF-07295324 and PF-07259955 in humans, risks to study participants will be minimized by conducting dosing in an inpatient setting and with cautious inpatient monitoring. Monitoring of local and systemic AEs, clinical safety laboratory tests (Appendix 2), vital signs, electrocardiograms (ECGs), and physical examinations will provide essential data to investigate the safety of PF-07295324 and PF-07259955 following topical application.



4.2.1. Diversity of Study Population

Not applicable

4.2.2. Choice of Contraception/Barrier Requirements

Studies to evaluate the development toxicity of PF-07259955 and PF-07295324 have not been conducted. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

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

4.3. Justification for Dose

As this is a first experience of administering topical PF-07295324 and PF-07259955 in humans, no prior clinical data is available to guide topical dose selection. Maximum feasible formulations of PF-07295324 (0.12%) and PF-07259955 (2%) will be evaluated in Cohort 1 and Cohort 2, respectively, as shown in the Schema. The vehicle formulations have been optimized using excipients that are precedented and are below the limits of toleration; therefore vehicles are expected to be well-tolerated. Prior precedence with topical JAKs (in mild to moderate AD) and oral JAK inhibitors (in HVs) enables progression of a JAK inhibitor in humans at maximum feasible topical formulation.

The maximal BSA for application area has been determined to be approximately 20%, to adequately support early clinical development in mild-to-moderate AD participants. Systemic exposures of the maximum feasible formulation on approximately 20% BSA and corresponding safety multiples of PF-07295324 and PF-07259955 have been projected below.

4.3.1. Dose rationale for PF-07295324

Solubility and chemical stability of PF-07295324 with topical excipients were key drivers to nominate the maximal strength ointment formulation of 0.12% (w/w).

The PF-07295324 formulation when applied to human skin (stimulated ex-vivo), caused dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 stimulation of gene expression of filaggrin, a protective skin barrier protein. Maximum effects were observed at the formulation strength proposed in this study. (IB Section 5.1.2.1.4. and summarized in protocol Section 2.2.1).

Steady state systemic exposures following topical administration of PF-07295324 (0.12%), once daily or Q12H, on approximately 20% BSA, have been projected assuming ointment application rate of approximately 2.5 mg/cm^2, dermal availability of approximately 10%, (similar to that estimated in minipigs at steady-state, following topical administration of 0.12% PF-07295324 ointment, BID) and predicted human hepatic clearance of 7.4 mL/min/kg (Section 2.2.2.1). The projected steady-state systemic exposures following topical administration of 0.12% PF-07295324, are summarized in Table 3.

Table 3. Projected steady-state exposures and Safety Margins Following Administration of Multiple Topical Doses of PF-07295324 (0.12%), once daily or twice daily on 10-20% BSA, in Healthy Adult Participants

COH.	FORM. STRENGTH (%)	QD/ BID	%BSA	TDD[a] (mg)	DOSE SYS.[b] (mg)	AUC24[b] (ng*h/mL)	uCavg (ng/mL)	uCavg.IFNγ[c]	uCAVG.SM[d]
Coh. 1	0.12	BID	20	24	2.4	77	0.48	18	183
Optional Coh. 3	0.12	BID	10	12	1.2	39	0.24	35	367
Optional Coh. 3	0.12	QD	20	12	1.2	39	0.24	35	367

a. Total daily dose calculated as appropriate for once daily or twice daily application and as a product of formulation strength and body surface area, assuming an ointment application rate of approximately 2.5 mg/cm^2.
b. Assuming median healthy participants BW ~70 kg, unbound exposures were predicted using CL_p=30.8 L/h, V_d=56 L, Fa.Fg=1, F=0.1, and in vitro fraction unbound in human plasma $f_{u,p}$=0.148; MW = 467.5; 1 ng/mL unbound PF-07295324 is equivalent to 2.08 nM.
c. Multiples have been calculated relative to PF-07295324 unbound plasma IFNγ IC_{50} of 18 nM.
d. Margins have been calculated relative to PF-07295324 NOAEL unbound C_{avg}=88 ng/mL in 6 week oral GLP toxicology study in rat; systemic safety margins have been calculated based on unbound plasma exposures.

As summarized in Table 3, following topical administration of maximum feasible formulation (0.12%) of PF-07295324, Q12H, on approximately 20% BSA the projected steady-state average unbound plasma concentration (C_{avg}) is 0.48 ng/mL.

Based on the projected steady-state systemic exposure [0.48 ng/mL (1 nM) is ~18-fold below the unbound IFNγ IC_{50} (18 nM)] following topical administration of PF-07295324 (0.12%, Q12H, 20%BSA).

