A PHASE 2B, RANDOMIZED, DOUBLE BLIND, VEHICLE CONTROLLED, PARALLEL GROUP STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF MULTIPLE DOSE LEVELS OF PF-07038124 OINTMENT FOR 12 WEEKS IN PARTICIPANTS 12 YEARS AND OLDER AND WITH MILD-TO-MODERATE ATOPIC DERMATITIS OR MILD-TO-SEVERE PLAQUE PSORIASIS

Study Intervention Number:	PF-07038124
Study Intervention Name:	N/A
US IND Number:	144217
EudraCT Number:	N/A
ClinicalTrials.gov ID:	NCT05375955
Protocol Number:	C3941005
Phase:	2b

Brief Title: A Phase 2b Efficacy, Safety, Tolerability and Pharmacokinetics Study with Multiple Dose Levels of PF-07038124 Ointment in Participants 12 Years and Older and With Mild to Moderate Atopic Dermatitis or Mild to Severe Plaque Psoriasis

Document History

Document	Version Date
Amendment 1	02 November 2022
Original protocol	21 April 2022

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

Protocol Amendment Summary of Changes Table

Amendment 1 (02 November 2022)

Overall Rationale for the Amendment: The amendment is making a substantial change in permitted contraception methods of female participants.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 10.4.2 Female Participant Reproductive Inclusion Criteria	1. Added requirement of concurrent use of a barrier method when highly effective contraception methods that are user-dependent are used.	Concurrent use of a barrier method of contraception provides additional protection with highly effective user dependent methods as required per Section 4.2.2.	Substantial
Section 10.4.4 Contraception Methods	1. Modified list of highly effective contraception methods by adding "+ barrier" to methods which were user dependent. 2. Highlighted acceptable use of barrier methods. 3. Deleted list of methods (#9 -#12) to avoid those being considered as highly effective, when not used in conjunction with other methods.	Concurrent use of a barrier method of contraception provides additional protection with highly effective user dependent methods.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Title Page	Added clinicaltrials.gov ID	Availability of ID as trial is registered on clinicaltrials.gov.	Nonsubstantial
Section 1.3.1 Atopic Dermatitis, Footnote 'j' Section 1.3.2. Plaque Psoriasis Footnote 'i'	Updated footnotes in SoA tables to clarify that if a participant hasn't withdrawn consent from participation from the study, e-diary may be collected at ET or EOS visits.	Clarification provides sites with option of not collecting e-diary if storage space at the site is limited, thereby reducing burden.	Nonsubstantial
Section 1.3.1 Atopic Dermatitis, Footnote 'k' Section 1.3.2. Plaque Psoriasis, Footnote 'j'	Updated footnotes in SoA tables to clarify instance when local tolerability assessment is not required.	Local tolerability assessment performed immediately after application of the IP on non-lesional skin and prior to application on lesional skin. Therefore, if IP application is not planned, local tolerability assessment is not required.	Nonsubstantial
Section 10.4.3. Women of Childbearing Potential	Added note to allow FSH testing for women over 60 years of age, per PI discretion.	Although not anticipated, on rare occasions, based on the medical and medication history of a female participant, PI may deem it necessary to confirm post-menopausal status using FSH levels.	Nonsubstantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title:

A Phase 2b efficacy, safety, tolerability and pharmacokinetics study with multiple dose levels of PF-07038124 ointment in participants 12 years and older and with mild-to-moderate atopic dermatitis or mild-to-severe plaque psoriasis.

Rationale

This multicenter, randomized, double blind, vehicle controlled, parallel group study is being conducted to assess efficacy, safety, tolerability and PK of PF-07038124 ointment versus vehicle control in the treatment of participants 12 years and older, and with mild-to-moderate AD or mild-to-severe PsO.

Objectives, Endpoints, and Estimands

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA success as the 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 12.	• Estimand E1: the difference in proportions of the binary endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle using EASI-75 as an endpoint in participants with mild or moderate AD.	• Proportion of participants achieving EASI-75 (75% improvement from baseline) at all study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA success as the 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 all study visit time points specified in the SoA, except at Week 12.	• Estimand E1 described above.

• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using percent CFB in EASI as the endpoint in participants with mild or moderate AD.	• Percent CFB in EASI total score at all study visit time points specified in the SoA.	• Estimand E2: the difference in mean of the continuous endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA clear or almost clear as the endpoint in participants with mild or moderate AD.	• Proportion of participants achieving IGA score of clear (0) or almost clear (1) at all study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using measures of PP-NRS PRO, in participants with mild or moderate AD.	• Proportion of participants having ≥4 points of reduction from baseline in weekly averages of PP-NRS at study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using BSA as the endpoint in participants with mild or moderate AD.	• Percent CFB in affected BSA at all study visit time points specified in the SoA.	• Estimand E2 described above.
• To characterize the safety and tolerability of 2 dose levels of PF-07038124 ointment versus vehicle in participants with mild or moderate AD.	• Incidence of treatment emergent AEs and serious adverse events SAEs, clinically significant changes in vital signs, ECG, and laboratory tests. • Incidence of increase in local tolerability severity grades at times indicated in the SoA.	• Not Applicable.
Complete list of Exploratory/Tertiary Objectives and Endpoints are in Section 3.		

