A PHASE 1, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PARALLEL COHORT STUDY TO EVALUATE THE SAFETY, TOLERABILITY, SKIN IRRITATION POTENTIAL AND PHARMACOKINETICS OF MULTIPLE-DOSE, TOPICAL ADMINISTRATION OF PF-07038124 TO JAPANESE HEALTHY PARTICIPANTS

Study Intervention Number:	PF-07038124
Study Intervention Name:	N/A
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Protocol Number:	C3941003
Phase:	1

Short Title: A Phase 1 Study to Evaluate the Safety, Local and Systemic Tolerability, and PK of Multiple-Dose Topical Administration of PF-07038124 in Japanese Healthy Participants.

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 1	12 March 2021	Added descriptions in Section 6.1.1.3. Rationale: Addition to define additional application sites appropriately to secure planned application area. Added descriptions in Section 8.5. Rationale: Addition to add an instruction of wash around PK sampling to avoid contamination. Added "X" in Section 1.3 Schedule of Activities. Rationale: Addition to be consistent with PK sampling schedule. Revised descriptions in Section 6.5. Rationale: Revision of the period of prior therapy to consistent with Section 5.2. Revised descriptions in Section 1.3 Schedule of Activities, Section 8, Section 8.2.2, Section 9.4.6, Section 10.8. Rationale: Updates to distinguish between pulse rate and PR interval. Revised descriptions in Section 8.8. Rationale: Updates descriptions according to the protocol template instruction.
Original protocol	08 January 2021	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study to Evaluate the Safety, Local and Systemic Tolerability, and PK of Multiple-Dose Topical Administration of PF-07038124 in Japanese Healthy Participants.

Rationale

The purpose of this study is to evaluate the multiple-dose safety, tolerability, skin irritation potential, and PK of PF-07038124, applied to Japanese healthy adult participants. This study will be randomized, vehicle-controlled, double-blinded to treatment assignment to permit an unbiased assessment of safety and tolerability.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety, tolerability, and skin irritation potential of PF-07038124, following multiple doses applied topically, in Japanese healthy participants.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests during the entire study. • Incidence and severity of local skin irritation at times indicated in SoA.
Secondary:	**Secondary:**
• To characterize the PK of PF-07038124, following topical administration, in Japanese healthy participants.	• PF-07038124 PK parameters following topical application on Days 1 and 10, as data permit: AUC_{tau}, and C_{max}, if applicable.
CCI [redacted]	[redacted]
[redacted]	[redacted]

Overall Design

This is a Phase 1, randomized, double-blind, vehicle-controlled, parallel cohort study to evaluate the safety, tolerability, skin irritation potential, and PK of PF-07038124 in Japanese healthy adult participants. Both cohorts can be conducted simultaneously.

This study will evaluate the safety, tolerability, skin irritation potential and PK following application of PF-07038124 at 0.01% concentration and vehicle to 2000 cm^2 (Cohort 1; approximately 10% BSA) or 4000 cm^2 (Cohort 2; approximately 20% BSA).

Number of Participants

A sample size of 12 participants (4 PF-07038124: 2 vehicle per cohort) has been selected empirically to permit adequate characterization of safety, tolerability, skin irritation potential, and PK at each dose level in Japanese healthy participants. Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the PI and Sponsor.

Intervention Groups and Duration

Participants will be randomized to receive PF-07038124 or vehicle in a ratio of 4 PF-07038124: 2 vehicle, per cohort. Each participant will receive multiple doses of PF-07038124 or vehicle starting on Day 1 topically applied for 10 consecutive days; applied QD in the AM for Cohort 1 and Cohort 2.

The total participation time for each participant is approximately 66 days, including the screening period of up to 28 days, the double-blind treatment period of 10 days, and the follow-up period of 28 days from last dose of the study intervention.

Participants will be screened within 28 days prior to application of the study intervention to confirm that they meet the selection criteria for the study. Participants will be admitted to the CRU at least 12 hours prior to their planned dose application time, and will be required to remain in the CRU until completion of procedures on Day 11 as described in the SoA.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

All analyses described below will be conducted by treatment and cohort. In addition, data from vehicle in Cohort 1 and Cohort 2 will be pooled.

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

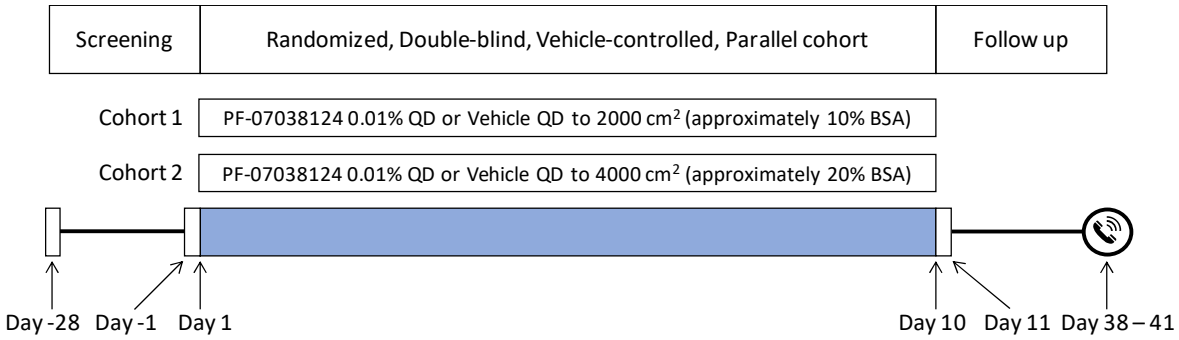
The primary endpoints of this study are treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, laboratory tests, and incidence and severity of local skin irritation.

The primary endpoints will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations in order to evaluate the safety, tolerability, and skin irritation potential of PF-07038124.

The PK parameters for PF-07038124 following multiple-dose topical application will be derived from the plasma concentration-time profiles. PK parameters CCI [redacted] of PF-07038124 will be descriptively summarized by treatment group and nominal time, as appropriate.

1.2. Schema

Figure 1. Schema of Study C3941003



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.