This highest projected average unbound exposure is approximately 183-x below the rat unbound NOAEL C_{avg} of 88 ng/mL. In minipigs, topical administration of an equivalent dose resulted in minimal, non-adverse local irritation (Section 2.2.3.1). The NOAEL in the PF-07295324 pivotal 6-week dermal toxicity study in minipigs was 0.0528 mg/cm2/day, resulting in an ~8.8-x dose margin based on an anticipated clinical application rate of 2.5 mg/cm^2 and dose of 0.006 mg/cm^2/day (0.12% ointment, BID).

Overall, multiple topical administrations of PF-07295324 (0.12%), in healthy adult participants is expected to be safe and well tolerated, locally and systemically.

4.3.2. Dose rationale for PF-07259955

Solubility and chemical stability of PF-07259955 with topical excipients were key drivers to nominate the maximal strength cream formulation of 2% (w/w).

The PF-07259955 formulation when applied to human skin (stimulated ex-vivo), caused dose-dependent inhibition of gene expression of pro-inflammatory molecules CXCL10, CCL26 and MMP12 stimulation of gene expression of filaggrin, a protective skin barrier protein. Maximum effects were observed at the formulation strengths proposed in this study. (IB Section 5.1.2.1.4. and summarized in protocol Section 2.2.1).

Steady state systemic exposures following topical administration of PF-07259955, once daily or Q12H, on approximately 20% body surface area, have been projected assuming cream application rate of approximately 2 mg/cm^2, dermal availability of approximately 8.7%, (similar to that estimated in minipigs at steady-state, following topical administration of 2% PF-07259955 cream, BID) and predicted human hepatic clearance of 6.1 mL/min/kg (Section 2.2.2.2). The projected steady-state systemic exposures following topical administration of 2% PF-07259955, are summarized in Table 4.

Table 4. Projected steady-state exposures and Safety Margins Following Administration of Multiple Topical Doses of PF-07259955 (2%), once daily or twice daily on 10-20% BSA, in Healthy Adult Participants

COH.	FORM. STRENGTH (%)	QD/ BID	%BSA	TDD[a] (mg)	DOSE SYS.[b] (mg)	AUC24[b] (ng*h/mL)	uCAVG (ng/mL)	uCavg.IFNγ[c]	uCAVG.SM[d]
Coh. 2	2	BID	20	320	28	1100	16	3.7	110
Optional Coh. 4	2	BID	10	160	14	540	7.8	7.7	220
Optional Coh. 4	2	QD	20	160	14	540	7.8	7.7	220

a. Total daily dose calculated as appropriate for once daily or twice daily application and as a product of formulation strength and body surface area, assuming an ointment application rate of approximately 2 mg/cm^2.
b. Assuming median healthy participants BW ~70 kg, unbound exposures were predicted using CL_p=26 L/h, V_d=77 L, Fa.Fg=1, %F=8.7, and in vitro fraction unbound in human plasma $f_{u,p}$=0.345; MW = 417.5; 1 ng/mL unbound PF-07259955 is equivalent to 2.4 nM.
c. Multiples have been calculated relative to PF-07259955 unbound plasma IFNγ IC_{50} of 143 nM.
d. Margins have been calculated relative to PF-07259955 NOAEL unbound C_{avg}=1691 ng/mL in 6 week oral GLP toxicology study in rat; systemic safety margins have been calculated based on unbound plasma exposures.

As summarized in Table 4, following topical administration of maximal feasible formulation (2%) of PF-07259955, Q12H, on approximately 20% BSA, the projected average steady state unbound plasma concentration (C_{avg}) is approximately, 16 ng/mL (38.4 nM).

Based on the projected steady-state systemic exposure [16 ng/mL (38.4 nM) is ~3.7-fold below the unbound IFNγ IC_{50} (143 nM)], following topical administration of PF-07259955 (2%, Q12H, 20%BSA).

This highest projected exposure is approximately 110-x below the rat unbound NOAEL C_{avg} of 1691 ng/mL. Similarly, minimal, non-adverse local irritation is anticipated at this maximum feasible formulation based on 6 week dermal toleration assessment in minipigs (Section 2.2.3.2). The NOAEL in the PF-07259955 pivotal 6-week dermal toxicity study in minipigs was 0.74 mg/cm^2/day, resulting in an ~9.3x dose margin based on an anticipated clinical application rate of 2 mg/cm^2 and dose of 0.08 mg/cm^2/day (2% cream, BID).

Overall, multiple topical administrations of PF-07259955 (2%), in healthy adult participants are expected to be safe and well tolerated, locally and systemically.