PLAQUE PSORIASIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA success as the endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12.	Estimand E1: the difference in proportions of the binary endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild-to-severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle using PASI-75 as an endpoint, in participants with mild-to-severe PsO.	• Proportion of participants achieving PASI-75 (75% improvement from baseline) at times indicated in the SoA.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA success as the endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at times indicated in the SoA, except at Week 12.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using CFB PASI as the endpoint in participants with mild-to-severe PsO.	• Change from baseline in PASI at times indicated in the SoA.	Estimand E2: the difference in mean of the continuous endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild-to-severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA clear or almost clear as the endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) at all study visit time points specified in the SoA.	• Estimand E1 described above.

• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using measures of PP-NRS PRO, in adult participants (18–75 years old) with mild-to-severe PsO.	• Proportion of adult participants (18–75 years old) having ≥4 points of reduction from baseline in weekly averages of PP-NRS at study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using BSA as the endpoint in participants with mild-to-severe PsO.	• Percent CFB in affected BSA at all study visit time points specified in the SoA.	• Estimand E2 described above.
• To characterize the safety and tolerability of multiple dose levels of PF-07038124 ointment versus vehicle in participants with mild-to-severe PsO.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests. • Incidence of increase in local tolerability severity grades at times indicated in the SoA.	• Not Applicable
Complete list of Exploratory/Tertiary Objectives and Endpoints are in Section 3.		

Overall Design

Brief Summary

This is a multicenter, Phase 2b, randomized, double-blind, vehicle-controlled, parallel-group study and will assess efficacy, safety, tolerability, and PK of multiple doses of PF-07038124 ointment in the treatment of mild-to-moderate AD and mild-to-severe PsO.

Participants will be screened within 4 weeks prior to the Day 1 application of study intervention to confirm they meet the selection criteria for the study. The treatment period will be once-daily application of PF-07038124 ointment or vehicle ointment for 12 weeks, with a follow-up period of 4 to 5 weeks.

There will be 2 sub-studies: Tape stripping and Photography. These sub-studies will be conducted at selected sites and optional for participants.

Number of Participants

A total of approximately 240 participants with AD or PsO will be randomly assigned to study intervention (PF-07308124 or vehicle).

- For AD, approximately 120 participants will be randomly assigned 1:1:1 to receive either 0.01% PF-07038124 ointment, 0.03% PF-07038124 ointment or a vehicle ointment.

- For PsO, approximately 120 participants will be randomly assigned 1:1:1:1 to receive either 0.01% PF-07038124 ointment, 0.03% PF-07038124 ointment, 0.06% PF-07038124 or a vehicle ointment.

Intervention Groups and Duration

Participant Population	Study Intervention	Approximate Number of Participants Randomized
AD	0.01% PF-07038124	40
	0.03% PF-07038124	40
	Vehicle	40
PsO	0.01% PF-07038124	30
	0.03% PF-07038124	30
	0.06% PF-07038124	30
	Vehicle	30

Data Monitoring Committee or Other Independent Oversight Committee:

An independent, internal review committee will be used to review efficacy, safety and tolerability data as described in Section 10.1.5.1.

Statistical Methods

AD:

The primary estimand will be the difference in proportions of the binary endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.

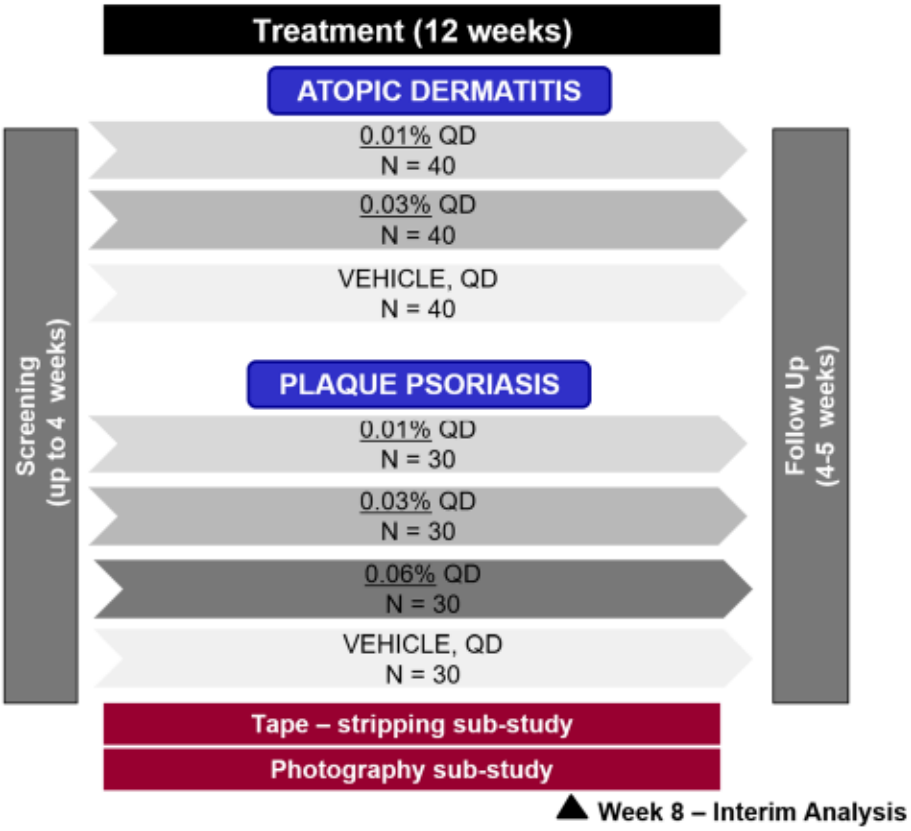
The secondary estimand will be the difference in mean of the continuous endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.