Schedule of Activities

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	**Screening**		**Treatment Phase**											**Follow-Up**[b]	**Early Termination/ Discontinuation**
Days Relative to Day 1	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**38+3**	
Informed consent	X														
CRU confinement[c]		X	→	→	→	→	→	→	→	→	→	→	→		
Outpatient visit	X														
Inclusion/exclusion criteria	X	X	X												
Randomization			X												
Medical/medication history (update)	X	X													
Physical exam[d]	X	X													X
Height and weight	X														
Review prior or concomitant treatments, as applicable	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Safety laboratory, including fibrinogen and hsCRP[e]	X	X				X						X	X		X
Demography	X														
Contraception check	X	X											X	X	X
Single, supine 12-Lead ECG[f]	X		X			X						X	X		X
Single, supine BP and pulse rate, and temperature[f]	X		X			X						X	X		X
FSH[g]	X														
Pregnancy test (WOCBP only)	X	X											X		X
HIV, HBsAg, HBcAb, HCVAb, syphilis	X														
COVID-19 testing	X[h]					X									

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	Screening		Treatment Phase											Follow-Up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**38+3**	
Urine drug test	X	X													
Study intervention administration (QD)[i]			X	X	X	X	X	X	X	X	X	X			
Skin Irritation Evaluation[j]			X	X	X	X	X	X	X	X	X	X	X		
CCI [redacted]															
[redacted]															
CRU discharge[l]													X		
Serious and nonserious AE monitoring[m]	X	→	→	→	→	→	→	→	→	→	→	→	→	X	X
PK blood sampling[n]			X	X		X			X			X	X		X

a. Day relative to start of study intervention (Day 1).

b. All cohorts: Follow-up contact to occur 28-31 days post last dose with a phone call; additional follow-up at investigator discretion, including to monitor open AE, or based on emerging data.

c. Participants will be admitted at least 12 hours prior to dosing. Admission procedures will be conducted once, unless deemed necessary by investigator or sponsor.

d. Physical examination may be performed at non-specified timings if there are findings during the previous exam or new/open AEs, if appropriate and at investigator discretion.

e. For screening visit, test results must be reviewed and deemed acceptable in order to proceed with participation in study.

f. 12-lead ECGs, BP, pulse rate and temperature will be collected at screening. For Days 1, 4, and 10, ECGs, BP, pulse rate, and temperature will be collected prior to and at approximately 6 hours post-dose. Day 11 is 24 hours post-dose on Day 10 and is prior to discharge.

g. For confirmation of postmenopausal status only.

h. COVID-19 viral test to occur between Day -5 and Day -3 to permit availability of test result prior to admission on Day -1.

i. Study intervention (PF-07038124 or vehicle) will be applied QD in the AM. Refer to Section 6.1.1 for additional details.

j. Skin irritation assessment of the application sites will be conducted on Days 1-10 prior to each application of the study intervention and 24 hours post-dose on Day 10. Refer to Section 8.2.5.

CCI [redacted]

l. CRU discharge should occur following collection of PK sample at 24 hours post-dose on Day 10. Participants who have AEs or dermatological

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 8.	Screening		Treatment Phase											Follow-Up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**38+3**	

observations on Day 11 will return to the CRU up to the discretion of the investigator, and follow-up contact will be made.

m. If unexpected reactions (eg, rash, hives) other than irritation reactions outlined in Table 4, Section 8.2.5 occur at an application site, the application site location must be recorded.

n. Refer to Pharmacokinetic Sampling Schedule table below.

Pharmacokinetic Sampling Schedule

Visit Identifier								
Day	**PK Blood Sampling**							
	Hours Before/After AM Dose							
	0[a]	**1**	**2**	**4**	**6**	**8**	**12**	**24**
1	X	X	X	X	X	X	X	X
4	X				X			
7	X				X			
10	X	X	X	X	X	X	X	X

a. Predose sample collection.

2. INTRODUCTION

PF-07038124 is a topical PDE4 inhibitor that is currently being developed for the treatment of AD and plaque psoriasis (psoriasis).

2.1. Study Rationale

The purpose of this study is to evaluate the multiple-dose safety, tolerability, skin irritation potential, and PK of PF-07038124 in Japanese healthy participants. This study will evaluate application of PF-07038124 and vehicle to a surface area of 2000 cm^2 (approximately 10% BSA) and 4000 cm^2 (approximately 20% BSA). These data will provide support for clinical development in Japanese participants with AD and psoriasis.

2.2. Background

2.2.1. Role of Proinflammatory Cytokines in AD and Psoriasis

ATOPIC DERMATITIS: AD, also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. AD can affect any age group. Prevalence estimates suggest approximately 10% of adults and 10%-20% of children suffer from AD, and up to 18% of those affected with AD suffer with severe disease.

There are a limited number of treatments available for AD. Current treatments for AD include emollients, topical corticosteroids (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (eg, pimecrolimus, tacrolimus), and coal tar preparations. Crisaborole ointment, 2% (weight by weight) (20 mg/g), a PDE4 inhibitor, is approved in the United States (US; Eucrisa®) as a topical treatment therapy in patients 3 months of age and older with mild to moderate AD; and in Canada (Eucrisa®), Israel, the EU, Australia and China (Staquis®) as a topical treatment therapy in patients 2 years of age and older with mild to moderate AD. Additional treatments generally reserved for severe AD include phototherapy (eg, UVA light with or without psoralen) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate). None of the currently available therapies offer a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, increase the time between relapses, reduce pruritus and reduce the resulting sleep disturbances.

For most AD patients not responding to topical therapies and phototherapy, off-label use of systemic agents, which includes both oral corticosteroids and oral immunosuppressants remain the last viable treatment option. Dupilumab injection, an IL-4 receptor alpha antagonist, was approved for use in patients with moderate to severe AD. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. Therefore, the prominent unmet medical need in AD is for an effective, safe topical agent for once a day dosing without restrictions on long-term or continuous use, and without local or systemic side effects.

The T-helper-2 response contribute to AD-associated skin inflammation and itch.[1] The pathogenic role that the Th2 derived cytokines, IL-4 and IL-13, play in AD has been demonstrated through the clinical efficacy of dupilumab, an antibody to the IL-4 receptor that blocks the activity of both IL-4 and IL-13.[2]

PSORIASIS: The most common variant of psoriasis, plaque psoriasis (psoriasis vulgaris), is a chronic inflammatory skin disease characterized by red, scaly, raised plaques. Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2%. Although psoriasis primarily affects the skin and is not a life-threatening disease, it can profoundly impact the patient's QoL resulting in an impairment akin to other major diseases, such as type 2 diabetes, myocardial infarction, and arthritis. Current treatments for psoriasis include topicals, phototherapy, systemic non-biological therapies (methotrexate, cyclosporin, acitretin, apremilast [Otezla®]) and biologics.

