A PHASE 2A, RANDOMIZED, DOUBLE BLIND, VEHICLE CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07038124 OINTMENT FOR 6 WEEKS IN PARTICIPANTS WITH MILD TO MODERATE ATOPIC DERMATITIS OR PLAQUE PSORIASIS

Study Intervention Number:	PF-07038124
Study Intervention Name:	N/A
US IND Number:	CCI [redacted]
EudraCT Number:	2020-003977-23
Protocol Number:	C3941002
Phase:	2a

Short Title: A Phase 2a, randomized, double-blind, vehicle-controlled, parallel group study to assess efficacy, safety, tolerability and pharmacokinetics of PF-07038124 ointment in participants with atopic dermatitis or plaque psoriasis

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Original protocol	19 August 2020	N/A

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 2a, randomized, double blind, vehicle controlled, parallel group study to assess efficacy, safety, tolerability and pharmacokinetics of PF-07038124 ointment in participants with atopic dermatitis (AD) or plaque psoriasis.

Rationale: This multicenter, randomized, double blind, vehicle controlled, parallel group, study is being conducted to provide data on efficacy, safety, tolerability and PK of PF-07038124 ointment versus vehicle control in the treatment of mild to moderate AD and mild to moderate plaque psoriasis. This is the first study where PF-07038124 ointment is being administered to participants with AD or psoriasis.

Objectives, Estimands, and Endpoints

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
Primary Objective	**Primary Endpoint(s)**	**Primary Estimands**
• To compare the efficacy of PF-07038124 versus vehicle on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with mild or moderate atopic dermatitis (AD).	• Percent change from baseline in EASI total score at Week 6.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) on a continuous endpoint; without the benefit of additional prohibited medications during treatment and regardless of participant compliance with the IP dosing.
Secondary Objective(s):	**Secondary Endpoints**	**Secondary Estimands**
• To compare the efficacy of PF-07038124 versus vehicle, using Investigator's Global Assessment (IGA) score assessment as endpoint in participants with mild or moderate AD.	• Proportion of participants achieving IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 6.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
• To compare the efficacy of PF-07038124 versus vehicle, using measures of disease severity and symptoms as endpoints in participants with mild or moderate AD.	• Proportion of participants achieving EASI 75 (75% improvement from baseline) at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant.
• To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or moderate AD.	• Proportion of participants having ≥4 points of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant.
• To compare the efficacy of PF-07038124 versus vehicle, on measures of disease and symptom severity in participants with mild or moderate AD.	• Change from baseline in EASI total score at study visit time points specified in the SoA. • Proportion of participants achieving IGA score of clear (0) or almost clear (1) at study visit time points specified in the SoA. • Percent change from baseline in body surface area (BSA) at study visit time points specified in the SoA.	• All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate. • All categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above, when appropriate.
• To characterize the safety and tolerability of PF-07038124 versus vehicle in participants with mild or moderate AD.	• Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests. • Incidence of severity grades in skin tolerability at study visit time points specified in the SoA.	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

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PSORIASIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07038124 versus vehicle on change from baseline in Psoriasis Area and Severity Index (PASI) score in participants with mild to moderate plaque psoriasis.	• Change from baseline in PASI score at Week 6.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of PF-07038124 versus vehicle on Physician Global Assessment (PGA) score in participants with mild to moderate plaque psoriasis.	• Proportion of participants with PGA score of clear (0) or almost clear (1) (on a 5-point scale) and ≥2 points improvement from baseline at Week 6.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle on the proportion of participants with mild to moderate plaque psoriasis achieving PASI 75.	• Proportion of participants achieving PASI 75 (75% or greater improvement from baseline) at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or moderate plaque psoriasis.	• Proportion of participants who achieved a Psoriasis Symptoms Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle on measures of disease and symptom severity in participants with mild to	• Change from baseline in PASI scores at study visit time points specified in the SoA (except Week 6). • Percent change from baseline	• All other continuous secondary endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.

PSORIASIS		
Objectives	**Endpoints**	**Estimands**
moderate plaque psoriasis.	in PASI scores at study visit time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • Percent change from baseline in BSA at study visit time points specified in the SoA.	• All other categorical secondary endpoints will be analyzed descriptively and using estimand E1 described above when appropriate.
• To assess safety and tolerability of PF-07038124 in participants with mild to moderate plaque psoriasis.	• Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests. • Incidence of severity grades in skin tolerability at times indicated in SoA.	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

CCI [redacted]

Overall Design

This is a Phase 2a, randomized, double-blind, vehicle-controlled, parallel group, multicenter study in the adult participants with mild to moderate AD or mild to moderate plaque psoriasis. The study will assess the efficacy, safety, tolerability, and PK of PF-07038124 ointment.

Number of Participants

A total of approximately 88 participants with AD or psoriasis will be randomly assigned to study intervention in this basket trial.

For AD, a maximum of approximately 56 participants will be randomly assigned to study intervention such that approximately 42 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 28 participants will be randomized to either PF-07038124 or vehicle control to achieve approximately 21 completers in each group. Randomization will be stratified by baseline disease severity (mild [Investigator's Global Assessment or IGA = 2] vs. moderate [IGA = 3]). Up to 25% of AD participants will have an IGA score of 2 at baseline.

For psoriasis, a maximum of approximately 32 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 16 participants will be randomized to PF-07038124 or vehicle control to achieve 12 completers in each group. Randomization will be stratified by baseline disease severity (mild [Physician Global Assessment or PGA = 2] vs. moderate [PGA = 3]). Up to 25% of psoriasis participants will have a PGA score of 2 at baseline.

Intervention Groups and Duration

The total duration of study participation will be approximately 17 weeks, including a screening period of up to 6 weeks, a double-blind treatment period of 6 weeks, and a safety follow-up period of 4-5 weeks from last dose of study drug to last study visit.

Study intervention arms are shown in the following table.

Table 1. Study Intervention Groups

Study Intervention Group (Indication)	Target Number of Participants Randomized	Approx. Number of Completers	Study Intervention
A (atopic dermatitis)	28	21	PF-07038124 ointment at 0.01% with QD dosing for 6 weeks
B (atopic dermatitis)	28	21	Vehicle ointment with QD dosing for 6 weeks
C (plaque psoriasis)	16	12	PF-07038124 ointment at 0.01% with QD dosing for 6 weeks
D (plaque psoriasis)	16	12	Vehicle ointment with QD dosing for 6 weeks

The study intervention for AD and psoriasis participants are the same.

A study design schematic is presented in Section 1.2.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Statistical Methods for AD

The primary estimand will be estimated population-based average treatment effect on percent change from baseline in Eczema and Severity Index (EASI) score relative to vehicle at 6 weeks for all randomized participants in the absence of prohibited medication without regard to compliance.

The secondary estimand will be the estimated population-based average treatment effect on the rates of Investigator's Global Assessment (IGA) response (percentage of participants with a score of 0 or 1 and a 2 point or greater decrease from baseline) at Week 6 relative to vehicle without regard to compliance with Investigational Product (IP) in the absence of prohibited medication.

All other secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. Other estimands may be used for some of the primary and secondary endpoints to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the Statistical Analysis Plan (SAP).

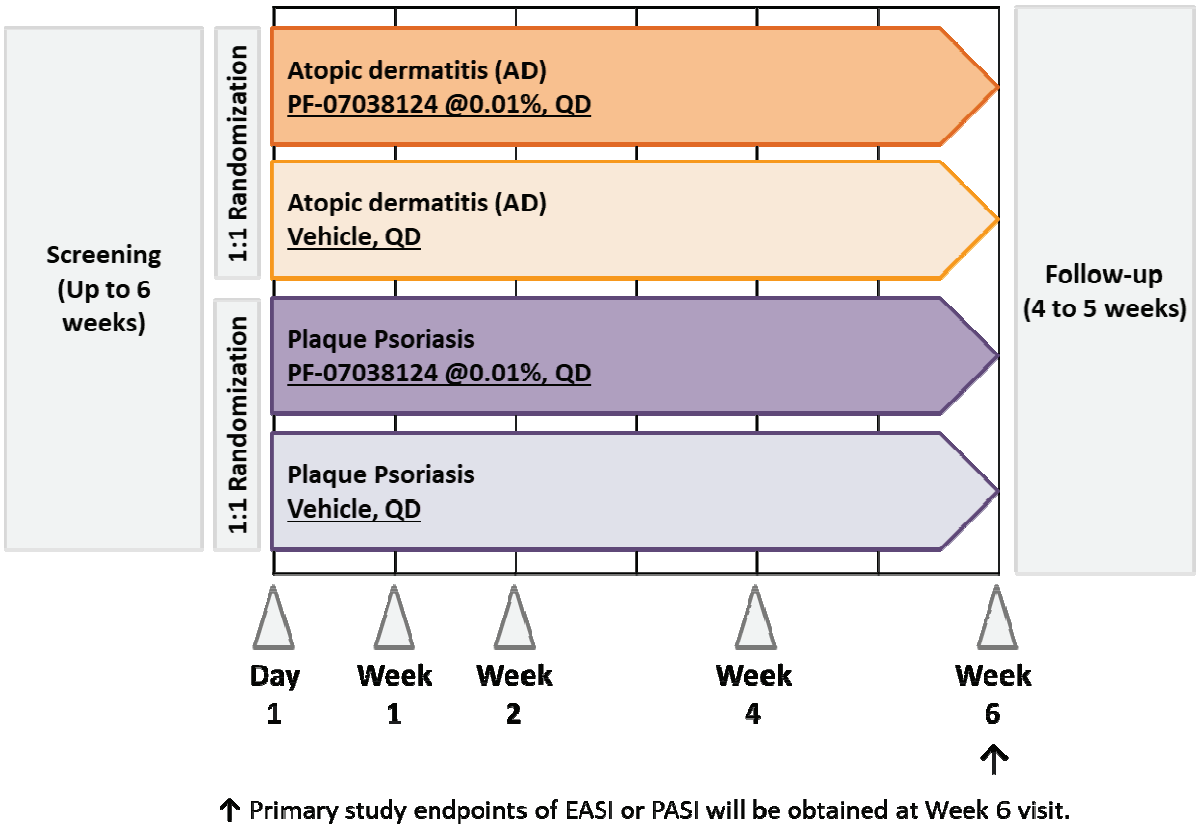
Statistical Methods for Psoriasis

The primary estimand will be the population average treatment effect on change from baseline in Psoriasis Area and Severity Index (PASI) scores at Week 6 relative to vehicle without regard to compliance in the absence of prohibited medication. Measurements after the initiation of prohibited medication will be censored and treated as missing data.

The secondary estimand will be the population average treatment effect on the Physician Global Assessment (PGA) response rate: percentage of participants with a score of clear (0) or almost clear (1) and a 2 point or greater improvement from baseline at Week 6 relative to vehicle without regard to compliance with IP in the absence of prohibited medication.

All other secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. Other estimands may be used for some of the primary and secondary endpoints to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the SAP.

1.2. Schema


Screening
(Up to 6
weeks)
1:1 Randomization
1:1 Randomization
Atopic dermatitis (AD)
PF-07038124 @0.01%, QD
Atopic dermatitis (AD)
Vehicle, QD
Plaque Psoriasis
PF-07038124 @0.01%, QD
Plaque Psoriasis
Vehicle, QD
Follow-up
(4 to 5 weeks)
Day
1
Week
1
Week
2
Week
4
Week
6
↑ Primary study endpoints of EASI or PASI will be obtained at Week 6 visit.