Beyond Cohort 1 and Cohort 2, up to 2 optional cohorts (Cohort 3 and potentially Cohort 4) of up to 6 healthy adult participants in each cohort may be enrolled in this study. The optional cohorts may be used to repeat the doses studied in previous cohorts, explore lower formulation strength, or repeat the 0.12% formulation strength on lower body surface area, or at less frequent dosing interval on approximately 20% BSA. All cumulative safety data from Cohort 1 and Cohort 2 will be used to determine the formulation strength, %BSA, and dosing regimen to be administered to participants enrolled in optional cohorts. The formulation strengths and frequency of dosing of PF-07295324 or PF-07259955 to be investigated in the optional Cohort 3 and/or Cohort 4 will not exceed that of Cohort 1 or Cohort 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 scheduled follow-up contact shown in the SoA.

The end of the study is defined as the date of the final follow-up contact shown in the SoA for the last participant in the trial.

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. Healthy (except obese) female participants of non-childbearing potential and/or male participants, at the time of screening, must be 18 to 60 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 of non-child bearing potential.

Type of Participant and Disease Characteristics:

2. Male and female of non-child bearing potential participants, who are healthy as determined by medical evaluation including medical history, physical examination, vital assessments, 12-lead ECGs, and laboratory tests.

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

Weight:

4. Body mass index (BMI) of 17.5 to 35 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

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

2. Participants who have any visible skin damage or skin condition (eg sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurations) in or around the application site which, in the opinion of the investigative personnel, will interfere with the evaluation of the test site reaction.

3. Participants who have a history of or have active AD/eczema/urticaria.

4. Evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) as defined by both of the following:

    - A positive QuantiFERON-TB Gold In-tube or equivalent test (QFT).

    - History of either untreated or inadequately treated latent or active TB infection, or current treatment for the same.

5. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody (HCVAb). Hepatitis B vaccination is allowed. As an exception a positive HBsAb test due to hepatitis B vaccination is permissible.

6. Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1.

7. A history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

8. Acute disease state (unstable medical condition such as nausea, vomiting, fever or diarrhea, etc) within 7 days of Day 1.

9. 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.

10. Have a first-degree relative with hereditary immunodeficiency.

11. A history of any lymphoproliferative disorder (such as Epstein Barr Virus [EBV] – related lymphoproliferative disorder), history of lymphoma, leukemia, malignancies or signs and symptoms suggestive of current lymphatic disease.

12. Have undergone significant trauma or major surgery within 4 weeks of screening.

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

Prior/Concomitant Therapy:

14. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.8 Concomitant Therapy for additional details).

15. Participants who are vaccinated with vaccines that have live components (or live attenuated vaccines) within the 6 weeks prior to the first dose of PF-07295324/vehicle or PF-07259955/vehicle or who are expected to be vaccinated during treatment or during follow-up period.

    NOTE regarding COVID-19 vaccines with authorization or approval for emergency use:

    There is no requirement for washout of COVID-19 vaccines prior to the first dose of PF-07295324/vehicle or PF-07259955/vehicle if the vaccine is not live attenuated (eg, mRNA, utilizing a viral vector, inactivated virus).There is no protocol-specified requirement for the interruption of IP dosing prior to or after vaccination if the COVID-19 vaccine is not live attenuated.

16. Participants in any cohort of this study can only be randomized **and** receive the IP in only 1 cohort of this study.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

18. A positive urine drug test.

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

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

21. 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) **or** alanine aminotransferase (ALT) level ≥1.5 × upper limit of normal (ULN);

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

Other Exclusions:

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

23. Use of tobacco/nicotine containing products more than 5 cigarettes/day.

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

25. History of serious adverse reactions or hypersensitivity to any topical drug; or known allergy to any of the test product(s) or any components in the test product(s) or history of hypersensitivity; or allergic reactions to any of the study preparations as described in the PF-07295324 IB and PF-07259955 IB.

26. Not willing to refrain from shaving, the use of depilatories or other hair-removal activities, antiperspirants, lotions, skin creams, fragrances or perfumes, or body oils (eg, baby oil; coconut oil), use of hair products, hair gels, and hair oil in the treatment areas for 48 hours prior to admission to the CRU and for the duration of the stay in the CRU.

27. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

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

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 at least 4 hours prior to any safety laboratory evaluations conducted at pre-AM application.

- Otherwise, water, meals, and snacks may be consumed without restriction.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing and during confinement in the CRU.

- Participants will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

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

5.3.3. Activity

- Showering/Bathing: Participant's dosing areas of skin are required to be dry for at least 30 minutes prior to each study drug application. To help facilitate this, participants will not be permitted to shower or bathe within 1 hour prior to and 4 hours after any study drug dose application. Participants are not required to shower or bathe prior to each dose application. If participants choose to shower or bathe, it will occur at least 1 hour prior to the AM and PM dose.

- Participant should not use any products in the area where the investigational product is applied during confinement in the CRU.