Proinflammatory cytokines such as TNF-α, IFN-γ and IL-23/T-helper-17 response cytokines play an important role in the pathogenesis of psoriasis.[3] Several biologics monoclonal antibodies that target these proinflammatory cytokines have been shown to be effective for the treatment of psoriasis in clinical trials.[4] Biologic agents used in the treatment of psoriasis include multiple anti-TNF agents (such as infliximab, adalimumab, etanercept), anti-IL-12/IL-23 antibodies and anti-IL-17 antibodies. PDE4 inhibitors such as apremilast (Otezla®) may reduce production of pro-inflammatory TNF-α and IFN-γ by increasing cAMP levels.

2.2.2. Description of Study Intervention: Mechanism of Action

PDE are a family of enzymes that breakdown the ubiquitous second messengers, cAMP and cGMP, that regulate various cellular processes. PDE4 is a subfamily that includes the four isozymes, each encoded by separate genes, PDE4 A, B, C and D. Inhibitors of the PDE4 family have been the focus of intense drug development over many years due to their broad potential in inflammatory diseases such as AD and psoriasis. For example, apremilast (Otezla®) is an oral small-molecule inhibitor of PDE4 that is approved for the treatment of patients with moderate to severe plaque psoriasis and active psoriatic arthritis. Crisaborole (Eucrisa®, Staquis®) is a topically delivered PDE4 inhibitor that has demonstrated efficacy in clinical trials[5] and is approved for the treatment of mild to moderate AD as described previously. In addition, other topical PDE4 inhibitors, such as roflumilast (ARQ-151), have shown activity in the treatment of psoriasis.[6]

PF-07038124 is designed to be a best-in-class, oxaborole-based potent PDE4 inhibitor that has increased immunomodulatory activity in T-cell based assays, which correlates with inhibition of additional PDE family members that are active in immune cells. This enhanced activity contributes to greater inhibition of cytokines IL-13 and IL-4 from activated T cells which may lead to increased clinical activity.

PF-07038124 is a potent and selective PDE4 inhibitor intended to be used for topical administration for the treatment of AD and psoriasis. PF-07038124 inhibits the enzymatic activity of the PDE4 isoforms that have been tested with an IC_{50} of 0.505 nM and 0.3 nM on PDE4B and PDE4D, respectively. PF-07038124 inhibits cytokine production and release from T cells and monocytes in PBMC over a range of concentrations that is dependent on the cytokine that is being modulated. The IC_{50} for release of LPS stimulated TNF-α is most sensitive with an IC_{50} of 0.15 nM. The IC_{50}'s for inhibition of IFN-γ, IL-4, and IL-13 from lectin stimulated PBMCs are 1, 4 and 135 nM, respectively. PF-07038124 exhibited greater inhibitory activity on IL-13 release than was seen with other PDE4 specific inhibitors, consistent with its inhibitory activity on additional PDEs, such as PDE3 at higher concentrations. PF-07038124 increased the level of cAMP in human PBMCs in a dose dependent manner, consistent with its primary mechanism of action as a PDE inhibitor.

An ex vivo human skin model of Th2 inflammation was used to measure the activity of PF-07038124 in its ointment formulation with topical application. This model has been used to test the activity of other topical therapeutic compounds, including topical corticosteroids, JAK inhibitors and the PDE4 inhibitor crisaborole (Eucrisa®). In this model system with a single dose application on excised human skin 20 hours prior to stimulation of the T cells in the skin tissue, PF-07038124 inhibited inflammatory cytokine gene expression at the dose strengths of 0.1, 0.06, 0.03 and 0.01%, with little to no activity at 0.001% strength relative to the vehicle (placebo) control.

Based on its cytokine inhibition profile, topical administration of PF-07038124 is anticipated to provide potential therapeutic benefit in the treatment of AD and psoriasis by targeting the T-helper-2 response cytokines and TNF-α.

2.2.3. Preclinical Safety Data

In the pivotal 3-month toxicity studies in rats (oral) and minipigs (dermal), the systemic NOAEL were identified as 4 mg/kg/day and 0.0104 mg/cm^2/day (0.0052 mg/cm^2, BID) to 10% BSA, respectively, with systemic exposures of 2x and 1.2x, respectively, the projected maximum human exposure (uC_{av} = 9 pg/mL). The systemic NOAEL exposure identified in the more sensitive nonclinical species (minipig) was 11 pg/mL (C_{av}, unbound). The local (dermal) NOAEL was identified at the 0.03% concentration (BID) corresponding to 0.0052 mg/cm^2/day (0.0026 mg/cm^2, BID) and represents an 17x multiple to the projected maximum human dermal dose of 0.0003 mg/cm^2/day in the current study. Based on the completed nonclinical studies, local (skin) and systemic (cardiovascular, nervous, and gastrointestinal) target organs/systems were identified. Local reactions (erythema, edema) were observed in minipigs at ≥0.00174 mg/cm^2/day (5.8x the highest planned clinical dermal dose, 0.0003 mg/cm^2/day). A potential for skin sensitization by PF-07038124 was identified in a mouse local lymph node assay with a NOEL of 0.015 mg/cm^2/day (50x the highest planned clinical dermal dose, 0.0003 mg/cm^2/day). Cardiovascular effects included increases in heart rate, contractility, and/or blood pressure in rats and/or dogs, and vascular injury/compromise (in mesentery, kidney, adrenal gland, and/or bladder) in rats and/or minipigs. Clinical signs indicative of nervous system effects (eg, ataxia, decreased activity, hunched posture, twitching, and/or tremors) and gastrointestinal effects (emesis, salivation,

and/or soft/liquid feces) were also observed in rats, dogs, and/or minipigs, mostly at non-tolerated doses. These systemic effects in nonclinical species are consistent with those reported for oral selective PDE4 inhibitors. PF-07038124 was negative for mutagenicity, positive in an in vitro micronucleus assay at high concentrations via aneugenic mechanism, but negative in an in vivo rat micronucleus assessment. PF-07038124 was not phototoxic and no further photosafety testing is recommended. Rat and rabbit EFD was assessed after oral administration of PF-07038124 to pregnant animals. PF-07038124 did not cause any effects on EFD following oral administration at doses up to 4 mg/kg/day (rats) and 8 mg/kg/day (rabbits), respectively. The developmental NOAEL exposures in pregnant rats and rabbits corresponded to 1.7x and 2.7x the maximum planned clinical exposure on an uC_{av} basis. In addition, no effects on fertility were observed in female rats after oral administration of PF-07038124 up to 4 mg/kg/day (4.1x the maximum planned dose on an uC_{av} comparison basis).