1.3. Schedule of Activities

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

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

1.3.1. Atopic Dermatitis

ATOPIC DERMATITIS								
Visit Identifier[a]	**Screening & Washout**	**Day 1 (Baseline)**	**Week 1**	**Week 2**	**Week 4**	**Week 6 (EOT)**	**Follow-up (EOS)**	**Early Termination (ET)**
Visit Window	**Day-42 to -1**	**N/A**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**28–35 Days post-last Dose**	**N/A**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Enrollment Procedures								
Informed Consent	X							
Register Subject Using IRT System	X							
Medical History	X	X						
Concomitant/Prior Treatments	X	X	X	X	X	X	X	X
Demography	X							
Eligibility Assessment	X	X						
Randomization		X						
Clinical Assessments								
Complete Physical Examination[b]	X	X				X		
Targeted Physical Examination[b]			X	X	X		X	X
Weight	X	X						
Height	X							
Vital Signs[c]	X	X		X	X	X		X
ECG[d]	X	X				X		
C-SSRS[e]	X							
Laboratory Assessments								
Serum FSH (WONCBP only) or Serum Pregnancy Test (WOCBP only)[f]	X							

ATOPIC DERMATITIS								
Visit Identifier[a]	**Screening & Washout**	**Day 1 (Baseline)**	**Week 1**	**Week 2**	**Week 4**	**Week 6 (EOT)**	**Follow-up (EOS)**	**Early Termination (ET)**
Visit Window	**Day-42 to -1**	**N/A**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**28–35 Days post-last Dose**	**N/A**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Urine Pregnancy Test (conducted at study site)[g]		X	X	X	X	X	X	X
Hematology, Chemistry and Urinalysis[h]	X	X	X	X	X	X	X	X
Fibrinogen, hsCRP[h]	X	X	X	X	X	X	X	X
CCI [redacted]								
IP Related Processes								
Dispense dosing diary/PROs and instruct on usage	X							
Assess BSA & calculate IP need	X	X	X	X	X			
Body Map		X	X	X	X	X		
Weigh and dispense IP		X	X	X	X			
IP application and observation (at site/at home in case of Home Health Visits)		X	X	X	X	X		
Record dose and time of IP application in dosing diary		X	→	→	→	X		
Collect and weigh returned IP tubes for compliance check			X	X	X	X		X
Review of dosing diary/PROs		X	X	X	X	X	X	X
Collect dosing diary/PROs		X[k]					X	X
AD-Related Clinical Assessments								
EASI	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X

ATOPIC DERMATITIS								
Visit Identifier[a]	**Screening & Washout**	**Day 1 (Baseline)**	**Week 1**	**Week 2**	**Week 4**	**Week 6 (EOT)**	**Follow-up (EOS)**	**Early Termination (ET)**
Visit Window	**Day-42 to -1**	**N/A**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**28–35 Days post-last Dose**	**N/A**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
BSA	X	X	X	X	X	X	X	X
Safety Monitoring								
Contraception check	X	X	X	X	X	X	X	X
Local Tolerability Assessments[l]		X	X	X	X	X	X	X
Serious and non-serious AE monitoring	X	→	→	→	→	→	X	X
Patient Reported Outcomes (PRO)								
In-clinic completion								
CCI [redacted]								
At-home completion								
PP-NRS[m]	X	→	→	X	X	X	X	X

Abbreviations: →= ongoing/continuous event; AD = Atopic Dermatitis; BSA = Body Surface Area; CCI C-SSRS = Columbia Suicide Severity Rating Scale; CCI EASI = Eczema Assessment Severity Index; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early termination; FSH = Follicle Stimulating Hormone; hsCRP= High-sensitivity C-reactive protein (hsCRP); IGA = Investigator's Global Assessment; CCI IP = Investigational Product; PD = Pharmacodynamics; CCI CCI ; PP-NRS = Peak Pruritis Numerical Rating Scale; PRO = Patient Reported Outcomes; CCI .

a. Day relative to start of study treatment (Day 1). Except for Screening Visit and Day 1 Visit, Alternative Measures (Section 10.9) may be implemented in case of public emergencies. Please refer to Section 10.9 for the details about the assessments that may be performed during a Telehealth Visit (including Efficacy Assessments) or a Home Health Visit.

b. Physical Examination: Physical assessments may be performed in the event of Home Health Visit.

c. Vital Signs: Temperature (Oral or tympanic temperature), pulse rate, and blood pressure will be taken in supine position, after the participant has been lying calmly for a minimum of 5 minutes. Assessment of vital signs should precede blood draw for clinical laboratory tests.

d. Local read, single ECG (in supine position) at all time points indicated. To ensure safety of the participant, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1. Triplicate ECG will be conducted as appropriate per Section 8.2.4.

e. Site staff is to administer the Columbia Suicide Severity Rating Scale (C-SSRS) to all participants at screening and score immediately. Participants who have recent or active suicidal ideation or behavior or clinically significant depression will be excluded from the study per Section 5.2.

f. Serum FSH (WONCBP only) or Serum Pregnancy test (WOCBP only): For Women of Non-Childbearing Potential (WONCBP), serum follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months. Serum Pregnancy test is required for all Women of Childbearing Potential (WOCBP).

g. Urine Pregnancy Tests must be performed prior to dosing with the investigational product for female subjects of childbearing potential. Two negative pregnancy tests are required before receiving investigational product (1 negative Serum Pregnancy Test at screening and 1 negative Urine Pregnancy Tests at the baseline visit before investigational product administration).

h. Blood draw for Protocol-Required Safety Laboratory Assessments (Appendix 2) on Day 1 will be performed before the in-clinic IP application. Laboratory tests with abnormal results may be repeated once during the screening period; the last value will be used to determine eligibility.

c [redacted]

c [redacted]

k. Only for participants who do not meet eligibility criteria.

l. Local tolerability at the site of IP application will be assessed pre-dose and immediately after post-dose.

m. PP-NRS: At the screening visit or at least 7 days prior to Day 1, site staff will dispense the ePRO device (or paper PROs) and review instructions for completion.

1.3.2. Psoriasis

PSORIASIS								
Visit Identifier[a]	**Screening & Washout**	**Day 1 (Baseline)**	**Week 1**	**Week 2**	**Week 4**	**Week 6 (EOT)**	**Follow-up (EOS)**	**Early Termination (ET)**
Visit Window	**Day -42 to -1**	**N/A**	**Day 8±2**	**Day 15±2**	**Day 29±2**	**Day 43±2**	**28–35 Days post-last Dose**	**N/A**
Visit Number	1	**2**	**3**	**4**	**5**	**6**	**7**	**N/A**
Informed Consent	X							
Register Subject Using IRT System	X							
Medical History	X	X						
Concomitant/Prior Treatments	X	X	X	X	X	X	X	X
Demography	X							
Eligibility Assessment	X	X						
Randomization		X						
Clinical assessments								
Complete Physical Examination[b]	X	X				X		
Targeted Physical Examination[b]			X	X	X		X	X
Weight	X	X						
Height	X							
Vital Signs[c]	X	X		X	X	X		X
ECG[d]	X	X				X		
C-SSRS[e]	X							
Laboratory assessments								
Serum FSH (WONCBP only) or Serum Pregnancy Test (WOCBP only)[f]	X							
Urine Pregnancy Test (conducted at study site)[g]		X	X	X	X	X	X	X
Hematology, Chemistry and Urinalysis[h]	X	X	X	X	X	X	X	X
Fibrinogen, hsCRP[h]	X	X	X	X	X	X	X	X

CCI [redacted]

PSORIASIS								
Visit Identifier[a]	**Screening & Washout**	**Day 1 (Baseline)**	**Week 1**	**Week 2**	**Week 4**	**Week 6 (EOT)**	**Follow-up (EOS)**	**Early Termination (ET)**
Visit Window	**Day -42 to -1**	**N/A**	**Day 8±2**	**Day 15±2**	**Day 29±2**	**Day 43±2**	**28–35 Days post-last Dose**	**N/A**
CCI [redacted]								
IP Related Processes								
Dispense dosing diary/PROs and instruct on usage	X							
BSA & calculate IP need	X	X	X	X	X			
Body Map		X	X	X	X	X		
Weigh and dispense IP		X	X	X	X			
IP application and observation (at site/at home in case of Home Health Visits)		X	X	X	X	X		
Record dose and time of IP application in dosing diary		X	→	→	→	X		
Collect and weigh returned IP tubes for compliance check			X	X	X	X		X
Review of dosing Diary/PROs		X	X	X	X	X	X	X
Collect dosing Diary/PROs		X[k]					X	X
Psoriasis-Related Clinical assessments								
PASI	X	X	X	X	X	X	X	X
PGA	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X
Safety Monitoring								
Contraception check	X	X	X	X	X	X	X	X
Local Tolerability Assessments[l]		X	X	X	X	X	X	X
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	X
Patient Reported Outcomes (PRO)								
In-clinic completion								
CCI [redacted]								
At-home completion								
PSI[m]	X	→	→	X	X	X	X	X

Abbreviations: → = ongoing/continuous event; BSA = Body Surface Area; C-SSRS = Columbia Suicide Severity Rating Scale; CCI ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = Follicle Stimulating Hormone; hsCRP= High-sensitivity C-reactive protein (hsCRP); CCI ; IP = Investigational Product; PASI = Psoriasis Area and Severity index; PGA = Physicians Global Assessment; CCI CCI ; PRO = Patient Reported Outcomes; PSI=Psoriasis Symptom Inventory.

a. Day relative to start of study treatment (Day 1). Except for Screening Visit and Day 1 Visit, alternative measures (Section 10.9) may be implemented in case of public emergencies. Please refer to Section 10.9 for the details about the assessments that may be performed during a Telehealth Visit (including Efficacy Assessments) or a Home Health Visit.

b. Physical Examination: Physical assessments may be performed in the event of Home Health Visit.

c. Vital Signs: Temperature (Oral or tympanic temperature), pulse rate, and blood pressure will be taken in supine position, after the participant has been lying calmly for a minimum of 5 minutes. Assessment of vital signs should precede blood draw for clinical laboratory tests.

d. Local read, single ECG (in supine position) at all time points indicated. To ensure safety of the participant, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1. Triplicate ECG will be conducted as appropriate per Section 8.2.4.

e. Site staff is to administer the Columbia Suicide Severity Scale (C-SSRS) to all participants at screening and score immediately. Participants who have recent or active suicidal ideation or behavior or clinically significant depression will be excluded from the study.

f. Serum FSH (WONCBP only) or Serum Pregnancy test: For Women of Non-Childbearing Potential (WONCBP), serum follicle stimulating hormone (FSH) test to be performed at Screening to confirm postmenopausal status in female subjects who have been amenorrheic for at least 12 consecutive months. Serum Pregnancy test is required for all Women of Childbearing Potential (WOCBP).

g. Urine Pregnancy Tests must be performed prior to dosing with the investigational product for female subjects of childbearing potential. Two negative pregnancy tests are required before receiving investigational product (1 negative Serum Pregnancy Test at screening and 1 negative Urine Pregnancy Tests at the baseline visit before investigational product administration).

h. Blood draw for Protocol-Required Safety Laboratory Assessments (Appendix 2) on Day 1 will be performed before the in-clinic IP application. Laboratory tests with abnormal results may be repeated once during the screening period; the last value will be used to determine eligibility.

C

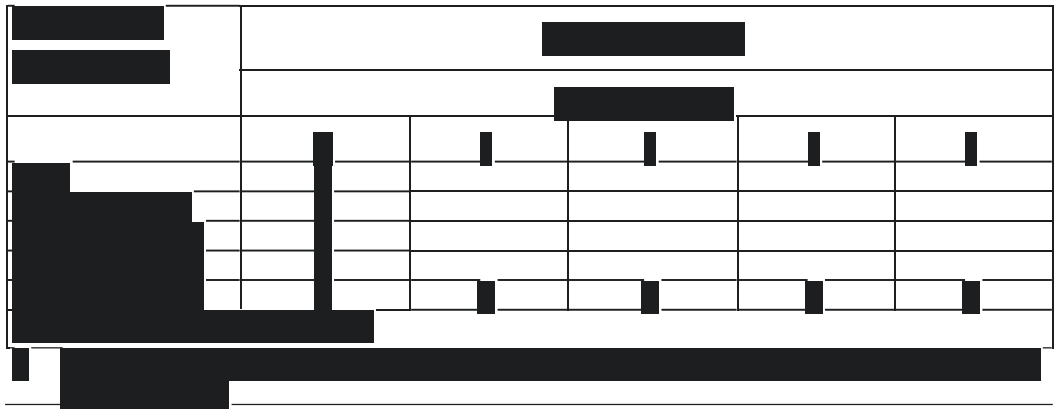
C

k. Only for participants who do not meet eligibility criteria.

l. Local tolerability at the site of IP application will be assessed pre-dose and immediately after post-dose.

m. PSI: At the screening visit or at least 7 days prior to Day 1, site staff will dispense the ePRO device (or paper PROs) and review instructions for completion.

CCI



2. INTRODUCTION

PF-07038124 is a topical phosphodiesterase 4 (PDE4) inhibitor that is being investigated for the treatment of atopic dermatitis (AD) and plaque psoriasis (psoriasis).

2.1. Study Rationale

The purpose of the study is to investigate the efficacy, safety, tolerability and pharmacokinetics of topical PF-07038124 in participants with mild to moderate AD or mild to moderate psoriasis. Participants will receive either PF-07038124 or a vehicle control for 6 weeks.