- Participants should be encouraged not to touch the area of application.

- Participants should be encouraged not to put hands in the mouth to avoid ingestion of investigational product.

- Participants should avoid wiping the investigational product off the skin.

- 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.

- Participants are permitted to participate in light recreational activities during the study (eg, watching television, reading). Following application, study participants are required to wear loose-fitting clothing and avoid activity for at least 4 hours post AM and PM dose, to minimize the study medication being wiped off the skin or the treated areas to become occluded.

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 his or her partner(s) from the permitted list of contraception methods (see Appendix 4 Section 10.4) and 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) considering that their risk for pregnancy may have changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued 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 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 be rescreened and enrolled in a subsequent group or cohort.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(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-07295324 (0.12%), ointment and PF-07259955 (2%), cream, as well as the corresponding vehicles for each IP.

Both the IPs (PF-07295324 and PF-07259955) and vehicles (ointment and cream) will be supplied by Pfizer to the CRU as packaged 60 gram tubes and labeled according to local regulatory requirements in an unblinded fashion.

Both the IPs (PF-07295324 and PF-07259955) and vehicle doses will be prepared by the unblinded CRU pharmacist and provided to the blinded investigational site staff.

During the stay in the CRU, study drug applications will be performed by trained study staff to ensure proper study drug application.

6.1.1. Administration

6.1.1.1. PF-07295324 and PF-07259955 Administration

The IP will be applied in blinded fashion, at the CRU. All applications of the IP will be dispensed and applied by study site staff from D1 AM through D10 AM dose. For Cohort 1 and Cohort 2, topical formulation will be applied Q12H on D1-D9 to the area identified on D-1 or D1. Only the AM dose will be applied on D10. Every effort must be made for the AM applications on D2 to D10 to be completed approximately 24±2 hour intervals from the recorded time of completion of the D1 dose application, for each participant. The PM dose application on D1 through D9 will be applied approximately 12±1 hour after the recorded time of completion of each of the AM dose application, for each participant.

For optional Cohort 3 and Cohort 4, formulation may be of a lower strength or equal to that of the planned cohort; administration procedures will be similar to that of planned cohorts. If study intervention in the optional cohort/s is once daily, formulation will be applied at AM only, from D1 to D10.

The per application dose will be calculated using the formula provided below in Section 6.1.1.2. The intended application rate is approximately 2.5 or 2 mg/cm^2 for PF-07295324 or PF-07259955, respectively. The IP should be applied evenly to all pre-specified areas. The per application dose will be expressed as the weight of ointment or cream in grams. The per application dose will remain fixed and the IP will be applied to the areas identified on Day 1.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down for at least 4 hours post application (except when required for BP, pulse rate, and ECG measurements).

6.1.1.2. Calculation of Per Application Dose

The per application dose (expressed in g) will be calculated by study site staff, for each participant, using the formula below:

BSA × Application rate (g/cm^2) = Weight of investigational product (in g) per application.

where BSA is less than or equal to 4000 cm^2 () and application rate is 2.5 mg/cm^2 (for cohorts assigned to PF-07295324/vehicle) and 2 mg/cm^2 (for cohorts assigned to PF-07259955/vehicle).

6.1.1.3. Application of Investigational Product

Before the D1 AM dose is applied for each participant, the designated areas for treatment will be identified on D-1 or D1 and documented in the participants' study records. The treatment areas will be mapped using surgical markers (on D-1 or D1) to outline areas to ensure they remain the same throughout the double-blind treatment period. For each subsequent investigational product application, study site staff will refer to the documented locations as determined on D-1 or D1.

To standardize the application, the investigational products will be applied to a BSA of approximately 20% (±10%) or less than or equal to 4000 cm^2±400, for 10 consecutive days, at an approximate formulation rate of 2.5 mg/cm^2 or 2 mg/cm^2 for PF-07295324 or PF-07259955, respectively.

For participants in Cohort 1 and Cohort 2, the application area will include the back as well as other extremities identified by the investigator.

For participants in optional Cohort 3 and Cohort 4, if study intervention is planned for lower body surface areas, smaller treatment area may be mapped for topical administration.

Wearing gloves, study site staff will apply the formulation to the areas determined on D-1 or D1. Study drug will be applied as a thin layer on participants' skin. Care must be taken to avoid study drug contamination of designated venous access areas used for PK sampling, by leaving an untreated margin of at least 5 cm radius around each venipuncture site. Following investigational product application, participants will be instructed to wear loose fitting clothing, to not wipe investigational product off the skin, and to refrain from bathing, sauna or washing the treated areas within 4 hours after application. At 4 hours postdose, investigational product will be wiped from all application sites, with a clean towel.