The nonclinical safety profile of PF-07038124 has been adequately characterized to support progression into clinical trials of up to 3 months.

2.2.4. Clinical Overview

To date the clinical experience with PF-07038124 comprises one Phase 1 study in adult healthy Western participants designated C3941001; a multiple ascending dose study following topical administration.

PF-07038124 was generally safe and well tolerated in healthy participants (C3941001). There were no clinically meaningful findings in vital signs, ECG, or laboratory tests reported during this study. A summary is provided in Table 1 below, further details are provided in the current IB.

Table 1. PF-07038124 Clinical Development Program – Completed Studies as of January 2021

Study ID	Description	PF-07038124 Dose/Regimen	Number of Participants
C3941001 (completed)	The study consisted of 2 parts: Part A: Randomized, double-blind, sponsor-open, vehicle-controlled multiple doses application to assess skin irritation. Part B: Randomized, double-blind, sponsor-open, vehicle-controlled multiple doses application to assess safety, tolerability, PK, and skin irritation.	Part A: 0.06% BID applied to 20 cm^2 (0.1% BSA) for 7 days. Part B: 0.01% QD and BID, and 0.03% QD applied to 2000 cm^2 (10% BSA), as well as 0.01% QD applied to 4000 cm^2 (20% BSA) for 10 days.	8 (active and vehicle). 26 (8/cohort; 6 active and 2 vehicle, only 2 at 0.01% QD (20% BSA)).

2.2.4.1. Clinical Safety

In Study C3941001, PF-07038124 ointment was evaluated in Part A for the potential of skin irritation upon applying 0.06% BID for 7 days to 0.1% BSA and the evaluation of safety, tolerability and PK in Part B where the drug was applied at 0.01% QD and BID to 10 and 20% BSA and at 0.03% QD to 10% BSA. In the Part A PF-07038124 0.06% BID group, skin abrasion and skin irritation were reported by 2 participants. The most commonly reported all treatment-related AEs following 10 days of topical application of the PF-07038124 ointment during Part B across active healthy participants were skin irritation; including acne and erythema, which were reported as all mild. Mild systemic AEs were also reported including headache, dizziness, and nausea, but were considered unrelated to study intervention. There were no deaths or SAEs reported in this Phase 1 study. Please refer to the IB for further details from the C3941001 study.

2.2.4.2. Clinical Pharmacokinetics

Following multiple topical administration of PF-07038124 following 10 days of dosing, the majority of concentrations on Day 1 were BLQ and a limited number of participants had valid parameter values. PF-07038124 was absorbed rapidly followed by a biexponential decline, with C_{max} achieved at a median T_{max} of 4 to 6 hours for treatments where median values could be reported. Individual values ranged between 2 to 8 hours for all treatments. For the 0.01% QD (Cohort 1), 0.01% BID (Cohort 2), and 0.03% QD (Cohort 3) cohorts, geometric mean C_{av} on Day 10 was 37.43, 88.82, and 187.1 pg/mL, respectively in Table 2. Individual $t_{½}$ on Day 10 ranged from 8.49 to 17.4 hours for treatments where $t_{½}$ could be reported. Geometric mean CL/F values ranged from 400.5 to 668.4 L/hr for treatments where mean values could be reported. In general, plasma PF-07038124 exposure appeared to increase in a greater than dose-proportional manner for AUC_{tau}, and an approximate dose-proportional manner for C_{max}.

Individual accumulation ratios were 3.59 for AUC_{tau} (R_{ac}) and ranged from 2.69 to 35.8 for C_{max} ($R_{ac,Cmax}$), respectively on Day 10. The PF-07038124 median trough plasma concentrations approached steady state following 10 days of dosing.

Table 2. Descriptive Summary of Day 10 Plasma PF-07038124 PK Parameters, C3941001

Day 10 PK Parameter[a,b]	Part B Cohort 1 (2000 cm^2) PF-07038124 0.01% QD (N=6)	Part B Cohort 2 (2000 cm^2) PF-07038124 0.01% BID (N=6)	Part B Cohort 3 (2000 cm^2) PF-07038124 0.03% QD (N=6)	Part B Cohort 4 (4000 cm^2) PF-07038124 0.01% QD (N=2)
AUC_{tau} (pg.hr/mL)	897.2 (44)	1068 (44)	4491 (57)	N/A
C_{av} (pg/mL)	37.43 (44)	88.82 (44)	187.1 (57)	N/A
C_{max} (pg/mL)	52.78 (59)	104.7 (49)	264.7 (70)	48.8, 96.0[b]

C_{trough} (pg/mL)	26.95 (48)	87.73 (47)	147.4 (66)	41.8, 86.2[b]

a. Geometric mean (geometric %coefficient of variation)

b. Individual values are listed when there are less than 3 evaluable measurements.

2.3. Benefit/Risk Assessment

PF-07038124 is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate safety, tolerability, skin irritation potential, and pharmacokinetic data for further clinical development.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07038124 may be found in the IB, 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 PF-07038124		
Adverse Nonclinical findings – PDE4 inhibitor associated vasculitis	Vasculitis is an effect associated with administration of oral PDE4 inhibitors in nonclinical species, correlates with an acute phase reaction, and occurs at doses above the NOAEL and also systemic exposures at the clinical MRHD for oral PDE4 inhibitors.	Participants will be assessed for safety throughout the study (including monitoring of acute-phase reactions such as fibrinogen and C-reactive protein).
Adverse Nonclinical findings – PDE4-related nervous system and gastrointestinal effect (a class effect of AEs observed with PDE4 inhibitors)	Clinical signs indicative of nervous system effects (eg, ataxia, decreased activity, hunched posture, twitching, and/or tremors) and gastrointestinal effects (emesis, salivation, and/or soft/liquid feces) were observed in rats, dogs, and/or minipigs, at non-tolerated doses.	Participants will be assessed for safety throughout the study.
Nonadverse Nonclinical findings – PDE4-related cardiovascular effect	Cardiovascular effects (eg, increases in heart rate, contractility, and/or blood pressure) in rats and/or dogs. A NOEL for the heart rate effect was not determined in either species.	Participants will be assessed for safety throughout the study.
Adverse Nonclinical findings – Potential Skin Sensitization	The potential for skin sensitization was identified as a risk in nonclinical species at dermal concentrations 50x above the planned dose concentration of 0.01%, with a no observed effect level of 0.06% ointment.	Participants will be assessed for safety 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 study interventions will be excluded from the study.
Other		
Risk of COVID-19 exposure during study	During the pandemic, study participants could be infected with the SARS-CoV-2 virus during study participation. This could lead to increased health risk for this participant and others in the study.	Participants undergo COVID-19 specific assessments prior to admission to study site and Day 4 according to SoA.