2.2. Background

2.2.1. Role of Proinflammatory Cytokines in AD and Psoriasis

ATOPIC DERMATITIS: 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 European Union (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, ultraviolet A [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 interleukin (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 T-helper 2 cells (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 quality of life (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 tumor necrosis factor (TNF) α, interferon (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 cyclic adenosine monophosphate (cAMP) levels.

2.2.2. Description of Investigational Product: Mechanism of Action

Phosphodiesterases (PDE) are a family of enzymes that breakdown the ubiquitous second messengers, cAMP and cyclic guanosine monophosphate (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. CCI [redacted]

PF-07038124 inhibits cytokine production and release from T cells and monocytes in peripheral blood mononuclear cells (PBMC) over a range of concentrations that is dependent on the cytokine that is being modulated. CCI [redacted] 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, Janus kinase (JAK) inhibitors and the PDE4 inhibitor crisaborole (Eucrisa®). CCI [redacted]

CCI [redacted]

2.2.3. Preclinical Safety Data

In the pivotal 3-month toxicity studies in rats (oral) and minipigs (dermal), the systemic no-observed-adverse-effect levels (NOAEL) were identified as 4 mg/kg/day and 0.0104 mg/cm^2/day (0.0052 mg/cm^2, BID), 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 No Observed Effect Level (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 embryo-fetal development (EFD) was assessed after oral administration of PF-07038124 to pregnant animals. PF-07038124 did not cause any effects on embryo-fetal development 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 unbound C_{av} (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.

In summary, the nonclinical studies adequately support the planned clinical trials with PF-07038124.

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2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07038124 may be found in the investigator's brochure (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 Maximum Recommended Human Dose (MRHD) for oral PDE4 inhibitors.	Participants will be assessed for safety at regular intervals throughout the study (including monitoring of acute-phase reactants such as fibrinogen and C-reactive protein), systemic exposure will also be assessed.
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 at regular intervals 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 at regular intervals throughout the study, including assessment of the administration site. Participants with any history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products will be excluded from the study.
Use of a placebo arm	Participants on placebo may experience a worsening of disease.	Participants will be assessed for safety at regular intervals throughout the study. AD and psoriasis are not life-threatening diseases.

2.3.2. Benefit Assessment

Based on its cytokine inhibition profile, topical administration of PF-07038124 is anticipated to provide potential therapeutic benefit in the treatment of AD by targeting the signaling of cytokines in T-helper-2 response and in the treatment of psoriasis by targeting TNF-α. Other PDE4 inhibitors, such as crisaborole (Eucrisa®, Staquis®), apremilast (Otezla®), and roflumilast (ARQ-151)[6] have demonstrated efficacy in the treatment of AD or psoriasis. Based on the clinical data for these PDE4 inhibitors, participants in this study may receive a beneficial effect, in addition to regular intensive clinical trial assessment to support participants' management of AD or psoriasis.

The included vehicle has important emollient properties. Some vehicle excipients have a more pronounced beneficial effect on the skin and can improve clinical appearance and skin barrier function. In particular, white petrolatum, the primary excipient and base of PF-07038124 ointment, 0.01%, was selected for its emollient properties and favorable tolerability profile. The use of topical emollients is an essential element of AD and psoriasis treatment and is recommended by published guidelines.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to participants 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 or psoriasis.

The Benefit/Risk balance of PF-07038124 in Study C3941002 is considered favorable and supported by:

- The satisfactory safety and local tolerability profile on PF-07038124 to date based on non-clinical studies CCI [redacted]
- The expected efficacy of PF-07038124 for the treatment of AD and psoriasis based on pre-clinical data generated with PF-07038124 as well as the efficacy of other approved topical PDE4 inhibitors for the treatment of mild to moderate AD (Eucrisa®/Staquis®) and oral PDE4 inhibitors for the treatment of moderate to severe psoriasis (Otezla®).

Participants will be monitored closely during the study for safety and local tolerability adverse events by the study investigators and sponsor to ensure participant safety.

In conclusion, Pfizer considers that the clinical experience to date with PF-07038124 support the continued development of PF-07038124 for the treatment of AD and psoriasis supporting the initiation of Phase 2a study C3941002. Additional background information on PF-07038124 can be found in the current version of the IB, especially the Summary of Data and Guidance for the Investigator (Section 7 of the IB).

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. Atopic Dermatitis

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
Primary Objective	**Primary Endpoint**	**Primary Estimands**
• To compare the efficacy of PF-07038124 versus vehicle on percent change from baseline in Eczema Area and Severity Index (EASI) in participants with mild or moderate atopic dermatitis (AD).	• Percent change from baseline in EASI total score at Week 6.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) on a continuous endpoint; without the benefit of additional prohibited medications during treatment and regardless of participant compliance with the IP dosing.
Secondary Objectives:	**Secondary Endpoints**	**Secondary Estimands**
• To compare the efficacy of PF-07038124 versus vehicle, using Investigator's Global Assessment (IGA) score assessment as endpoint in participants with mild or moderate AD.	• Proportion of participants achieving IGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 6.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle, using measures of disease severity and symptoms as endpoints in participants with mild or moderate AD.	• Proportion of participants achieving EASI 75 (75% improvement from baseline) at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit of additional prohibited medications and regardless of a participant compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or	• Proportion of participants having ≥4 points of reduction in weekly averages of Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline at study visit time points specified in the	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP on a binary responder endpoint; without the benefit

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
moderate AD.	SoA.	of additional prohibited medications and regardless of a participant compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle, on measures of disease and symptom severity in participants with mild or moderate AD.	• Change from baseline in EASI total score at study visit time points specified in the SoA. • Proportion of participants achieving IGA score of clear (0) or almost clear (1) at study visit time points specified in the SoA. • Percent change from baseline in affected Body Surface Area (BSA) at study visit time points specified in the SoA.	• All continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above, when appropriate. • All categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above, when appropriate.
• To characterize the safety and tolerability of PF-07038124 versus vehicle in participants with mild or moderate AD.	• Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests. • Incidence of severity grades in skin tolerability at times indicated in SoA.	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

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3.2. Psoriasis

PSORIASIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of PF-07038124 versus vehicle on change from baseline in Psoriasis Area and Severity Index (PASI) score in participants with mild to moderate plaque psoriasis.	• Change from baseline in PASI score at Week 6.	• Estimand E1: This estimand is intended to provide a population level estimate of the treatment effect of the investigational product (IP) alone on a continuous endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of PF-07038124 versus vehicle on Physician Global Assessment (PGA) score in participants with mild to moderate plaque psoriasis.	• Proportion of participants with PGA score clear (0) or almost clear (1) (on a 5-point scale) and ≥2 points improvement from baseline at Week 6.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of

PSORIASIS		
Objectives	**Endpoints**	**Estimands**
		participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle on the proportion of participants with mild to moderate plaque psoriasis achieving PASI 75.	• Proportion of participants achieving PASI 75 (75% or greater improvement from baseline) at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle, using measures of patient reported outcomes (PRO), in participants with mild or moderate plaque psoriasis.	• Proportion of participants who achieved a Psoriasis Symptoms Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item at study visit time points specified in the SoA.	• Estimand E2: This estimand is intended to provide a population level estimate of the treatment effect of the IP alone on a binary responder endpoint; without the benefit of additional prohibited medications, regardless of participants compliance with the IP dosing.
• To compare the efficacy of PF-07038124 versus vehicle on measures of disease and symptom severity in participants with mild to moderate plaque psoriasis.	• Change from baseline in PASI scores at study visit time points specified in the SoA (except Week 6). • Percent change from baseline in PASI scores at study visit time points specified in the SoA. • Proportion of participants with PGA score clear (0) or almost clear (1) and ≥2 points improvement from baseline at time points specified in the SoA. • Percent change from baseline in BSA at study visit time points specified in the SoA.	• All other continuous secondary endpoints will be analyzed descriptively and using estimand E1 described above when appropriate. • All other categorical secondary endpoints will be analyzed descriptively and using estimand E2 described above when appropriate.
• To assess safety and tolerability of PF-07038124 in participants with mild to moderate plaque psoriasis.	• Incidence of treatment emergent adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in vital signs, electrocardiogram (ECG), and laboratory tests. • Incidence of severity grades in	• There is no defined estimand for these endpoints and they will be analyzed using Pfizer data standards as applicable.

PSORIASIS		
Objectives	**Endpoints**	**Estimands**
	skin tolerability at times indicated in SoA.	

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4. STUDY DESIGN

4.1. Overall Design

This is a phase 2a, randomized, double blind, vehicle controlled, parallel group, multicenter study on the efficacy, safety, tolerability and PK of PF-07038124 0.01% QD versus vehicle control in the treatment of adult participants with mild to moderate AD or mild to moderate plaque psoriasis. In this study the efficacy of PF-07038124 ointment versus vehicle will be assessed in two different indications – there is a separate vehicle control group for each indication.

A total of approximately 88 participants with AD or psoriasis will be randomly assigned to study intervention in this basket trial design.

For AD, a maximum of approximately 56 participants will be randomly assigned to study intervention such that approximately 42 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 28 participants will be randomized to either PF-07038124 or vehicle control to achieve approximately 21 completers in each group. Randomization will be stratified by baseline disease severity (mild [Investigator's Global Assessment or IGA = 2] vs. moderate [IGA = 3]). Up to 25% of AD participants will have an IGA score of 2 at baseline.

For psoriasis, a maximum of approximately 32 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. Assuming a 25% drop out rate, approximately 16 participants will be randomized to PF-07038124 or vehicle control to achieve 12 completers in each group. Randomization will be stratified by baseline disease severity (mild [Physician Global Assessment or PGA = 2] vs. moderate [PGA = 3]). Up to 25% of participants will have a PGA score of 2 at baseline.

The total duration of study participation will be approximately 17 weeks, including a screening period of up to 6 weeks, a double-blind, placebo-controlled treatment period of 6 weeks, and a safety follow-up period of 4-5 weeks from last dose of study drug to last study visit. The study intervention arms and duration for AD and psoriasis participants are the same (See Section 1.1 for detailed Study Intervention Groups and Section 1.2 for Study Schema).

4.2. Scientific Rationale for Study Design

This 6-week study is the first time a topical PF-07038124 ointment is being evaluated in the AD and psoriasis populations. Previous Pfizer trials in these indications indicate that a 6-week duration is appropriate to assess the efficacy, safety and tolerability. The current nonclinical toxicology package supports the study durations of up to 12 weeks.

For AD the primary endpoint is percent change from baseline in Eczema Area and Severity Index (EASI); secondary endpoints include Investigator’s Global Assessment (IGA).

For psoriasis the primary endpoint is percent change from baseline in Psoriasis Area and Severity Index (PASI); the secondary endpoints include Physician Global Assessment (PGA).

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.

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4.2.1. Participant Input into Design

Not applicable.

4.3. Justification for Dose

The nonclinical safety profile of PF-07038124 following systemic administration to rats and topical application to minipigs supports human clinical studies of up to 3 months in duration (See Section 2.2). 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.

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4.4. End of Study Definition

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

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

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

The inclusion criteria for AD and psoriasis are overlapping but different. Details of the overlapping inclusion criteria are provided in Section 5.1.1; Disease-specific inclusion criteria are provided in Section 5.1.2.1 and Section 5.1.2.2 for AD and psoriasis respectively.

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

5.1.1. General Inclusion Criteria Applicable for <u>both AD and psoriasis</u>

1. Male or female participants between the ages of 18 and 70 years, inclusive, at Visit 1 (Screening Visit/time of informed consent).

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

2. Body weight ≥50 kg and Body Mass Index (BMI) ≥17.5 kg/m^2 up to 40 kg/m^2 (inclusive).

3. 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.

4. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures. Refer to Section 5.3 for Lifestyle considerations.

5.1.2. Disease-Specific Inclusion Criteria

5.1.2.1. AD Specific Inclusion Criteria

1. Have been diagnosed with AD for at least 3 months prior to Day 1; the clinical diagnosis of AD will be confirmed according to the criteria of Hanifin and Rajka[7] (Appendix 11).

2. Have an Investigator's Global Assessment (IGA) score of 2 (mild), or 3 (moderate) at both the Screening and Day 1/Randomization. Note: Refer to Section 8.1.2.2 for the assessment of 5-point IGA.

3. Have AD covering 5% to 20% (inclusive) of BSA (excluding the scalp) at both the Screening and Day 1/Randomization. Note: Refer to Section 8.1.2.3 for detailed methods of calculating treatable BSA.