6.2. Preparation, Handling, Storage, and 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.

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 temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. 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. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers and in accordance with the labels.

6. 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), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

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

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

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

Prior to application, the per application dose will be carefully weighed out by CRU pharmacy staff. All study drug accountability will be recorded on the Investigational Product Accountability Log (IPAL).

PF-07295324 and PF-07259955 will be prepared by qualified unblinded site pharmacist according to the IP manual. Blinded investigational product will be applied to the participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

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

Investigators and participants will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an otherwise uninvolved third party (for example, pharmacist) will be responsible for the preparation and dispensing of all treatments, according to the randomization schedule and assigned treatment for the individual participant.

6.3.2. Breaking the Blind

The method for breaking the blind in this study will be manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the

investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participants' treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the data collection tool (DCT).

CRU Pharmacy must ensure that any opened randomization information is secured appropriately again after consultation.

Blinding codes should be broken only under exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the participant. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary.

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

6.4. Study Intervention Compliance

Investigational product will be applied under the supervision of investigator site personnel. The application site of each participant will be examined following dosing to ensure the investigational product was topically applied. The date and time of each dose administered will be recorded in the source documents.

6.5. Dose Modification

No dose modification is anticipated for Cohort 1 and Cohort 2 in this study. Dose and dosing regimen in Cohort 3 and Cohort 4 may be determined based on review of emerging data from Cohort 1 (for Cohort 3 only) and Cohort 1, Cohort 2 and Cohort 3 (for Cohort 4 only).

6.5.1. Dose Stopping Rules

No dose escalation is planned for this study.

The dosing will be terminated based on the following criteria:

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

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

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

- Draize score will be incorporated in individual dose application decisions. The dose will not be considered well-tolerated and application of corresponding IP will be terminated if:

    - Persistent Draize scoring of ≥3 in more than 50% participants in each cohort.

    - Persistent Draize score of 4 in 2 or more participants in a cohort. In addition, the study will be paused for further assessment of any Draize score of 4.

    - Clinically significant skin abnormalities following application of the IP (based on the judgment of the medical provider/investigator) in 2 or more participants in a cohort. These include persistent moderate to severe skin findings at the site of active drug application: edema, papules, vesicles, bullae, weeping, fissuring, and erosions.

        - Within a participant, "Persistent" is defined as the presence of skin findings in at least 2 consecutive assessment periods at least 8 hours apart.

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

Optional cohort dosing will occur after review of all available safety data in a minimum of 4 participants (3 active: 1 vehicle) dosed in Cohort 1 , Cohort 2 and Cohort 3 (for Cohort 4 only) up to 10 days post-dose.

6.5.2. Individual Stopping Rules

If an individual participant exceeds any of the following, the participant will be discontinued from the study and will enter early termination visit as per SoA:

- Any of the following values (to be confirmed at 24 hours [±8 hours window]):
  - ECG changes (as described in Section 7.1.1), potential acute kidney injury (as described in Section 7.1.2), and potential drug-induced liver injury (as described in Appendix 6);
  - Any laboratory values or clinically significant findings meeting criteria of CTCAE v5.0 Grade 3 or greater.
- Any SAE (irrespective of relatedness to study drug).
- Any adverse dermal findings that, at the discretion of the study team and investigator, indicate that dosing should be halted.
- Please refer to Section 7 for additional individual discontinuation criteria.

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

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

6.7. Treatment of Overdose

For this study, the maximum feasible formulation of IP specified below, Q12H to designated surface area within a 24-hour time period ±2 hour will be considered an overdose:

- any dose of PF-07295324 greater than 0.12% within a 24-hour time period ±2 hours will be considered an overdose.
- any dose of PF-07259955 greater than 2% within a 24-hour time period ±2 hours will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07295324 and PF-07259955 (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

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

6.8. Concomitant Therapy

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

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.

6.8.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07295324 and PF-07259955; standard medical supportive care must be provided to manage the AEs.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

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

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

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

7.1.1. ECG Changes

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

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec.

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

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.2. Potential Cases of Acute Kidney Injury

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

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

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

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical

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

7.2. 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. Reasons for discontinuation from the study include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- 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 enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

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

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

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations 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.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with 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 study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Participants who withdraw from the study for ***non-safety reasons*** may be replaced at the discretion of the investigator upon consultation with the sponsor.

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. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

Participants will be screened within 28 days prior to application of the study intervention to confirm that they meet the study population criteria. 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.

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.

Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

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

The total blood sampling volume for individual participants in this study is approximately 165 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

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

8.1. 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 issues.

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.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the

definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to Section 8.3.3.