2.3.2. Benefit Assessment

While PF-07038124 is not expected to provide any clinical benefit to healthy participants, this study is designed to generate the safety, tolerability, skin irritation potential, and PK data of PF-07038124 in Japanese healthy participants for further clinical development.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with PF-07038124 are justified by the anticipated benefits that may be afforded to participants with AD and psoriasis.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To evaluate the safety, tolerability, and skin irritation potential of PF-07038124, following multiple doses applied topically, in Japanese healthy participants.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests during the entire study. • Incidence and severity of local skin irritation at times indicated in SoA.
Secondary:	**Secondary:**
• To characterize the PK of PF-07038124, following topical administration, in Japanese healthy participants.	• PF-07038124 PK parameters following topical application on Days 1 and 10, as data permit: AUC_{tau}, and C_{max}, if applicable.
CCI [redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, randomized, double-blind, vehicle-controlled, parallel cohort study to evaluate the safety, tolerability, skin irritation potential, and PK of PF-07038124 in Japanese healthy adult participants. Both cohorts can be conducted simultaneously.

This study will evaluate the safety, tolerability, skin irritation potential and PK following application of PF-07038124 at 0.01% concentration and vehicle to 2000 cm^2 (Cohort 1; approximately 10% BSA) or 4000 cm^2 (Cohort 2; approximately 20% BSA).

Participants will be randomized to receive PF-07038124 or vehicle in a ratio of 4 PF-07038124: 2 vehicle, per cohort. Each participant will receive multiple doses of

PF-07038124 or vehicle starting on Day 1 topically applied for 10 consecutive days; applied QD in the AM for Cohort 1 and Cohort 2. Participants will not be randomly assigned to cohort. The first group of participants will be enrolled Cohort 1 followed by Cohort 2. All participants will have the study interventions randomly assigned, for the purpose of determining skin irritation potential, as well as PK, safety and tolerability. 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.

The total participation time for each participant is approximately 66 days, including the screening period of up to 28 days, the double-blind treatment period of 10 days, and the follow-up period of 28 days from last dose of the study intervention.

Approximately 12 Japanese healthy adult participants are planned to participate in this study.

Participants will be screened within 28 days prior to application of the study intervention to confirm that they meet the selection criteria for the study. Participants will be admitted to the CRU at least 12 hours prior to their planned dose application time (see Section 6.1.1), and will be required to remain in the CRU until completion of procedures on Day 11 as described in the SoA.

Participants will be followed-up with a phone call per the SoA following the last dose of study intervention to assess for AEs, SAEs, concomitant treatments, and contraception check. 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.

4.2. Scientific Rationale for Study Design

The purpose of this study is to evaluate the multiple-dose safety, tolerability, skin irritation potential, and PK of PF-07038124, applied to Japanese healthy adult participants. This study will be randomized, vehicle-controlled, double-blinded to treatment assignment to permit an unbiased assessment of safety and tolerability.

Although no significant differences related to safety, tolerability, skin irritation potential or PK are expected between Japanese and Westerner healthy adult participants, this study can provide a preliminary characterization of the safety, tolerability, skin irritation potential, and PK profile of PF-07038124 to support potential inclusion of Japanese participants in future studies.

This study consists of two cohorts to evaluate two administration areas of PF-07038124 applied to 2000 cm^2 (approximately 10% BSA) and 4000 cm^2 (approximately 20% BSA) in parallel. This approach is based on the result of C3941001 study which was generally safe and well tolerated in Westerner healthy participants.

Assessment of clinical safety laboratory tests (Appendix 2), vital signs, 12-lead ECG, physical examinations, and AE monitoring will provide essential data to evaluate the safety and tolerability of PF-07038124 following topical application. Based on the findings from

the toxicology studies, fibrinogen and C-reactive protein will be added to safety laboratory assessments as a precaution to monitor for inflammation.

COVID-19 specific assessments have been incorporated to minimize the risks of COVID-19 related complications to participants and the study site personnel.

Human reproductive safety data are limited for PF-07038124, but there is no suspicion of human teratogenicity based on the intended pharmacology of the compound. In addition, EFD studies conducted in pregnant rats and rabbits at exposures that correspond to 1.7x and 2.7x the maximum planned clinical exposure did not cause any effects on embryo-fetal development. See Appendix 4 for contraceptive requirements.

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

4.3. Justification for Dose

The nonclinical safety profile of PF-07038124 following systemic administration (oral) to rats and topical application (dermal) to minipigs supports human clinical studies of up to 3 months in duration (See Section 2.2.3). The dose proposed for this study was determined considering all relevant information obtained from nonclinical safety studies, incorporating the NOAEL from 3-month studies in minipigs, together with the systemic exposure observed following topical application of PF-07038124 to healthy participants. As a result, the dose strength of PF-07038124 selected for this study is 0.01%, applied once daily.

Regarding the high-dose cohort (Cohort 2), PF-07038124 at 0.01% concentration to 4000 cm^2 (approximately 20% BSA), has been selected to evaluate the safety and tolerability of PF-07038124 in Japanese healthy adult participants so that safety and tolerability can be examined in the dose range including the maximum potential dose in the planned global late phase studies. And regarding the low-dose cohort (Cohort 1), PF-07038124 at 0.01% concentration to 2000 cm^2 (approximately 10% BSA), has been selected to allow the direct comparison of PK with Cohort 1 (0.01% QD to 10% BSA) of FIH study.

Summarized in Table 3 are the predicted exposures and safety margin for the 0.01% dose strength in this protocol following topical application of PF-07038124. The overall estimate of systemic exposure of PF-07038124 is based upon the systemic exposure observed in healthy participants, drug concentration and application area (eg, 10% BSA) with an application rate of 3 mg/cm^2.

The systemic exposure of PF-07038124 was predicted as the topically applied QD dose of 0.01% applied to 2000 and 4000 cm^2 (approximately 10% and 20% BSA, respectively). The clinical exposure limit for this study is based on the systemic NOAEL of 0.06% (0.0104 mg/cm^2/day) with a corresponding systemic exposure (C_{av} free) of 11 pg/mL following 3 months of twice daily topical administration in minipigs (see Section 2.2.3).