4. Have an EASI total score of ≥3 to ≤21 at Screening and at Day 1/Randomization. Note: Refer to Section 8.1.2.1 for method of calculating EASI scores.

5. Have a Baseline Peak Pruritis Numerical Rating Scale (PP-NRS) average score of ≥2 assessed at Day 1/Randomization.

5.1.2.2. Psoriasis Specific Inclusion Criteria

1. Participants with a diagnosis of plaque psoriasis (psoriasis vulgaris) for at least 6 months prior to Day 1.

2. Participants with a Physician Global Assessment (PGA) score of 2 (mild), or 3 (moderate) at Screening and Day 1. Note: Refer to Section 8.1.4.2 for the assessment of 5-point PGA.

3. Having plaque psoriasis covering 5% to 15% (inclusive) of BSA (excluding the scalp) at both the Screening and Day 1/Randomization. Note: Refer to Section 8.1.4.3 for detailed methods of calculating treatable BSA.

5.2. Exclusion Criteria

The exclusion criteria for AD and psoriasis are the same.

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

Medical Conditions:

1. Presence of skin comorbidities that would interfere with study assessment or response to treatment.

2. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria at Screening or Day 1:

    a. Suicidal ideation associated with actual intent and/or plan in the past year: "Yes" answers on items 4 "some intent to act without specific plan" or 5 "specific plan and intent" of the Columbia Suicide Severity Rating Scale (C-SSRS);

    b. Previous history of suicidal behaviors in the past 5 years: "Yes" answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS;

    c. Any lifetime history of serious or recurrent suicidal behavior;

    d. The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria;

    e. In the opinion of the investigator or Pfizer (or designee) exclusion is required.

3. Current or recent history (within approximately 3 months prior to Day 1) of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiovascular, or neurological disease.

4. A history of systemic (within approximately 3 months prior to Day 1), chronic or acute skin infection (within approximately 2 weeks prior to Day 1) requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator.

5. A known immunodeficiency disorder or a first degree relative with a hereditary immunodeficiency.

6. Undergone significant trauma or major surgery within 1 month prior to screening.

7. Have a history of cancer within 5 years or has undergone treatment for any type of cancer, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ with no evidence of recurrence.

8. Have a history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products.

9. 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.

Prior/Concomitant Therapy:

10. Has received any of the prohibited medications/therapies that may alter the course of the diseases under study without the required minimum washout period or anticipated concomitant use of any of the prohibited medications/therapy (see Appendix 10).

Prior/Concurrent Clinical Study Experience:

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

    Note: Any investigational or experimental therapy taken or procedure performed for AD, psoriasis, psoriatic arthritis or rheumatoid arthritis in the previous 1 year should be discussed with the Pfizer Medical Monitor (or designee). Participants cannot participate in studies of other investigational or experimental therapies or procedures at any time during their participation in this study.

Diagnostic Assessments:

12. Baseline 12 lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTc 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 QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc 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 (the last value will be used to determine eligibility), if deemed necessary:

    a. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2;

    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) values ≥2 times the ULN;

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

14. In the opinion of the investigator or sponsor, have any uncontrolled clinically significant laboratory abnormality that would affect interpretation of study data or the participant's participation in the study.

Other Exclusions:

15. 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.

16. A history of alcohol or substance abuse within 6 months prior to Screening that in the opinion of the investigator will preclude participation in the study.

17. In the opinion of the investigator or Sponsor Clinician or Sponsor Medical Monitor, the participant is inappropriate for entry into this study.

5.3. Lifestyle Considerations

5.3.1. 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 acceptable 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 permitted 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.

5.3.2. Dietary Supplements

For the purposes of this protocol, dietary supplements are defined as vitamins, minerals, purified food substances, and herbals with pharmaceutical properties. Vitamins, minerals and purified food substances are allowed in amounts not known to be associated with adverse effects (such as hypervitaminosis). Herbals supplements are only allowed on a case by case basis; please contact the Pfizer staff. Herbals eg, St. John's Wort that are known to have an effect on drug metabolism must be discontinued at least 4 weeks or 5 half-lives (whichever is longer) before Day 1.

5.3.3. Medications/Treatments Discontinuation, Non-Medicated Emollients

Participants are required to discontinue and avoid using certain medications and treatments as described in Section 10.10 Appendix 10. Prohibited Prior and Concomitant Medications including medications which may result in Drug-Drug Interaction (DDI).

All topical medications and treatments that could affect atopic dermatitis and psoriasis skin areas must be discontinued for the duration of the study, if the skin areas are to be treated with IP.

Unless specified in Appendix 10, any other concomitant medication for AD or psoriasis will be considered on a case by case basis by the investigator in consultation with the Sponsor Medical Monitor.

Non-medicated emollient and sunscreen are the only topical products permitted to be used on AD and psoriasis skin during the Screening period. Participants will stop applying non-medicated emollient and sunscreen on atopic dermatitis/psoriatic skin 24 hours prior to Day 1/Randomization. During the study treatment period, use of non-medicated emollient and sunscreen are allowed only on skin that was considered normal or non-lesional at Day 1 (ie, never treated with IP). Any non-medicated emollient used by the participant during the study should be documented in study records and the Case Report Form (CRF).

Low or least potent (Class 6 or 7) topical corticosteroids (Hydrocortisone ≤1% and hydrocortisone acetate ≤1%) are the only topical corticosteroids permitted for the treatment of areas never treated with IP (eg, palms, soles, face, and intertriginous). Scalp tar preparations, salicylic acid preparations and shampoos free of corticosteroids are permitted for the treatment of scalp.

Due to the potential to affect atopic dermatitis and psoriasis with ultraviolet light exposure, participants must avoid prolonged exposure to the sun and avoid the use of tanning booths, sun lamps or other ultraviolet light sources during the study. Please see Appendix 10 for details on prohibited light therapy.

5.3.4. Other Lifestyle Requirements

- Participants should not apply occlusive dressing(s) to the areas treated with IP.
- Participants should not swim, bathe, be bathed or have treatment areas washed for at least 4 hours after application of the IP.
- Use of sunscreen and regular moisturizes is permitted, but only on areas which are not treated with IP.
- The participant should avoid wiping the IP off the skin and the IP should not be re-applied to areas that were inadvertently wiped until the next scheduled dose.
- Participants will agree to avoid strenuous exercise during the study, especially within 48 hours prior to the scheduled study visits and maintain adequate hydration, if possible.

- On study visit days, the participants will not smoke or use nicotine-containing products, or ingest caffeine (eg, tea, coffee, some soft drinks/colas/energy drinks and power bars) during the 2 hours prior to blood pressure and pulse (heart) rate measurements.

- On study visit days, showering or bathing is permitted prior to attending the study visit, but moisturizing will not be done.

- On study visit days, prescribed permitted concomitant medication will be taken, as needed, prior to the study visit, if it can be administered with water only.

- The participants will contact the study site investigator if there are any changes or additions to concomitant medications.

- The participants will avoid having major elective surgery until after the final study assessments.

- The participants should continue all non-pharmacological therapies, such as physical therapy, as indicated. However, the participants should avoid changing the type or intensity of therapy or initiating new therapy until after Week 6 visit.

- When applying the IP, the participant will not be required to wear gloves. However, participants should be instructed to wash their hands with mild soap and water before and after each application.

- If study participants need someone else to assist with applying investigational product on hard to reach areas (eg back), this person must wear gloves to avoid accidental exposure to the IP.

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. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened **once** if they fail the screening evaluation for reasons related to incidental transitory conditions, unless the reason for the screen failure is the disease severity inclusion criteria. Participants may not be rescreened unless approved by the sponsor. Rescreened participants should be assigned a new participant number.

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 (placebo).

6.1. Study Intervention Administered

Intervention Name	PF-07038124 0.01% ointment	PF-07038124 vehicle ointment
ARM Name (group of patients receiving a specific treatment (or no treatment)	Participants with mild or moderate AD, or mild or moderate psoriasis	Participants with mild or moderate AD, or mild or moderate psoriasis
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.

CCI [redacted]

6.1.1. Administration

6.1.1.1. Treatable Areas

AD treatable areas will be all areas affected by AD, except scalp.

Psoriasis treatable areas will be all areas affected by psoriasis, except scalp and nails.

A thin layer of IP ointment will be applied at a target application rate of approximately 3 mg/cm^2 by using a fingertip unit (FTU) method.

Day 1 Visit

At the Day 1 Visit, before the Day 1 initial IP application is performed, the designated areas for treatment will be identified and documented in the participant's source document study records (body map). The participant and/or caregiver will be provided with a paper version of the body map.

On Day 1 through the final dose at Week 6 visit, the IP should be applied once daily (around same time of the day), to all treatable AD or psoriasis involved areas identified at the Day 1 visit.

All participants will be supplied with instructions on application and dose frequency commensurate to assigned treatment arm. Those participants having difficulty reaching treatment-eligible areas (eg, back) may be assisted by another person who will need to apply the IP to the participant according to the investigational product application instructions. The person assisting with the application must wear gloves to avoid any exposure to the IP.

Participants and/or caregivers will be encouraged to observe and participate in the initial IP application on Day 1.

Post Day 1 Visits

After Day 1/Randomization, all subsequent doses will be applied at home except the dose on the days of in-clinic visits. CCI [redacted] The last dose of IP will be applied during the Week 6 in-clinic visit (EOT visit) as specified in Section 1.3.3 of the SoA.

The participant and/or caregiver will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1 through Week 6 (each time IP is applied) for all IP doses applied. If a participant misses applying a dose, the participant should apply this dose provided this dose should have been applied within the last 6 hours. For longer intervals, the dose should be skipped. The missed dose should be recorded in the dosing diary. The next dose should be applied according to the regular dosing regimen.

Treated area identified on Day 1 should be continued to be treated even if substantial improvement or clearing of AD or psoriasis occurs. The reason for maintaining IP treatment areas the same as identified at Day 1 is to understand the efficacy, systemic safety, and local tolerability of PF-07038124 ointment when applied to for 6 weeks in participants with mild or moderate AD or psoriasis.

Post Day 1, any new AD or psoriasis on treatment-eligible areas identified by the participant or caregiver(s) should also be treated with the IP. Decision to apply the IP to new eligible areas should be made following assessment by the Investigator or his/her designee. An unscheduled visit for assessment of the new lesion may be required at the discretion of the investigator. Body map will be updated, and IP need will be re-assessed at every site visit during the treatment period. If the total, treatable BSA exceeds 20% (AD) or 15% (psoriasis) during the six-week treatment period, the participant will still remain eligible for the study, given that the total, treatable BSA does not exceed 22% (for AD) or 16.5% (for psoriasis). If the total, treatable BSA exceeds 22% (AD) or 16.5% (psoriasis), the Sponsor may decide to discontinue the participant.

Participants and/or caregivers will be instructed not to wipe investigational product off the skin, avoid applying an occlusive dressing to the treated areas, and refrain from swimming or bathing/washing the treated areas within 4 hours after application.

Under no circumstances will the investigational drug application regimen be modified (eg, frequency of application increased or reduced, not stopped, or the application rate [target 3 mg/cm^2] increased or reduced) during the study. Temporary discontinuation of investigational drug may be appropriate under some circumstances (eg, surgery, non-serious infections) and should be discussed with the Medical Monitor (or designee) preferably prior to temporary discontinuation of investigational drug.

Study intervention administration details will be recorded on the CRF.

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. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

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

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

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the IP ready for application or dispensing to the participant/caregiver by qualified staff.

Dispensing is defined as the provision of IP, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

The IP will be dispensed in a blinded fashion using an interactive response technology (IRT) system at Day 1/Baseline, Week 1, Week 2 and Week 4 visits. A qualified staff member will dispense the IP via unique container numbers on the cartons provided, in quantities appropriate for the study visit schedule and the treatable % BSA.

For doses to be applied at home, the participant or caregiver should be instructed to maintain the product in its original package provided throughout the course of dosing and return the product and its original package (including empty, partial used and unused tubes) to the site at the next study visit.

IP will be assigned to participants at the Day 1 visit once the participant is successfully randomized through the IRT system. The investigator, appropriate delegate or site personnel will access the IRT system at screening and all subsequent IP dispensing visits to enter information including, but not limited to, the participants height, weight and % affected BSA to receive correct tube numbers to be dispensed to the participant. Alternatively, the tool to standardize the IP need calculation across participants and study sites may be provided by the sponsor.

The calculation of treatable BSA is described in Section 8.1.2.3 and Section 8.1.4.3 for AD and psoriasis respectively.

All tubes of investigational product dispensed or returned will be recorded and documented.