8.2.2. Vital Signs

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

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

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

8.2.3. Electrocardiograms

12-Lead ECGs should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

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

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements for any postdose QTcF interval is increased by ≥30 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG. If either of these conditions occur, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a postdose QTcF 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).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the

same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 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. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically 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 36 hours after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or 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.

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 study intervention.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

8.2.5. Application Site Assessments

Local toleration will be assessed as specified in the SoA, by Draize scoring (Table 5) and via clinical observation.

A clinical research site staff member trained in the evaluation of skin will assess local toleration at the treatment test areas by examining the skin under standard light conditions for visible skin irritation; findings on this scale do not require reporting as an AE unless the skin response is deemed to be clinically significant by the investigator. Unscheduled Draize evaluations may be performed at any time during the study as deemed necessary by the investigator.

Scores for erythema, edema, papules, and vesicles are judged to be present if they involve 25% or more of the test area. Identifiable reaction(s) encompassing less than 25% of the test areas are to be documented as a comment rather than a score or grade. All numerical, letter grades, and superficial observations will be collected on the designated CRF.

The site staff member will be recommended to adequately describe the appearance of the skin irritation in addition to the Draize score assessment.

Table 5. Skin Irritation Assessment Using Draize Scoring

Definition	Score
No reaction visible	0
Trace reaction – barely perceptible pinkness	1
Mild reaction – readily visible pinkness	2
Moderate reaction – definite redness	3
Strong to severe reaction – very intense redness	4

Definition of letter grades appended to a numerical grade:

J	Burning, stinging, itching
E	Edema – swelling, spongy feeling when palpated
P	Papules – red, solid, pinpoint elevations, granular feeling
V	Vesicles – small elevation containing serous fluid (blister-like), diameter 5 mm or less
B	Bulla reaction – fluid-filled lesion greater than 0.5 cm in diameter
S	Spreading – evidence of the reaction beyond the test site
W	Weeping – result of a vesicular or bulla reaction – serous exudates – clear fluid oozing or covering test area
I	Induration – solid, elevated, hardened, thickening skin reaction
XC	Additional comments appear in Comments section

Definition of superficial observations appended to a numerical and/or letter grade:

G	Glazing
Y	Peeling
C	Scab, dried film of serous exudates of vesicular or bulla reaction
D	Hyperpigmentation (reddish-brown discoloration of test area)
H	Hypopigmentation (loss of visible pigmentation at test area)
F	Fissuring – grooves in the superficial layers of the skin to glistening
R	Erosion(s)
U	Ulceration(s)
K	Scaling – flaking of skin

Photographs of dosing area are taken to document Draize scoring reaction ≥3 or AE at the treatment application site. These photographs are for illustrative reference only and will be used to document Draize scores ≥3.Photographs will be taken in a non-identifiable manner without participants face in frame.

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

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

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

8.3.1. 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 study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of 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

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

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

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

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

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

Further information on follow-up procedures is 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:

    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.

    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

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

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

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

An 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, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

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

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.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

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

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

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

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

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

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

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

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. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of PF-07295324 or PF-07259955 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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 application that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples collected for measurement of plasma concentrations of PF-07295324 or PF-07259955 will be analyzed using a validated analytical method in compliance with applicable SOPs.

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

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

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

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.4.1. Pharmacokinetics of PF-07295324

Blood samples of approximately 4 mL, to provide approximately 1.2 mL of plasma, will be collected for analysis of plasma concentrations of PF-07295324 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24 hour clock time) of each sample will be recorded.

CCI

8.4.2. Pharmacokinetics for PF-07259955

Blood samples of approximately 4 mL, to provide approximately 1.2 mL of plasma, will be collected for analysis of plasma concentrations of PF-07259955 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24 hour clock time) of each sample will be recorded.

CCI

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 (dispotassium edetic acid [ethylenediaminetetraacetic acd] [K_2EDTA] whole-blood collection optimized for DNA analysis) will be collected according to the SoA, as local regulations and IRBs/ECs allow.

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

See Appendix 5 (Section 10.5)for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the lab manual and supporting documentation.


CCI

[redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. 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 statistical hypotheses will be tested in this study.

9.2. Analysis Sets

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

Population	Description
Enrolled	All participants who sign the ICD.
Randomly assigned to investigational product	All participants who sign the ICD and determined eligible to participate in the study.
Evaluable	The evaluable population is defined as all participants who are randomly assigned to IP and who are applied at least 1 dose of IP.
Safety	All participants randomly assigned to IP and who are applied at least 1 dose of IP. Participants will be analyzed according to the product they actually received.
PK concentration	All participants randomly assigned to investigational product who received a application of PF-07295324 or PF-07259955 and in whom at least 1 plasma sample concentration value is reported.
PK parameter	All participants randomly assigned to investigational product who received an application of PF-07295324 or PF-07259955

Population	Description
	and who have at least 1 of the PK parameters of interest calculated.