Table 3. Proposed Doses, Predicted Free Exposures, and Safety Margins following QD Topical Application of PF-07038124[a]

Formulation Strength (%)	Population	BSA (cm^2, %)	Dose Applied (mg/day)	Total AUC_{24} (pg•hr/mL)	C_{av} total (pg/mL)	C_{av} free (pg/mL)	Predicted C_{av} free Safety Margin
0.01 QD	Healthy participants	2000 cm^2 (10%)	0.6	897.2	37.43	1.8	6.1
0.01 QD	Healthy participants	4000 cm^2 (20%)	1.2	1794	74.86	3.6	3.1

a. Assume QD dosing.
NOAEL exposure in minipig was 11 pg/mL.
Maximum application rate of formulation: 3 mg/cm^2.
Maximum concentration: 0.01% (0.1 mg PF-07038124/g formulation).
Topical daily dose = BSA (cm^2) × formulation concentration (µg/mg) × formulation applied (mg/cm^2).
Fraction unbound in plasma (fup) = 0.0482, molecular weight (MW)=327, where C_{av} free = AUC/24hr × fup.

Based on the PK findings in the FIH study (C3941001), the free C_{av} exposure was approximately 1.8 pg/mL at the 0.01% formulation upon application to 10% BSA. The predicted exposure margin at the 0.01% formulation following QD is approximately 6-fold and 3-fold for 2000 cm^2 and 4000 cm^2 respectively, relative to the NOAEL exposure in the minipig.

The projected systemic C_{av} concentrations following 0.01% QD topical application to 20% BSA is less than the observed systemic C_{av} concentrations (Study C3941001: Total C_{av} = 187 pg/mL; free ~9 pg/mL) at 0.03% QD topical application to healthy participants, which was well tolerated. As a result, there is low potential that participants could experience PDE4-related side effects.

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 Follow-Up.

The end of the study is defined as the date of the Follow-Up of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male and female participants must be 20 to 55 years of age, inclusive, at the time of signing the ICD.

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

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and 12-lead ECG.

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

4. Participants must have 4 biologically Japanese grandparents who were born in Japan.

Weight:

5. BMI of 17.5 to 25 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. 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.

2. Participants who have a history of or have active forms of dermatitides/eczematous conditions (eg, contact dermatitis, seborrhhoeic, discoid, gravitational, asteatotic and dishydrotic eczema) or other inflammatory skin diseases(eg, psoriasis, viral infection, fungal infection, bacterial infection) that would interfere with evaluation of the test site reaction.

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

4. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb, HCVAb, or syphilis at screening. Hepatitis B vaccination is allowed.

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

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

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

Prior/Concomitant Therapy:

8. Use of prescription or nonprescription drugs and dietary and herbal supplements within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. (Refer to Section 6.5 for additional details).

Prior/Concurrent Clinical Study Experience:

9. Previous administration with an investigational drug within 4 months (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:

10. A positive urine drug test at screening and/or Day -1.

11. 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.

12. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval

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

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

    - AST **or** ALT level ≥1.5 × 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.

14. A positive COVID-19 test at screening.

Other Exclusions:

15. 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).

16. Blood donation (excluding plasma donations) of approximately ≥400 mL within 3 months or ≥200 mL within a month prior to dosing. Additionally, approximately ≥400 mL within 4 months for female participants.

17. History of serious adverse reactions or hypersensitivity to any topical drug; or known allergy to any of the study intervention or any components in the study intervention or history of hypersensitivity; or allergic reactions to any of the study preparations.

18. Not willing to refrain from shaving (***Note:*** shaving around face is permitted), 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.

19. History of sensitivity to heparin or heparin-induced thrombocytopenia ***only if*** heparin is planned to flush intravenous catheters.

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

21. 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 4 hours prior to any safety laboratory evaluations.

- 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 are required to be dry for at least 30 minutes prior to each study intervention application. To help facilitate this, participants will not be permitted to shower or bathe within 2 hours prior to and 4 hours after any study intervention 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 2 hours prior to the AM dose. Participants will be allowed to take a shower on Day -1 prior to the first application of the study intervention.

- The use of any products in the area where the study intervention is applied is prohibited 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 study intervention.

- Participants should avoid wiping the study intervention off the skin until 4 hours post-dose.

- 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 that may cause either the study medication to be 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 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, 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, study intervention refers to PF-07038124 0.01% ointment and PF-07038124 vehicle ointment.

6.1. Study Intervention(s) Administered

Intervention Name	PF-07038124 0.01% ointment	PF-07038124 vehicle ointment
ARM Name (group of patients receiving a specific treatment (or no treatment)	Active	Vehicle
Type	Drug	Drug
Dose Formulation	Ointment	Ointment
Unit Dose Strength(s)	0.1 mg/g ointment in 60-gram tube	0 mg/g ointment in 60-gram tube
Dosage Level(s)	0.01% (wt/wt), QD	0% (wt/wt), QD
Route of Administration	Topical	Topical
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in cartons. Each carton will contain one tube. Both the carton and tube will be labeled in a blinded format as required per country requirement.	Study intervention will be provided in cartons. Each carton will contain one tube. Both the carton and tube will be labeled in a blinded format as required per country requirement.

PF-07038124 topical ointment, 0.1 mg/g will be provided as the active ingredient with precedented excipients: white petrolatum, mono- and di-glycerides, hexylene glycol and paraffin wax.

Vehicle (placebo, no active drug in the formulation) topical ointment will be provided as the precedented excipients only: white petrolatum, mono- and di-glycerides, hexylene glycol and paraffin wax.

PF-07038124 and vehicle ointments will be supplied by Pfizer to the CRU as 60 gram tubes and labeled according to local regulatory requirements in a blinded fashion.

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

6.1.1. Administration

6.1.1.1. Study Treatment Regimen

The study intervention will be applied in blinded fashion, at the CRU. All applications of the study intervention will be dispensed and applied by study site staff from Day 1 through Day 10 dose. Every effort must be made for the dose applications on Days 2-10 to be completed at 24±2 hour intervals from the recorded time of completion of the Day 1 dose application, for each participant.

The study intervention will be applied QD for 10 consecutive days from Day 1 AM through Day 10 AM.

The per application dose will be calculated using the formula provided below in Section 6.1.1.2. The intended dose of the study intervention application is approximately

3 mg/cm^2. The study intervention should be applied evenly to all identified areas. The per application dose will be expressed as the weight of ointment in grams. The per application dose will remain fixed and the study intervention will be applied to the areas identified on Day 1.