6.2.2. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the IP supplies. All investigational products will be accounted for using a drug accountability form/record. All tubes of the IP must be returned to the investigator by the participant at every visit and at the end of the trial.

The participant will be asked to bring all dispensed IP (including empty, partially used and unused tubes) at every 'compliance check' visit; participants will be asked to bring dosing diary to the clinic at every clinic visit. All previously dispensed IP tubes will be retained by the site. For each participant, IP tubes with caps will be weighed individually or collectively by the study site before dispensing and after return and the weights will be recorded. The sponsor will use the recorded weights to estimate usage (eg, mg/cm^2/application) for each participant. Note that the weight recorded on the IP label is a nominal weight and not an exact weight of the IP and tube. Detailed drug accountability records, including tube weights measured in the clinic, will be maintained by study staff for each participant.

The original IP accountability log, or equivalent document, must be accurately completed, signed by the Investigator, and retained at the study site (with a copy supplied to the Sponsor) when the study is complete.

6.2.3. Destruction of Investigational Product Supplies

For all IP returned to the investigator by the participant, the investigator will maintain the returned supply until destruction is authorized.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

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 visits summarized in the SoA.

Returned study intervention must not be redispensed to the participants.

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. However, discussion with the Sponsor in advance of unblinding is not required. 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 participant and/or a caregiver will apply IP at home or during in-clinic visits as specified in the SoA. The participant and/or caregiver will be instructed to complete the Dosing Diary starting with the first dose applied in the clinic on Day 1 through Week 6 (each time IP is applied) for the IP doses applied at home. Participants will be instructed to refrain from dosing at home on the day of the in-clinic visit, and are to bring to the clinic all used, partially used and empty IP tubes in their original containers for weighing, at each visit.

Participant compliance with IP will be assessed on visits identified in the SoA. Compliance will be assessed by review of the participant/caregiver completed Dosing Diary and by weighing of the returned IP tubes. The difference in weight(s) of the returned IP tubes will be used to estimate the doses applied. Source documents will be placed in the participant's study file. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

From Day 1 through Week 6 visit, non-compliance is defined as less than 80% or more than 120% of IP applications. If non-compliance is identified, or even if a few dose applications are missed or over-applied, then, participants will be re-trained on the importance and the process of proper IP application. If non-compliance persists, the investigator, in consultation with the Sponsor, may withdraw any participant from the study for reasons of non-compliance with the dosing regimen. Investigators should indicate on the appropriate CRF page noncompliance with study intervention and provide an explanation.

Inventory control of all IPs must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between drug dispensing records and the drug inventory must be reported to Pfizer.

6.5. Concomitant Therapy

All prior medications including non-medication therapies, as well as biologic drugs used for AD or psoriasis within 180 days prior to Screening will be recorded at the Screening Visit. Medications taken during Screening will be documented as prior medications. Medications taken after the first dose of study intervention has been administered will be documented as concomitant medications. All concomitant medications taken during the study must be recorded in study records with indication, daily dose, and start and stop dates of administration. Participants will be queried about concomitant medication (including topical medications and treatments, over the counter and prescription medications and treatments, and vaccinations) at each visit. Any new concomitant medications or dose changes to current concomitant medications should be evaluated for potential new or worsening AEs.

Refer to Appendix 10 for the list of prohibited concomitant medications and the timeframe for which they must be stopped.

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

Concomitant medications for other stable chronic medical conditions are permitted during the study unless the medication/therapy is specifically prohibited by the protocol or is expected to affect the study assessments. Nonsteroidal anti-inflammatory drugs are allowed throughout the study.

Routine preventative immunizations are permitted during the study; however, it is preferred that immunizations be administered at least 28 days before the start or following the completion of the subject's participation in study. Vaccines used in the event of a disease outbreak or pandemic are allowed.

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, pregnancy, 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 proceed to ET and remain in the study to be evaluated for follow up visits. 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. The site will inform the Sponsor Medical Monitor or Sponsor clinician if the below criteria for permanent discontinuation of the study intervention are triggered.

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.

Liver Injury

Please refer to Section 10.6 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: QTcF >60 msec.

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

Pregnancy

Pregnancy confirmed by serum β-hCG testing. Sponsor Clinician or Sponsor Medical Monitor should be notified immediately.

Two negative pregnancy tests are required before randomization (1 negative serum pregnancy test at screening and 1 negative urine pregnancy test at Day 1 visit). If urine pregnancy test is positive after study intervention application, serum pregnancy test will be conducted, study intervention application paused and sponsor clinician and sponsor medical monitor notified immediately.

Local Tolerability

If a participant experiences severity Grade 3 (severe) or 4 (very severe) on the local tolerability assessment (Section 8.2.7), study treatment will be discontinued permanently, and participant will proceed to ET visit and follow-up as described in SoA.

If a participant experiences application site reaction of Grade 2 (moderate) on the local tolerability assessment, investigator may temporarily discontinue application of IP for up to 48 hours without consulting the Sponsor. If in the clinical judgment of the investigator IP interruption beyond 48 hours is advisable, the investigator must obtain agreement from the Pfizer medical monitor to continue withholding IP. If temporary IP interruption for more than 5 consecutive days is needed, 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 investigational product, including contact urticaria, it must be discontinued immediately, and appropriate therapy initiated.

7.1.1. Temporary Discontinuation

Temporary discontinuations of IP

- Will occur in cases of positive urine pregnancy test which if confirmed by serum pregnancy test will lead to permanent discontinuation (Section 7.1).
- May apply in some cases application site reaction during local tolerability assessments (Section 8.2.7).
- Additional instances of temporary discontinuation may be appropriate (eg, surgery, infection, etc).

All temporary discontinuations should be discussed with Sponsor Clinician or Sponsor Medical Monitor to determine if participant may continue in the study. If possible, site will consult sponsor prior to temporary discontinuation.

7.1.2. Rechallenge

Not applicable.

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.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

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

The total blood sampling volume for individual participants in this study is approximately 185 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.

8.1. Efficacy Assessments

8.1.1. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Guide provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

EFFICACY ASSESSMENTS FOR AD

All efficacy assessments will be based on areas treated with IP, and excluding scalp, palms and soles from the assessment/scoring.

8.1.2. Physician Assessments for AD

8.1.2.1. Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a participant's AD based on both severity of lesion by clinical signs and the percent of BSA affected. EASI is a composite scoring of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.[8]

Lesion Severity by Clinical Signs

The basic characteristics of AD lesions (erythema, induration/papulation, excoriation, and lichenification) provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4-point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe. Morphologic descriptors for each clinical sign severity score are shown in Table 5 below.

Table 5. Clinical Sign Severity Scoring Criteria for EASI

Score		Description
Erythema (E)		
0	Absent	None; may have residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation)
1	Mild	Light pink to light red
2	Moderate	Red
3	Severe	Deep, dark red
Induration/Papulation (I)		
0	Absent	None
1	Mild	Barely palpable to slight, but definite hard thickened skin and/or papules
2	Moderate	Easily palpable moderate hard thickened skin and/or papules
3	Severe	Severe hard thickened skin and/or papules
Excoriation (Ex)		
0	Absent	None
1	Mild	Slight, but definite linear or picked scratch marks or penetrating surface injury
2	Moderate	Moderate linear or picked scratch marks or penetrating surface injury
3	Severe	Severe linear or picked scratch marks or penetrating surface injury
Lichenification (L)		
0	Absent	None
1	Mild	Barely perceptible to slight, but definite thickened skin, fine skin markings, and lichenoid scale
2	Moderate	Moderate thickened skin, coarse skin markings, and coarse lichenoid scale
3	Severe	Severe thickened skin with very coarse skin markings and lichenoid scale

* The EASI will exclude scalp, palms and soles from the assessment/scoring.

BSA with AD for EASI Assessment (excluding scalp, palms and soles)

BSA affected by AD should be calculated in each of the four body regions, ie, head and neck (h), upper extremities (u), trunk (t), and lower extremities (l). The area within each body region with the key signs of the disease is estimated using handprint as a measure, where the full palmar hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA.

Each region is typically assigned proportionate body surface areas of 10 (h), 20 (u), 30 (t), and 40 (l) handprints respectively. Refer to Table 6 to identify the surface area equivalent of 1 handprint in each respective body region.

Table 6. Handprint Determination of Body Region Surface Area for AD

Body Region	Total Number of Handprints in Body Region	Surface Area of Body Region Equivalent of One Handprint
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Area Score

The extent (%) to which each of the four body regions is involved with AD (by using Table 6 above) is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 7).

Table 7. EASI Area Score Criteria

Percent BSA with AD in a Body Region	Area Score
0%	0
>0-<10%	1
10-<30%	2
30-<50%	3
50-<70%	4
70-<90%	5
90-100%	6

Body Region Weighting

Each body region is weighted according to its approximate percentage of the whole body (Table 8).

Table 8. EASI Body Region Weighting

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin)	0.3
Lower Limbs (including buttocks)	0.4

Calculation of EASI Score

In each body region, the sum of the Clinical Signs Severity Scores for erythema, induration/papulation, excoriation, and lichenification is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all four body regions resulting in an EASI score as described in the following equation.

$$EASI = 0.1Ah(E_h+I_h+Ex_h+L_h) + 0.2Au(E_u+I_u+Ex_u+L_u) + 0.3At(E_t+I_t+Ex_t+L_t) + 0.4Al(E_l+I_l+Ex_l+L_l)$$

A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs.

The EASI score can vary in increments of 0.1 and range from 0.0 to 72.0, with higher scores representing greater severity of AD. Since the scalp, palms and soles will be excluded from the EASI assessment in this study (even if palms and soles are being treated with the IP), the maximum possible score will be less than 72.0.

8.1.2.2. Investigator's Global Assessment (IGA)

The IGA of AD is scored on a 5-point scale ranging from 0 (clear) to 4 (severe), reflecting a global consideration of the erythema, induration and scaling. The clinical evaluator of AD will perform an assessment of the overall severity of AD and assign an IGA score and category as described below. The assessment will be a static evaluation without regard to the score at a previous visit.

Table 9. Investigator's Global Assessment (IGA) Score

Score	Category	Description*
0	Clear	Atopic dermatitis (AD) is cleared, except for any residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Almost Clear	Overall, the AD is not entirely cleared and remaining lesions are light pink (not including post inflammatory hyperpigmentation) and/or; have barely palpable hard thickened skin and/or papules and/or; have barely perceptible lichenification; excoriation and oozing/crusting are absent.
2	Mild	Overall, the AD consists of lesions that are light red; with slight, but definite hard thickened skin and/or papules; with slight, but definite linear or picked scratch marks or penetrating surface injury; with slight, but definite thickened skin, fine skin markings, and lichenoid scale; oozing/crusting is absent.
3	Moderate	Overall, the AD consists of lesions that are red; with easily palpable moderate hard thickened skin and/or papules; with moderate linear or picked scratch marks or penetrating surface injury; with moderate thickened skin, coarse skin markings, and coarse lichenoid scale; with slight oozing/crusting.
4	Severe	Overall, the AD consists of lesions that are deep, dark red; with severe hard thickened skin and/or papules; with severe linear or picked scratch marks or penetrating surface injury; with severe thickened skin with very coarse skin markings and lichenoid scale; with moderate to severe oozing/crusting.

* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

8.1.2.3. BSA with AD

Assessment of BSA involved in AD is performed separately for four areas of the body: head (including neck), upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks). The percentage surface area affected by AD is estimated by means of the "handprint method", where the full hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA. Refer to Table 6 to identify the surface area equivalent of 1 handprint in each respective body region.

Body region value is then summed across all four body regions resulting in a total BSA with AD as described in the following equation:

$$BSA\ (\%) = 0.1Sh + 0.2Su + 0.3St + 0.4Sl$$

where S = body region surface area with AD; h = head & neck; u = upper limbs; t = trunk; l = lower limbs.

BSA with AD for Efficacy Assessment (Efficacy BSA)

BSA with AD for efficacy evaluation excludes scalp, palms, and soles.

BSA with AD for IP Need (Treatable BSA)

Evaluation of BSA for IP need is the total BSA across all body locations being treated with the IP. BSA for IP need evaluation method will be the same as the BSA with AD for efficacy assessment, except that the BSA for IP need will include AD on all IP treated body locations (including palms and soles but not scalp). If a participant has AD on palms, and/or soles, these body locations will be included in the BSA for IP need estimation.