9.3. Statistical Analyses

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

9.3.1. Efficacy Analyses

An efficacy analysis is not applicable to this study.

9.3.2. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, skin irritation assessment, 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 as source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.2.1. 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:

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

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

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

9.3.3. Pharmacokinetic Analyses

9.3.3.1. Derivation of Pharmacokinetic Parameters

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

PK parameters for PF-07295324 and PF-07259955, following topical administration, will be derived from the plasma concentration-time profiles using non-compartmental methods, as data permit.

The PK parameters to be assessed in this study, their definition, and method of determination are listed in Table 6. Actual PK sampling times will be used in the derivation of PK parameters.

Table 6. Plasma PK Parameters*

Parameter	Day	Definition	Method of Determination
C_{max}	1, 10	Maximum plasma concentration	Observed directly from data
T_{max}	1, 10	Time at which maximum plasma concentration occurs	Observed directly from data
C_{avg}	1, 10	Average plasma concentration	AUC_{tau}/tau; where tau is the dosing interval and AUC_{tau} is area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
C_{trough}	1, 5, 7 and 10	Pre-dose Concentration	Observed directly from data
$t_{½}$	10	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
AUC_{tau}	1, 10	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval	Linear/Log trapezoidal method up to tau, the dosing interval
CL/F	10	Apparent clearance	Dose/AUC_{tau}
V_z/F	10	Apparent volume of distribution	Dose/($AUC_{tau} \times k_{el}$)
R_{ac} (C_{max})	10	Accumulation ratio for C_{max}	$C_{max, Day 10}/C_{max, (first dose)}$
R_{ac} (AUC_{tau})	10	Accumulation ratio for AUC_{tau}	$AUC_{tau, Day 10}/AUC_{tau, (first dose)}$

*as data permits

9.3.3.2. Statistical Methods for PK Data

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

The plasma concentration of PF-07295324 and PF-07259955 will be listed and descriptively summarized, by nominal PK sampling time and by treatment group. Individual participant, mean and median profiles of the plasma concentration-time data of PF-07295324 and PF-07259955 will be plotted by treatment group using actual (for individual) and nominal (for mean and median) times, respectively. Mean and median profiles of PF-07295324 and PF-07259955 will be presented separately, on both linear and log scales.

The plasma PK parameters of PF07295324 and PF-07259955 listed in Table 6 above, will be summarized descriptively by treatment group in accordance with Pfizer data standards, as data permit. Additional PK analyses may be performed if deemed appropriate, and will not be included in the CSR.

CCI

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. 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 dosing decisions for optional cohorts, and/or supporting clinical development.

9.5. Sample Size Determination

The study consists of 2 planned cohorts and a total of approximately 12 participants in these planned cohorts. For this FIH study, a sample size of up to approximately 6 participants per cohort has been chosen based on the need to minimize first exposure of PF-07295324 and PF-07259955 to humans and the requirement to provide adequate safety and tolerability assessment at maximum feasible dose level. This sample size has been judged sufficient to obtain a preliminary evaluation of safety, tolerability and PK of PF-07295324 and PF-07259955, in healthy participants.

In addition, 2 optional cohorts of approximately 6 healthy participants/cohort may be included.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

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

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

10.1.2. Financial Disclosure

Not Applicable.

10.1.3. Informed Consent Process

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

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

The investigator must ensure that each 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 on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

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

10.1.4. Data Protection

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

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

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, 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 SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

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 corresponding study results are 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 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 contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 24 months after study completion. 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.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

Definition of what constitutes source data can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer Clinical Research Unit).

Description of the use of the computerized system is documented in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer Clinical Research Unit).

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

10.1.10. Publication Policy

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 the 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.

10.1.11. 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 CTMS.

To facilitate access to appropriately qualified medical personnel for study related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at

the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week.

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

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 7. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs) Reticulocytes (Abs)	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]	• COVID-19 testing • Urine drug screening[b] At screening only: • FSH[c] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • TB testing • Human immunodeficiency virus

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
c. For confirmation of postmenopausal status only.

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.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigator sites or other blinded personnel until the study has been unblinded.

Any remaining serum/plasma from samples collected for clinical safety laboratory measurements at baseline and at all times after dose application may be retained and stored for the duration of the study. CCI

CCI

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

10.3.1. Definition of AE

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

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

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

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

10.3.2. Definition of an SAE

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

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

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

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

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

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

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

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

- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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 study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

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

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

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

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic 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) 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 and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 90 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use contraception/barrier as detailed below:
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Male participants should be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak when having sexual intercourse with a WOCBP who is not currently pregnant.

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and the following condition applies:

- Is not a WOCBP.