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:

$$\text{BSA} \times 0.003\ (\text{g/cm}^2) = \text{Weight of study intervention (in g) per application.}$$

where BSA is 2000 cm^2 for Cohort 1, and 4000 cm^2 for Cohort 2.

6.1.1.3. Application of Study Intervention

Before the Day 1 AM dose is applied for each participant, the designated areas for treatment will be identified on Day 1 and documented in the participant's study records. For each subsequent study intervention application, study site staff will refer to the documented locations as determined on Day 1.

The application area will include a treatment area of 2000 cm^2±200 cm^2 (approximately 10% BSA) for Cohort 1. For Cohort 2, the treatment area is 4000 cm^2±400 cm^2 (approximately 20% BSA). The study intervention will be applied for 10 consecutive days. The application area will include the back as well as other extremities, abdomen and/or chest, identified by the investigator.

Wearing gloves, study site staff will apply the per application dose to the surface area determined on Day 1. Study intervention will be applied as a thin layer of participant's skin. Care must be taken to avoid study intervention 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 study intervention application, participants will be instructed to wear loose-fitting clothing, to not wipe study intervention off the skin, and to refrain from bathing, sauna or washing the treated areas within 4 hours after application. At 4 hours post-dose, study intervention will be wiped from all application sites, with a clean towel, prior to participants being released to shower.

6.2. Preparation/Handling/Storage/Accountability

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

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.

6. The head of the medical institution (where applicable) or study intervention administrator 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.

The study intervention will be dispensed in a blinded fashion using an IRT system at the study days as summarized in the SoA. A qualified staff member will dispense the study

intervention via unique container numbers on the cartons provided. A second staff member will verify the dispensing.

Prior to application, the per application dose will be carefully weighed out by the qualified CRU staff. Blinded study intervention will be applied to the participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files. Study intervention will be dispensed at the study days as summarized in the SoA.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. 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 sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

The study intervention will be applied by the investigator site personnel. The application site of each participant will be examined following dosing by the second staff member to ensure the study intervention was topically applied. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 14 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

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

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

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

6.5.1. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07038124; standard medical supportive care must be provided to manage the AEs.

6.6. Dose Modification

Not applicable.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following: Liver injury, ECG changes, local tolerability, and AEs.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for follow up. 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.

The site will inform the Sponsor Medical Monitor or Sponsor Clinician if the below criteria for permanent discontinuation of the study intervention are triggered.

Liver Injury

Please refer to Appendix 6 for Potential Cases of Drug-Induced Liver Injury (DILI; Hy's law).

ECG Changes

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

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

Local Tolerability

If a participant experiences severity Score 4 (Strong to severe) on the local tolerability assessment (Section 8.2.5), study treatment will be discontinued permanently, and participant will proceed to Early Termination/Discontinuation visit and follow-up as described in SoA.

If a participant experiences application site reaction of Score 3 (Moderate) on the local tolerability assessment, investigator may temporarily discontinue application of the study intervention for up to 5 consecutive days. If temporary withholding of the study intervention occurs for more than 5 consecutive days, then the participant should be permanently withdrawn from treatment and should follow-up with the site until complete or near complete resolution of the AE. This dosing gap may occur only once for the same participant.

AEs

Hypersensitivity Reactions: If signs and symptoms of hypersensitivity are attributable to the study intervention, including contact urticaria, it must be discontinued immediately, and appropriate therapy initiated.

Additional instances of temporary discontinuation may be appropriate (eg, surgery, infection, etc.).

7.2. Participant Discontinuation/Withdrawal From the Study

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

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

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 both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples 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.

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.

7.3. Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

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.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that 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.

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 180 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 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.

Physical examinations may be conducted by a physician.

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

8.2.2. Vital Signs

Supine BP 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.

8.2.2.1. Temperature

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

8.2.3. Electrocardiograms

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

limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 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 occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF 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 2 days after the last dose of study intervention should be

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

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

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

8.2.5. Skin Irritation Assessment

Local toleration will be assessed by Draize scoring and clinical observation in Table 4. [7]

The dermatologists will assess local toleration at the treatment test areas by examining the skin under standard light conditions (eg, using a 100-Watt incandescent blue bulb) 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. The same dermatologist should do all the skin response grading for any given participant during the course of the study, if possible. The skin response grading for any given participant by the second dermatologist will NOT be considered a protocol deviation. The dermatologists are to be blinded to the treatment assignments and must make daily assessment independently (without review) of the previous score(s). The dermatologists identification will be captured on the source document. 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.

Table 4. 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.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.7. COVID-19 Specific Assessments

Participants will be tested for SARS-CoV-2 infection at the timepoints specified in the SoA. Additional testing may be required by local regulations, institutional policies or by the Principal Investigator. The test result must be negative in order for a participant to proceed with admission on Day -1. COVID-19 tests may be conducted at central or local labs. COVID-19 specific assessments data will be considered source data. If the participant has had a positive COVID-19 test result, the result of such a test is recorded in the AE section of the CRF.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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 and Pfizer concurs with that assessment.

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

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

If a participant definitively 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 AE or SAE 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.

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.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

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 exposure during pregnancy:
    - 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 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

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

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

8.3.6. 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. Treatment of Overdose

For this study, any dose of study intervention greater than QD or greater than 24 g within a 24-hour time period ±2 hours will be considered an overdose.

Sponsor does not recommend 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 study intervention (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 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.

8.5. Pharmacokinetics

Blood samples of approximately 4 mL, to provide approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of PF-07038124 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 dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

The skin around PK sampling must be thoroughly cleansed prior to blood sample collection with mild soap and water followed by an isopropyl wipe.

Samples will be used to evaluate the PK of PF-07038124. Samples collected for analyses of plasma PF-07038124 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method[redacted]

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.

Samples collected for measurement of plasma concentrations of PF-07038124 will be analyzed using a validated analytical method in compliance with applicable SOPs. CCI [redacted]

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 would unblind the study will not be reported to investigator sites or blinded personnel until the study has been unblinded.

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

CCI [redacted]

CCI [redacted]

[redacted]

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. 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 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. Sample Size Determination

A sample size of 12 participants (4 PF-07038124: 2 vehicle per cohort) has been selected empirically to permit adequate characterization of safety, tolerability, skin irritation potential, and PK at each dose level in Japanese healthy participants. Participants who discontinue prior to completion of the study for non-safety related reasons may be replaced, at the discretion of the PI and Sponsor.