Investigational product should be applied to the BSA determined at Day 1 throughout the treatment period regardless of clearing or improvement of AD. Any new AD on treatment-eligible locations occurring after Day 1 should also be treated with the IP. Therefore, the BSA for IP requirements at subsequent visits should be equal to or greater than the value at Day 1.

A checklist of body site areas currently affected by AD (body map) will be completed at the Day 1 visit. The body map will be reviewed at every visit to the site to update for any new, treatable areas, if needed.

8.1.3. Patient Reported Outcome Measures for AD

Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other evaluations. The amount of time required for participants to complete the PRO questionnaires is approximately 10-30 minutes (depending on the visit and associated PROs). The PROs should be checked for completeness by the study site staff at every in-clinic visit.

Participants will be provided a handheld device (provided by the Sponsor) for dosing diary and electronic patient-reported-outcomes (ePROs) or paper versions of the above to be completed at home as per the time points defined in the SoA. The clinic sites may use paper versions of PROs.

The following PROs will be completed only on study visit days identified in SoA, CCI [redacted]
PP-NRS will be used by participants for daily completion of PROs at home, starting from the screening visit or at least 7 days prior to the dosing/randomization day (Day 1) and as defined in the SoA.

All participants will complete PROs at follow-up visit in clinic.

Delegated site staff will monitor completion of PROs for adherence and will review adherence with participants at each visit and counsel as appropriate. If a participant has repeated non-adherence, the participant should be retrained on use of the device or filling out paper versions. If a participant is unable to complete ePROs due to documented technical issue or disability or other limitation, the participant will be permitted to enter or remain in the study providing that a valid alternate source of daily data entry is completed and reviewed by investigational site staff. No protocol deviations will be recorded in regard to PRO completion adherence. In the event of electronic malfunction of an ePRO or misplacement of paper versions of the PROs, a replacement device or paper PROs will be shipped to the site.

8.1.3.1. Peak Pruritus Numerical Rating Scale (PP-NRS) for AD

The PP-NRS is a daily patient-reported assessment of intensity of pruritus on an 11-point numerical rating scale, ranging from 0 ('No Itch) to 10 ('Worst Itch Imaginable') with a 24-hour recall period.[2] The PP-NRS will be completed once daily at least 7 days prior to Day 1, and completed once daily every day from Day 1 to Week 6 before IP dose is applied preferably at the same time of each day if applicable, as noted in the SoA. Note that PP-NRS will be assessed daily during the 7 days immediately preceding randomization and a minimum of 4 daily scores out of the 7 days prior to Day 1 is required to calculate the baseline average score.

CCI [redacted]

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[redacted]

EFFICACY ASSESSMENTS FOR PSORIASIS

All efficacy assessments of psoriatic skin will be based only on areas treated with IP and excluding scalp, palms, soles, nails from the assessment/scoring.

8.1.4. Physician Assessments for Psoriasis

8.1.4.1. Psoriasis Area and Severity Index (PASI)

PASI quantifies the severity of a participant's psoriasis based on both lesion severity and the percentage of body surface area affected.[11]

Lesion Severity Score

The basic characteristics of psoriatic lesions (erythema, induration and scaling) provide a means for assessing the severity of lesions. Assessment of these three main signs is performed separately for four areas of the body: head, upper limbs, trunk, and lower limbs. Average erythema, induration and scaling are rated for each body area according to a 5-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked. Appropriate morphologic descriptors for each severity score are shown in Table 10.

Table 10. Component Scoring Criteria for PASI*

Component Score		Description
Erythema (E)		
0	No involvement	None; may have residual hyperpigmentation
1	Slight	Pink or light red
2	Moderate	Darker pink-red
3	Marked	Red
4	Very Marked	Extremely red, "beefy" red
Induration (I)		
0	No involvement	None
1	Slight	Minimal elevation relative to normal surrounding skin
2	Moderate	Easily palpable with rounded edges
3	Marked	Elevated with hard, sharp borders
4	Very Marked	Very elevated with very hard, sharp borders
Scaling (S)		
0	No involvement	None
1	Slight	Mainly fine scale, some lesion partially covered
2	Moderate	Coarser thin scale, most lesions partially covered
3	Marked	Coarser thick scale, nearly all lesions covered, rough
4	Very Marked	Very thick scale, all lesions covered, very rough

* The PASI will exclude scalp, palms, soles, nails from the assessment/scoring.

BSA with Psoriasis for PASI Assessment (excluding scalp, palms, soles and nails)

BSA affected by psoriasis should be calculated in each of the four body regions ie, head and neck (h), upper extremities (u), trunk (t), and lower extremities (l). The area within each body region with the key signs of the disease is estimated using handprint as a measure, where the full palmar hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA.

Each region is typically assigned proportionate body surface areas of 10 (h), 20 (u), 30 (t), and 40 (l) handprints respectively. Refer to Table 11 to identify the surface area equivalent of 1 handprint in each respective body region.

Table 11. Handprint Determination of Body Region Surface Area for Psoriasis

Body Region	Total Number of Handprints in Body Region	Surface Area of Body Region Equivalent of One Handprint
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Area Score

The extent (%) to which each of the four body regions is involved with psoriasis (by using Table 11 above) is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 12).

Table 12. PASI Area Score Criteria

Percent BSA with psoriasis in a Body Region	Area Score
0%	0
>0-<10%	1
10-<30%	2
30-<50%	3
50-<70%	4
70-<90%	5
90-100%	6

Body Region Weighting

Each body region is weighted according to its approximate percentage of the whole body (Table 13).

Table 13. PASI Body Region Weighting

Body Region	Body Region Weighting
Head and Neck	0.1
Upper Limbs	0.2
Trunk (including axillae and groin)	0.3
Lower Limbs (including buttocks)	0.4

Calculating of PASI score

In each body region, the sum of the Severity Scores for erythema, induration and scaling is multiplied by the Area Score and by the Body Region Weighting to provide a body region value, which is then summed across all four body regions resulting in a PASI score as described in the following equation:

$$PASI = 0.1Ah(E_h+I_h+S_h) + 0.2Au(E_u+I_u+S_u) + 0.3At(E_t+I_t+S_t) + 0.4Al(E_l+I_l+S_l)$$

A = Area Score; E = erythema; I = induration/papulation; S=scaling; h = head and neck; u = upper limbs; t = trunk; l = lower limbs.

The PASI score can vary in increments of 0.1 and range from 0.0 to 72.0*, with higher scores representing greater severity of psoriasis.

*Since the scalp, palms, soles and nails will be excluded from the PASI assessment in this study (even if palms and soles are being treated with the IP), the maximum possible score will be less than 72.0.

8.1.4.2. Physician Global Assessment

The Physician Global Assessment (PGA) of psoriasis is scored on a descriptive 5-point scale.[12] The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe" (Table 14). The assessment will be a static evaluation without regard to the score at a previous visit.

Table 14. Physician Global Assessment (PGA) Score

Physician's Global Assessment		Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost Clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

8.1.4.3. BSA with Psoriasis

Assessment of body surface area (BSA) involved in psoriasis is performed separately for four areas of the body: head (including neck), upper limbs, trunk (including axillae and groin), and lower limbs (including buttocks). The percentage surface area affected by psoriasis is estimated by means of the "handprint method", where the full hand of the participant (ie, the participant's fully extended palm, fingers and thumb together) represents approximately 1% of the total BSA. Refer to Table 11 to identify the surface area equivalent of 1 handprint in each respective body region.

Body region value is then summed across all four body regions resulting in a total BSA with psoriasis as described in the following equation:

$$BSA\ (\%) = 0.1Sh + 0.2Su + 0.3St + 0.4Sl$$

where S = body region surface area with psoriasis; h = head & neck; u = upper limbs; t = trunk; l = lower limbs.

BSA with Psoriasis for Efficacy Assessment (Efficacy BSA)

BSA with psoriasis for efficacy evaluation excludes scalp, palms, soles, and nails.

BSA with Psoriasis for IP Need (Treatable BSA)

Evaluation of BSA for IP need is the total BSA across all body locations being treated with the IP. BSA for IP need evaluation method will be the same as the BSA with psoriasis for efficacy assessment, except that the BSA for IP need will include psoriasis on all IP treated body locations (including palms and soles but not scalp and nails). If a participant has

psoriasis on palms, and/or soles, these body locations will be included in the BSA for IP need estimation.

Investigational product should be applied to the BSA determined at Day 1 throughout the treatment period regardless of clearing or improvement of psoriasis. Any new psoriasis on treatment-eligible locations occurring following Day 1 should also be treated with the IP. Therefore, the BSA for IP need at subsequent visits should be equal to or greater than the value at Day 1.

A checklist of body site areas currently affected by psoriasis (body map) will be completed at the Day 1 visit. The body map will be reviewed at every visit to the site to update for any new, treatable areas, if needed.

8.1.5. Patient Reported Outcome Measures for Psoriasis

Every effort should be made for the participant to complete all patient reported outcome (PRO) questionnaires before any other evaluations. The amount of time required for participants to complete the PRO questionnaires is approximately 10-30 minutes (depending on the visit and associated PROs). The PROs should be checked for completeness by the study site staff at every in-clinic visit.

Participants will be provided a handheld device (provided by the Sponsor) for dosing diary and electronic patient-reported-outcomes (ePROs) or paper versions of the above to be completed at home as per the time points defined in SoA. The clinic sites may use paper versions of PROs.

The following PROs will be completed only on study visit days identified in SoA, CCI [redacted] PSI will be used by participants for daily completion of PROs at home, starting from the screening visit or at least 7 days prior to the dosing/randomization day (Day 1) and as defined in the SoA.

8.1.5.1. Psoriasis Symptom Inventory (PSI) for Psoriasis

PSI is a self-administered 8 item questionnaire that measures the severity of psoriasis symptoms over the past 24 hours and the past 7 days.[13] The PSI will be completed once daily at least 7 days prior to Day 1 using a recall period of 24 hours. For the first 2 weeks up to Week 2 visit (inclusive), the PSI will also be administered daily using a recall period of 24 hours. After Week 2 visit, the PSI will be administered according to the SoA using a recall period of past 7 days. The measure includes concepts of itch, pain, burning, stinging, cracking, scaling, flaking, and redness. Patients are asked to respond to each item using a 5-point Likert response scale: 0: not all severe, 1: mild, 2: moderate, 3: severe and 4: very severe.

CCI

[redacted]

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. Medical History

Investigators should make all reasonable efforts to obtain an accurate and complete medical history and history of prior medication use when evaluating whether a participant is eligible for the study. The following will be collected at Screening: complete medical history, AD or psoriasis disease history (including disease duration and prior treatments) and alcohol and tobacco use history.

Complete AD or psoriasis disease history includes collection of details of AD or psoriasis at Screening: AD or psoriasis diagnosis, the use of topical treatments, systemic treatments and other treatments for AD or psoriasis taken during the 180 days prior to Screening with dose, duration of treatment, and reason for discontinuation. All other drugs (including sunscreen, over the counter medication, vitamins, and dietary supplements) taken within 28 days prior to the Screening visit should be recorded.

Medical history in addition to AD or psoriasis history including disease duration will be collected at screening. Medical history also includes history of alcohol and tobacco use. Smoking status and average weekly alcohol consumption (units/week) will be collected, where a unit contains 12 g of pure alcohol, an amount equivalent to that contained in 5 oz/150 mL (a glass) of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of 90 proof of spirits.

If the status of a participant's medical history is in doubt or information pertaining to a critical variable is conflicting, every reasonable step to secure proper documentation of correct medical status should be attempted. Documentation of the medical and medication histories over the protocol defined time periods should be available for sponsor review during the source data verification process. Questions about prior medications or eligibility should be directed to the Sponsor Clinician or Sponsor Medical Monitor.

Medical History will be collected at the Screening visit, and reviewed at Baseline Day 1 visit of any changes.

8.2.2. Physical Examinations (Including Height and Weight)

Physical examinations, including complete physical examination, targeted physical examination, height and weight will be performed at times specified in the SoA.

Physical examinations must be performed by the investigator, sub-investigator, or a qualified healthcare professional per local guidelines. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A Complete physical examination will include, at a minimum, assessments of the general appearance, skin (presence of rash), HEENT (head, eyes, ears, nose and throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), abdomen (palpation and auscultation), musculoskeletal (presence of peripheral edema), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes.

A Targeted physical examination consists of skin, heart, lungs, abdomen, and examination of body systems where there are symptom complaints by the participants.

It is recommended that weight be measured in kilograms (kg) to the nearest 0.1 kg and that height be measured in centimeters (cm) with shoes removed.

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.