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. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner.

    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;

    - Intravaginal;

    - Transdermal;

7. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

8. Sexual abstinence.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

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

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

- The samples may be analyzed as part of a multi-study 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 CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

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

- The samples will be retained as indicated:

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

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

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

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede 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 Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

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

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >280 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 PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as 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 (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second -degree (Mobitz II) AV block.
- Complete (third -degree) heart block.

ECG Findings That Qualify as SAEs

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

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

10.8. Appendix 8: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.8.1. Eligibility

Not applicable.

10.8.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (e.g., audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.8.3.1 of this appendix regarding pregnancy tests.

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

10.8.3. Alternative Facilities for Safety Assessments

10.8.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- See Table 7

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.8.3.2. Imaging

Not applicable.

10.8.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.8.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

10.8.5. Home Health Visits

Not applicable

10.8.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8.7. Efficacy Assessments

Not applicable.

10.8.8. Independent Oversight Committees

Not applicable.

10.9. Appendix 9: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time curve from 0 to 24 hours
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval
AV	atrioventricular
BBS	Biospecimen Banking System
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
BW	body weight
C_{av}/C_{avg}	average concentration
C_{trough}	pre-dose Concentration
CCL26	chemokine (C-C motif) ligand 26
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL_p	clearance of the drug from plasma
CL/F	apparent clearance
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
Coh	cohort
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CTMS	clinical trial management system
CXCL10	C-X-C motif chemokine 10
CYP	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
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
EMA	European Medicines Agency
EOS	end of study
EPO	erythropoietin
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database
Fa	fraction of drug absorbed
Fg	fraction of drug extracted at intestine
FIH	first-in-human
f_m	fraction metabolized
FSH	Follicle -stimulating hormone
$F_{u,p}$	Fraction Unbound in plasma
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte/macrophage colony stimulating factor
HBcAb	hepatitis B core antibody
HCVAb	hepatitis C antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HR	heart rate
CCI	[redacted]
IB	investigator's brochure
IC_{50}	50% inhibitive concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identity
IFN	interferon
IFNα	interferon alpha

Abbreviation	Term
IFNγ/IFNg	interferon gamma
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
CCI	[redacted]
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IQMP	integrated quality management plan
IRB	institutional review board
IV	intravenous
JAK	janus kinase
k_{el}	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MFD	maximum feasible dose
mL	milliliter
MMP12	matrix metallopeptidase 12
mRNA	messenger ribonucleic acid
msec	millisecond
N/A	not applicable
nM	nanomolar
NOAEL	No -observed -adverse -effect level
OCT2	organic cation transporter 2
SYS	systemic
PACL	Protocol Administrative Change Letter
PCRU	Pfizer Clinical Research Unit
PD	pharmacodynamic(s)
CCI	[redacted]
PI	principle investigator
PK	pharmacokinetic(s)
PT	prothrombin time
PVC	premature ventricular contraction/complex
Q12H	every 12 hours
QD	once daily
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative

Abbreviation	Term
R_{ac} (C_{max})	Accumulation ratio for C_{max}
R_{ac} (AUC_{tau})	Accumulation ratio for AUC_{tau}
RBC	red blood cell
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal half-life
T_{max}	time to first occurrence of C_{max}
TB	tuberculosis
TBili	total bilirubin
TDD	total daily dose
Th	T helper cell
THC	tetrahydrocannabinol
TSLP	thymic stromal lymphopoietin
TYK	tyrosine kinase
uC_{avg}	Unbound average concentration
UGT	uridine diphosphate-glucuronosyltransferase
ULN	upper limit of normal
US	United States
V_d	Volume of distribution
V_{ss}	volume of distribution at steady state
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

11. REFERENCES

[1] Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007;178(5):2623-9.

[2] O'Sullivan LA, Liongue C, Lewis RS, et al. Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease. Mol Immunol. 2007;44(10):2497-506.

[3] Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part II: immune cell subsets and therapeutic concepts. J Allergy Clin Immunol. 2011;127(6):1420-32.

[4] Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. J Allergy Clin Immunol. 2017;139(4S):S65-S76.

[5] Peeva E, Hodge MR, Kieras E, et al. Evaluation of a Janus kinase 1 inhibitor, PF-04965842, in healthy subjects: A phase 1, randomized, placebo-controlled, dose-escalation study. British Journal of Clinical Pharmacology. 2018: 84(8); 1776-78.

[6] Banfield C, Scaramozza M, Zhang W, et al. The safety, tolerability, pharmacokinetics, and pharmacodynamics of a TYK2/JAK1 inhibitor (PF-6700841) in healthy subjects and patients with plaque psoriasis The Journal of Clinical Pharmacology. 2018 Apr;58(4):434-447.