9.3. Analysis Sets

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

Participant Analysis Set	Description
Enrolled/Randomly assigned to study intervention	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.
PK concentration	All participants randomly assigned to study intervention who received a dose of PF-07038124 and in whom at least 1 plasma sample concentration value is reported.
PK parameter	All participants randomly assigned to study intervention who received a dose of PF-07038124 and who have at least 1 of the PK parameters of interest calculated.

9.4. 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.

9.4.1. General Considerations

All analyses described below will be conducted by treatment and cohort. In addition, data from vehicle in Cohort 1 and Cohort 2 will be pooled.

9.4.2. Primary Endpoint(s)

All safety analyses will be performed on the safety analysis set, which is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study

intervention. Participants will be analyzed according to the product they actually received. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

The primary endpoints of this study are treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, laboratory tests, and incidence and severity of local skin irritation.

The primary endpoints will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and/or graphical presentations in order to evaluate the safety, tolerability, and skin irritation potential of PF-07038124.

9.4.2.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS complex will be summarized by treatment and time. Changes from baseline will be defined as the change between the postdose QTcF value and the predose value on Day 1.

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

Safety QTcF Assessment

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

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

9.4.3. Secondary Endpoint(s)

9.4.3.1. Pharmacokinetic Analyses of PF-07038124

PK parameters (AUC_{tau}, and C_{max}) for PF-07038124, following multiple-dose topical administration, will be derived from the plasma concentration-time profiles using noncompartmental methods, as data permit.

The PK parameters to be assessed in this study, their definition, and method of determination are listed in Table 5. Actual PK sampling times will be used in the derivation of PK parameters.

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

The plasma PK parameters in Table 5 will be summarized descriptively by treatment group in accordance with Pfizer data standards, as data permit. The plot will include individual

participant values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

Table 5. Plasma PK Parameters

Parameter*	Day	Definition	Method of Determination
C_{max}	1, 10	Maximum plasma concentration	Observed directly from data
CCI			
AUC_{tau}	1, 10	Area under the plasma concentration-time profile from time zero to time tau (τ), the dosing interval, where tau = 24 hours	Linear/Log trapezoidal method up to (tau), the dosing interval, where tau = 24 hours
CCI			
CCI			
CCI			

CCI

CCI

[redacted]

CCI

[redacted]

9.4.6. Other Safety Analyses

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

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

9.5. Interim Analyses

No interim analyses are planned.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and 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 and submitted to an IRB/EC by the head of the medical institution and reviewed and approved by the IRB/EC before the study is initiated.

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the 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 ICH GCP 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 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, HIPAA requirements, where applicable, and the IRB/EC or study center.

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

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

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

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

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

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

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may

withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site 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 identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the 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 available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

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

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator or authorized site personnel 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 or authorized site personnel 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 or authorized site personnel will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

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

10.1.7. Source Documents

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

Data reported on the CRF or entered in the 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 study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. 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 sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or 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.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after 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.

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the SToD system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant’s participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or

problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride 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]	• Fibrinogen • hsCRP • Urine drug screening[c] • Pregnancy test (β-hCG)[d] • COVID-19 test[e] At screening only: • FSH[b] • Hepatitis B surface antigen • Hepatitis B core antibody • Hepatitis C antibody • Human immunodeficiency virus • Syphilis

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Serum or urine β-hCG for female participants of childbearing potential per SoA. Serum pregnancy test must be performed at screening.
e. May be conducted at central or local laboratory.

Investigators must document their review of each laboratory safety report.

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 conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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

10.3.2. Definition of SAE

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

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

baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. 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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality

assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the 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 completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

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

- Refrain from donating sperm.

PLUS either**:**

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

  OR

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

10.4.2. Female Participant Reproductive Inclusion Criteria

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

- Is not a WOCBP (see definitions below in Section 10.4.3);

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

10.4.3. Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

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

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

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

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
     - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.*
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.

5. Vasectomized partner.

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

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

    - Oral;
    - Intravaginal;*
    - Transdermal;*
    - Injectable.*

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.

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.*

10. Male or female* condom with* or without spermicide.

11. Cervical cap*, diaphragm*, or sponge with spermicide*.

12. A combination of male condom with either cervical cap*, diaphragm*, or sponge with spermicide* (double-barrier methods).

*) Not approved in Japan

CCI [redacted]

[redacted]

- [redacted]
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- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- [redacted]

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an “adaptor” 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 cases of Hy's law, 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, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum 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: Abbreviations

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

Abbreviation	Term
Abs	absolute
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{24}	area under the plasma concentration-time profile from time zero to time 24 hours
AUC_{tau}	area under the plasma concentration-time profile from time zero to time tau, the dosing interval, where tau = 24 hours
CCI [redacted]	[redacted]
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
C_{av}	average concentrations
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CCI [redacted]	[redacted]
C_{max}	maximum observed concentration
CCI [redacted]	[redacted]
COVID-19	coronavirus disease
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial
CCI [redacted]	[redacted]
DILI	drug-induced liver injury
DMC	data monitoring committee

Abbreviation	Term
CCI	[redacted]
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EFD	embryo-fetal development
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FIH	first-in-human
FSH	follicle-stimulating hormone
fup	fraction unbound in plasma
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IFN	interferon
IL	interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous
IWR	interactive Web-based response
JAK	Janus kinase
LBBB	left bundle branch block
LFT	liver function test

Abbreviation	Term
LPS	lipopolysaccharide
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRHD	maximum recommended human dose
msec	millisecond
MW	molecular weight
N/A	not applicable
NIMP	Noninvestigational Medicinal Product
NOAEL	no-observed-adverse-effect level
NOEL	no observed effect level
PBMC	peripheral blood mononuclear cells
PDE	phosphodiesterase
PDE4	phosphodiesterase 4
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PT	prothrombin time
CCI	[redacted]
PVC	premature ventricular contraction/complex
QD	once daily
QoL	quality of life
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
CCI	[redacted]
CCI [redacted]	[redacted]
RBC	red blood cell
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	single reference safety document
SToD	study team on demand
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
$t_{½}$	terminal phase half-life
Th2	T-Helper 2 Cells
THC	tetrahydrocannabinol
CCI	[redacted]

Abbreviation	Term
TNF	tumor necrosis factor
uC_{av}	unbound average concentrations
ULN	upper limit of normal
US	United States
UVA	ultraviolet A
CCI	[redacted]
WBC	white blood cell
WOCBP	woman of childbearing potential

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