Please see Section 8.2.7 for skin Local Tolerability Assessment.

8.2.3. Vital Signs

Temperature (oral or tympanic temperature), pulse rate, and blood pressure will be assessed.

Blood pressure and pulse rate measurements will be assessed with the participant in a supine position using a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Assessment of vital signs should precede blood draw for clinical laboratory visits.

Body temperature will be collected using the tympanic or oral methods and the same method should be used consistently throughout the study.

8.2.4. 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.

During screening, if participants have initial screening value QTcF >450 milliseconds (ms), ECG should be repeated two more times and the average of the three QTcF should be used to determine the participant eligibility.

To ensure safety of the participant, a qualified individual (eg, sub-investigator) at the investigator site will make comparisons to baseline measurements taken at Day 1. In the event of marked prolongation of the QTcF interval to >500 msec or >60 msec change from baseline (Day 1), the ECG should be repeated two more times and the average of the three QTcF should be used to determine the discontinuation of study intervention (Section 7.1 Discontinuation of Study Intervention).

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.

8.2.5. 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 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

8.2.6. Suicidal Ideation and Behavior Risk Monitoring - Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[14] At the Screening visit, per Exclusion Criterion #2, if there is suicidal ideation associated with actual intent and/or plan in the past year, or previous history of suicidal behaviors in the past 5 years, the participant will not be included in the study. Trained site staff is to administer the C-SSRS to all participants at Screening and assess the participant's eligibility based on the answers.

For participants meeting exclusionary results of the C-SSRS, it is recommended that the participant's primary care physician (PCP) should be informed, and the participant referred to a mental health professional, either by the PCP or the investigator according to their usual practice.

8.2.7. Local Tolerability Assessment

The investigator or designee will assess tolerability at the site of IP application (pre-dose and immediately post-dose). CCI [redacted] All participant reported and observed application site AEs should be recorded along with the body region location, severity, duration and outcome as indicated on the CRF. See Section 7.1 for permanent and temporary discontinuation criteria based on local tolerability assessment.

CCI [redacted]

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Serum pregnancy tests are required at Screening visit only. 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.

Two negative pregnancy tests are required before randomization (1 negative serum pregnancy test at Screening and 1 negative urine pregnancy test at Day 1 visit).

If urine pregnancy test is positive after study intervention application, serum pregnancy test will be conducted, study intervention application paused and sponsor clinician and sponsor medical monitor notified immediately.

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, except as indicated below after the last administration of the study intervention or until study completion or withdrawal, whichever is longer.

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 AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

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 immediately **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 one dose within a 12-hour time period will be considered an overdose.

The maximum surface area of administration is 22% BSA for AD and 16.5% for psoriasis participants. Investigators should be aware that administration to significantly greater area may also be treated as an overdose at Investigator discretion.

The 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 28 calendar days after the overdose of study intervention.
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.**

CCI [redacted]

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.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[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. Estimands and Statistical Hypotheses

9.1.1. Estimands for AD

The primary estimand will be the population average treatment effect on percent change from baseline in EASI score relative to vehicle at 6 weeks in the absence of prohibited medication without regard to compliance. All observations after the initiation of prohibited medication will be set to missing. Missing data from all causes, including post-randomization prohibited medication use will be imputed in the PF-07038124 arms using a copy to control method (ie, missing data in 0.01% QD regimen will be imputed from the distribution of participants on QD vehicle). Participants with inadequate compliance will have their recorded EASI scores used as is in the analysis. The population-based treatment effect will be the differences in the mean change from baseline in treatment arm compared to the vehicle.

The secondary estimand will be the estimated population average treatment effect on the rates of IGA response (participants with a score of 0 or 1 and a 2 point or greater decrease from baseline) at Week 6 relative to vehicle without regard to compliance with IP in the absence of prohibited medication. This is a composite estimand where success is defined as achievement of an IGA response as defined above while remaining on study, providing data and not taking prohibited medication; lack of compliance or adverse events will not be counted as a failure. The population-based treatment effect will be the differences in the proportions of success in each treatment arm compared to the corresponding vehicle. EASI 75 and other EASI scores will be treated in a similar manner.

All other secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. CCI [redacted] Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the Statistical Analysis Plan (SAP).

9.1.2. Estimands for Psoriasis

The primary estimand will be the population average treatment effect on change from baseline in PASI scores at Week 6 relative to vehicle without regard to compliance in the absence of prohibited medication. Measurements after the initiation of prohibited medication will be censored and treated as missing data. Missing data due to censoring, study withdrawal or other reasons will have data imputed using a copy to control method (ie, missing data in 0.01% QD regimen will be imputed from the distribution of participants on QD vehicle) assuming these participants no longer receive an efficacy benefit from the IP but rather, have a response similar to participants assigned to vehicle. Participants with inadequate compliance will have their recorded PASI scores used as is in the analysis. The population-based treatment effect will be the differences in the mean change from baseline in each treatment arm compared to the corresponding vehicle.

The secondary estimand will be the population average treatment effect on the PGA response rate (percentage of participants with a score of clear (0) or almost clear (1) and ≥2 point improvement from baseline at Week 6 relative to vehicle without regard to compliance with IP in the absence of prohibited medication. This is a composite estimand where success is defined as achievement of a PGA response while remaining on study, providing data and not taking prohibited medication; lack of compliance or adverse events will not be counted as a failure. The population-based treatment effect will be the differences in the proportions of successes in each treatment arm compared to the corresponding vehicle.

All other key secondary continuous clinical endpoints will be analyzed using the primary estimand, while all other key secondary categorical clinical endpoints will be analyzed using the secondary estimand described above. cci [redacted] Other estimands may be used for some of the primary and secondary endpoints as a means to examine the robustness of the results and to compare to available literature as needed. Details of these analyses will be presented in the SAP.

9.2. Sample Size Determination

9.2.1. Sample Size Determination for AD

The sample size calculation is based on the primary endpoint (percentage change from baseline in EASI score at Week 6). A total of 56 randomized participants in 1 treatment group and 1 vehicle group (28/arm) will provide approximately 90% power to detect a difference of 50 in percentage change from baseline with a common standard deviation 48% between PF-07038124 and a vehicle arm, controlling the two-sided error rate alpha 0.05. These calculations allow for a 25% dropout rate leaving 42 evaluable participants (21/arm).

For the key secondary endpoint, IGA response rate of clear or almost clear and ≥2 points improvement at Week 6, assuming 20% rate for vehicle and 55% rate for the treatment, this sample size provides 66% power controlling the two-sided error rate alpha 0.05.

9.2.2. Sample Size Determination for Psoriasis

The sample size is based on the primary efficacy endpoint, PASI change from baseline at Week 6. With an assumed standard deviation of 4.2 and treatment difference of 4.5, a total of 32 randomized participants in 2 treatment groups (16/arm) will provide approximately 80% power for the comparison of active versus vehicle group at a two-sided significance of 0.1. This calculation allows for an approximate 25% dropout rate, that is 12 participants evaluable per arm at Week 6, where evaluable is defined as included in the mITT set (defined in Section 9.3).

For the key secondary endpoint, PGA response rate of clear or almost clear and ≥2 points improvement at Week 6, assuming 20% rate for vehicle and 65% rate for the treatment, this sample size provides 61.9% power controlling the two-sided error rate alpha 0.05.

9.3. Analysis Sets

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

Population	Description
Safety Analysis Set	All participants randomly assigned to IP and who apply at least 1 dose of IP. Participants will be analyzed according to the product they actually have received.

Defined Population for Analysis	Description
Modified Intention to Treat (mITT)	All participants randomly assigned to IP and who apply at least 1 dose of IP.

CCI

[redacted]

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. Efficacy Analyses for AD

Endpoint	Statistical Analysis Methods
Primary: Percent Change from Baseline EASI at Week 6	A landmark analysis using analysis of covariance of percent change from baseline in EASI, adjusting for the baseline EASI score, to estimate the effect of the initially randomized treatment in the absence of prohibited medication regardless of treatment compliance. The analysis will use the mITT analysis set. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding vehicle arm, missing data in a vehicle arm will be imputed using data from the vehicle arm assuming data are missing at random (MAR). The analysis will combine the results from the multiple imputations using Rubin's rule as implemented in SAS PROC MIANALYZE.
Secondary: IGA Response at Week 6	A landmark analysis of the composite endpoint; achieving IGA without prohibited medication, while remaining on study and providing data. The analysis will use the mITT analysis set. Based on the definition of the composite endpoint all participants in the mITT set will have a response for all visits (ie, there is no missing data). The proportions responding and

Endpoint	Statistical Analysis Methods
	the corresponding risk difference comparing active treatment arm to vehicle group will be analyzed using the unconditional exact method; the risk differences and the corresponding 2-sided unconditional exact 90% confidence intervals will be computed using Chan and Zhang (1999)[16] method.

CCI [redacted]

Other continuous secondary endpoints at time points specified in the SoA including change from baseline EASI, will be analyzed as described for the primary estimand along with descriptive statistics and possibly graphical displays.

Other binary secondary endpoints at time points specified in the SoA including, CCI [redacted] EASI 75, CCI [redacted] IGA of clear or almost clear will be analyzed as described for the secondary estimand along with descriptive statistics and possibly graphical displays.

CCI [redacted]

9.4.2. Efficacy Analyses for Psoriasis

Endpoint	Statistical Analysis Methods
Primary: Change from Baseline PASI at Week 6	A landmark analysis using analysis of covariance of change from baseline PASI, adjusting for the baseline PASI score, to estimate the effect of the initially randomized treatment in the absence of prohibited medication regardless of treatment compliance. The analysis will use the mITT analysis set. Missing data due to any cause including censoring due to initiation of prohibited medication will be imputed using the corresponding vehicle arm, missing data in a vehicle arm will be imputed using data from the vehicle arm assuming data are missing at random (MAR). The analysis will combine the results from the multiple imputations using Rubin's rule as implemented in SAS PROC MIANALYZE.
Secondary: PGA Response at Week 6	A landmark analysis of the composite endpoint; achieving a PGA response (a score of clear (0) or almost clear (1) and ≥2 point improvement from baseline) without prohibited medication, while remaining on study and providing data. The analysis will use the mITT analysis set. Based on the definition of the composite endpoint all participants in the mITT set will have a response for all visits (ie, there is no missing data). The proportions responding and the risk difference between treated arms and their corresponding vehicle control arm will be analyzed using an unconditional exact method: risk differences and corresponding 2-sided unconditional exact 90% confidence intervals will be computed using the

Endpoint	Statistical Analysis Methods
	Chan and Zhang (1999)[16] method.
CCI [redacted]	

Other continuous secondary endpoints at time points specified in the SoA including: absolute PASI, change from baseline PASI, percent change from baseline PASI, absolute and change from baseline Itch Severity Score, absolute and change from baseline Psoriasis Symptom Inventory will be analyzed as described for the primary estimand along with descriptive statistics and possibly graphical displays.

Other binary secondary endpoints at time points specified in the SoA including, CCI [redacted] PASI 75, CCI [redacted] PGA of clear or almost clear will be analyzed as described for the secondary estimand along with descriptive statistics and possibly graphical displays.

CCI [redacted]

9.4.3. Safety Analyses

All safety analyses will be performed on the safety population.

Endpoint	Statistical Analysis Methods
Primary	The safety data will be summarized in accordance with Pfizer Data Standards. All participants who receive IP (safety population) will be included in the safety analyses. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include: Treatment-emergent AEs and SAEs; Withdrawals from active treatment due to AEs; Serious infections, defined as any infection (viral, bacterial, and fungal) requiring hospitalization or parenteral antimicrobials; Safety laboratory tests (eg, hematology [including coagulation panel], chemistry and lipid profiles); Vital signs. Change from baseline on laboratory data and vital signs will be additionally summarized. Participant listings will also be produced for these safety endpoints.
CCI [redacted]	

9.4.3.1. Electrocardiogram Analyses

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

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

Safety QTc Assessment

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

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

CCI

[redacted]

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 Data Monitoring Committee (DMC).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and 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 investigator and reviewed and approved by the IRB/EC before the study is initiated.

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 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

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

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. 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 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.

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

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

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

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

10.1.7. Source Documents

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

Data reported on the CRF or entered in the 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 study team on demand (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. 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 16. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count and indices (MCV, MCH MCHC, RBC Morphology) Reticulocytes count WBC count with differential Neutrophils (%, Abs) Eosinophils (%, Abs) Monocytes (%, Abs) Basophils (%, Abs) Lymphocytes (%, Abs) Platelet count	BUN/urea Creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) Alanine transaminase (ALT) Aspartate transaminase (AST) Total bilirubin Direct bilirubin [a] Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy [b]	FSH[c, e] Pregnancy test (β-hCG)[d] Fibrinogen High-sensitivity C-reactive protein (hsCRP)

a. Only if total bilirubin is elevated.
b. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
c. For confirmation of postmenopausal status, in females who are amenorrheic for at least 12 consecutive months.
d. Serum or urine β-hCG for female participants of childbearing potential per SoA. Serum pregnancy test must be performed at Screening.
e. At Screening only.

Investigators must document their review of each laboratory safety report.

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

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 adverse events (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	**None** 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.
- 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 of age 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).

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

Potential Cases of Drug-Induced Liver Injury

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

- 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 May Qualify as Serious Adverse Events

- 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 patients 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 patients 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 Serious Adverse Events

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

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

10.8. Appendix 8: Country-Specific Requirements

Not applicable.

10.9. Appendix 9: Alternative Measures During Public Emergencies

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

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

10.9.1. Telehealth Visits

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

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.9.2.1 of this appendix regarding pregnancy tests.
- Local Tolerability Assessments.
- Efficacy Assessments (See Section 10.9.6).

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

10.9.2. Alternative Facilities for Safety Assessments

10.9.2.1. Laboratory Testing

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

- List safety laboratory evaluations, including pregnancy testing (See Table 16 Protocol Required Safety Laboratory Assessments).

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

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

10.9.2.2. Electrocardiograms

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

A copy of the ECG should be available as source documents for review.

10.9.3. Study Intervention

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

In situations where participants are quarantined or self-isolating, arrangements to send study intervention via courier may be implemented where allowable by national law or by local guidance and with the participant's verbal consent documented on the Provision of Critical Study Information Form (if applicable). The decision to supply requires the investigator to obtain and evaluate protocol-specified safety laboratory tests, pregnancy tests (for female subjects of childbearing potential), ECGs, contraception, concomitant treatment, and adverse events.

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

10.9.4. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. Home health visits may be implemented if it is not possible for participants to attend a study visits at the site and where allowable by national law or by local guidance. The following may be performed during a home health visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.9.2.1 of this appendix regarding pregnancy tests.
- ECG.
- Vital signs.
- Physical assessment.
- Laboratory sample, CCI [redacted]
- Collect and weigh previous IP tubes.
- Dispensing of IP.
- IP application and observation.
- Local Tolerability Assessments.

10.9.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

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

10.9.6. Efficacy Assessments

If remote video visit is feasible and is being conducted as part of the Telehealth Visit in the event that in-clinic study visits cannot be conducted, the following procedures and assessments may be considered:

- Efficacy Assessments for AD, including EASI, IGA, and BSA.
- Efficacy Assessments for psoriasis, including PASI, PGA and BSA.

Only qualified raters will be allowed to evaluate participants remotely.

10.9.7. Independent Oversight Committees

Not applicable.

10.10. Appendix 10: Prohibited Prior and Concomitant Medications

10.10.1. Prohibited Prior and Concomitant Medications

Drug Category	Drugs (Examples below)	Required Washout Period Requirement Prior to Day 1/Randomization
Any cell depleting agents	rituximab or other selective B-lymphocyte depleting agents (including experimental agents), alemtuzumab (Lemtrada® or CamPath®), alkylating agents (eg, cyclophosphamide or chlorambucil), total lymphoid irradiation, etc.	6 months or 5 half-lives (if known), whichever is longer, or until lymphocyte count returns to normal, whichever is longer.
IL-17 inhibitor, IL-12/23 inhibitor, or IL-23 inhibitor	secukinumab (Cosentyx®), ixekizumab (Taltz®), ustekinumab (Stelara®), brodalumab (Siliq®), guselkumab (Tremfya®), risankizumab (Skyrizi®), tildrakizumab (Ilumya®), and bimekizumab,	12 weeks.
TNF inhibitor	adalimumab (Humira® or biosimilars), certolizumab (Cimzia®), golimumab (Simponi® and Simponi Aria®).	10 weeks or 5 half-lives (whichever is longer) (Note: Infliximab (Remicade® or biosimilars) 8 weeks, Etanercept (Enbrel® or biosimilars) 4 weeks).
Other biologics	dupilumab (Dupixent®), efalizumab (Raptiva®), abatacept (Orencia®).	12 weeks unless otherwise specified in this table.
Topical PDE4 inhibitors (anywhere on the body), oral PDE4 inhibitors	crisaborole (Eucrisa®), roflumilast (Daliresp®, ARQ-151), apremilast (Otezla®).	6 weeks.
Systemic corticosteroids (oral, parenteral)		4 weeks (stable use /regular regimen of intranasal/inhaled/ophthalmic corticosteroids with ≥14 days of consistent use prior to Day 1/Randomization are permitted to continue but must not alter or stop regimen during the study).
Systemic immunosuppressive agents and other oral nonbiologic treatments	methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, mizoribine, tacrolimus, mycophenolate mofetil (MMF), hydroxycarbamide (hydroxyurea), fumaric acid derivatives, acitretin.	4 weeks.
Oral JAK inhibitors	tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib, peficitinib, filgotinib.	4 weeks.

Drug Category	Drugs (Examples below)	Required Washout Period Requirement Prior to Day 1/Randomization
Interferon gamma	interferon gamma-1b (Actimmune®).	4 weeks.
Light therapy etc.	sunbathing, tanning bed use, or light therapy ultraviolet (UV), ultraviolet B (UV-B), psoralen-UV-A [PUVA]), excimer laser (308 nm).	4 weeks.
Topical retinoids, Vitamin D analogues, benzoyl peroxide (BPO), anthralin (dithranol), keratolytics (salicylic acid), tars, on study treatable lesions	tazarotene, calcipotriene.	2 weeks (stable regimen with ≥14 days of consistent use prior to Day 1/Randomization and not on the study treatable lesions are permitted to continue but must not alter or stop their regimen during the study.
Systemic antibiotics		2 weeks (Short courses (≤14 days) of systemic antibiotics may be given during the study if clinically necessary for the treatment of new onset infections).
Topical corticosteroids (TCS), class I to V, anywhere on the body	betamethasone, clobetasol, diflorasone, halobetasol, amcinonide, desoximetasone, fluocinonide, halcinonide, mometasone, triamcinolone, clocortolone, flurandrenolide, fluticasone, fluocinolone, prednicarbate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone valerate.	2 weeks.
Topical calcineurin inhibitor (TCI), anywhere on the body	topical tacrolimus (Protopic®), topical pimecrolimus (Elidel®).	2 weeks.
Topical antihistamines anywhere on the body	doxepin.	2 weeks (topical antihistamines for seasonal allergies are allowed provided stable doses within 7 days of Day 1/Randomization).
Topical antibacterial medications or products, including soaps, bleach baths, or topical sodium hypochlorite-based products anywhere on the body		7 days.
Systemic sedating antihistamines	hydroxyzine, diphenhydramine,	7 days,

Drug Category	Drugs (Examples below)	Required Washout Period Requirement Prior to Day 1/Randomization
Systemic non-sedating antihistamines in a nonstable (eg, escalating, decreasing, or PRN) regimen	cetirizine,	7 days (stable non-sedating systemic antihistamine regimen with ≥7 days of consistent use prior to Day 1/Randomization are permitted to continue but must not alter or stop their regimen during the study).
Use of bland (non-medicated) emollients on treatable lesions		24 hours (After the Day 1/Randomization Visit, use of bland (non-medicated) emollient(s) is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable lesions).
Any other biologic investigational therapy for AD, psoriasis or psoriatic arthritis		6 months unless otherwise specified in this table.
Any other non-biological investigational therapy or procedure for AD, psoriasis or psoriatic arthritis		12 weeks unless otherwise specified in this table.
Prohibited Concomitant Medications which may result in drug-drug interaction	See Section 10.10.2 below.	7 days or 5 half-lives (whichever is longer).

10.10.2. Prohibited Concomitant Medications which may result in Drug-Drug Interaction (DDI)

Upon topical application of PF-07038124, systemic exposure to date has been low. Maximum plasma concentration has not exceeded 1 nM; which is approximately 1000-fold less than the IC_{50} values for CYP450 and UGT inhibition, as well as various transporters. Therefore, PF-07038124 has a low risk of any drug-drug interaction. For more details, please refer to the Investigator's Brochure.

10.11. Appendix 11: Diagnosis Criteria for AD

Per AD Specific Inclusion Criteria, a participant is to have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka.

Hanifin and Rajka's Diagnostic Criteria for AD

Major Criteria (must have at least three)
Pruritus
Typical morphology and distribution:
Flexural lichenification in adults
Facial and extensor eruptions in infants and children
Chronic or chronically-relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinitis, AD)
Minor Criteria (must have at least three)
Xerosis
Ichthyosis/keratosis pilaris/palmar hyperlinearity
Immediate (type 1) skin test reaction
Elevated serum IgE
Early age of onset
Tendency toward cutaneous infections (esp. staph. aureus and herpes simplex), impaired cell-mediated immunity
Tendency toward non-specific hand or foot dermatitis
Nipple eczema
Cheilitis
Recurrent conjunctivitis
Dennie-Morgan infraorbital fold
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor, facial erythema
Pityriasis alba
Anterior neck folds
Itch when sweating
Intolerance to wool and lipid solvents
Periofollicular accentuation
Food intolerance
Course influenced by environmental and emotional factors
White dermographism, delayed blanch

Hanifin J, Rajka G. Diagnostic features of atopic dermatitis Acta Derm Venereol. 1980;92:44.[7]

10.12. Appendix 12: 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
AV	Atrioventricular
β-hCG	Beta-Human Chorionic Gonadotropin
BID	Twice Daily
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
bpm	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
cAMP	Cyclic Adenosine Monophosphate
C_{av}	Average Concentrations
CCI	[redacted]
CFR	Code of Federal Regulations
cGMP	Cyclic Guanosine Monophosphate
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
C_{max}	Peak Plasma Concentrations
CO_2	Carbon Dioxide (Bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	Clinical Trial
DCT	Data Collection Tool
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
CCI	[redacted]
DMC	Data Monitoring Committee
CCI	[redacted]
DU	Dispensable Unit
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram

Abbreviation	Term
eCRF	Electronic Case Report Form
EDP	Exposure During Pregnancy
EFD	Embryo-Fetal Development
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient-Reported Outcomes
ET	Early Termination
EU	European Union
EudraCT	European Clinical Trials Database
FIH	First-in-Human
FSH	Follicle-Stimulating Hormone
FTU	Fingertip Unit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HEENT	Head, Eyes, Ears, Nose and Throat
HIPAA	Health Insurance Portability and Accountability Act
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
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRC	Internal Review Committee
IRT	Interactive Response Technology
IWR	Interactive Web-Based Response
JAK	Janus Kinase
LBBB	Left Bundle Branch Block
LFT	Liver Function Test
MCH	Mean Corpuscular Hemoglobin

Abbreviation	Term
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mITT	Modified Intention to Treat
MMF	Mycophenolate Mofetil
MRHD	Maximum Recommended Human Dose
msec	Millisecond
N/A	Not Applicable
NIMP	Noninvestigational Medicinal Product
NOAEL	No-Observed-Adverse-Effect Level
NOEL	No Observed Effect Level
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamic(S)
PDE	Phosphodiesterase
PDE4	phosphodiesterase 4
PFS	Prefilled Syringe
PGA	Physician Global Assessment
CCI [redacted]	[redacted]
PK	Pharmacokinetic(S)
CCI [redacted]	[redacted]
PP-NRS	Peak Pruritus Numerical Rating Scale
PRO	Patient Reported Outcomes
PSI	Psoriasis Symptom Inventory
PUVA	Psoralen – Ultraviolet A
PVC	Premature Ventricular Contraction/Complex
QD	Once Daily
QoL	Quality of Life
QTc	Corrected QT
QTcF	QTc Corrected Using Fridericia's Formula
Qual	Qualitative
R_{ac}	Accumulation Ratio
RBC	Red Blood Cell
CCI [redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
SToD	Study Team on Demand
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	terminal half-life

Abbreviation	Term
CCI	[redacted]
TBili	Total Bilirubin
TCI	Topical Calcineurin Inhibitor
TCS	Topical Corticosteroids
Th2	T-Helper 2 Cells
TNF	Tumor Necrosis Factor
uCav	Unbound Average Concentrations
ULN	Upper Limit of Normal
US	United States
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non-Childbearing Potential

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