PsO:

The primary estimand will be the difference in proportions of the binary endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild, moderate, or severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.

The secondary estimand will be the difference in mean of the continuous endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild, moderate, or severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.

1.2. Schema



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] Abbreviations used in this table may be found in Appendix 13	Screening	Treatment Phase *All assessments/procedures are pre-dose, unless otherwise stated*								Follow-Up (EOS)	ET
		Day 1 (Baseline)	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (EOT)		
Visit Window	Day -28 to -1	N/A	Day 8 ±2	Day 15 ±2	Day 29 ±2	Day 43 ±2	Day 57 ±2	Day 71 ±2	Day 85 ±2	28–35 days post-last dose	NA
Visit Number	1	2	3	4	5	6	7	8	9	10	NA
Enrollment Procedures											
Informed consent/assent	X										
General medical and AD history	X	X									
Medication history	X	X									
Demography	X										
Eligibility assessment	X	X[b]									
Weight	X	X									
Height	X										
Clinical Assessments											
Physical examination[c]	X	X		X		X			X		X
ECG	X	X							X		X
Vital signs	X	X							X		X
C-SSRS[d]	X										

Atopic Dermatitis											
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13	**Screening**	**Treatment Phase** *All assessments/procedures are pre-dose, unless otherwise stated*								**Follow-Up (EOS)**	**ET**
		Day 1 (Baseline)	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 (EOT)**		
Visit Window	**Day -28 to -1**	**N/A**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**Day 57 ±2**	**Day 71 ±2**	**Day 85 ±2**	**28–35 days post-last dose**	**NA**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**NA**
AD-Related Clinical Assessments											
IGA	X	X	X	X	X	X	X	X	X	X	X
EASI		X	X	X	X	X	X	X	X	X	X
CCI											
BSA	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments											
Hematology, Chemistry and Urinalysis	X	X		X		X			X		X
Serum FSH (WONCBP only)	X										
Serum Pregnancy Test (WOCBP only)	X										
Urine Pregnancy test[f]		X	X	X	X	X	X	X	X	X	X
Pharmacokinetics											
CCI											
Biomarker Assessments											
CCI											
Retained Research Samples											
CCI											
Prep B1.5 (plasma)		X				X			X		X
Prep B2.5 (serum)		X				X			X		X
e-Diary											
Dispense e-diary and instruct on usage	X										

Atopic Dermatitis

Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13	Screening	Treatment Phase *All assessments/procedures are pre-dose, unless otherwise stated*								Follow-Up (EOS)	ET
		Day 1 (Baseline)	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (EOT)		
Visit Window	Day -28 to -1	N/A	Day 8 ±2	Day 15 ±2	Day 29 ±2	Day 43 ±2	Day 57 ±2	Day 71 ±2	Day 85 ±2	28–35 days post-last dose	NA
Visit Number	1	2	3	4	5	6	7	8	9	10	NA
Complete assigned PROs and record study intervention application	X[i]	X	→	→	→	→	→	→	X		
Collect e-diary		X[j]								X	X
Study Intervention											
Calculate BSA for study intervention need	X	X	X	X	X	X	X	X			
Mark/update areas of application on body map		X	X	X	X	X	X	X			
Weigh and dispense study intervention tubes		X	X	X	X	X	X	X			
Study intervention application and observation		X	X	X	X	X	X	X	X		
Collect and weigh returned study intervention tubes			X	X	X	X	X	X	X		X
Review of e-diary for compliance		X	X	X	X	X	X	X	X		X
Safety Monitoring											
Concomitant Medication		X	X	X	X	X	X	X	X	X	X
Contraception usage confirmation	X	X	X	X	X	X	X	X	X	X	X
Local tolerability assessment[k]		X	X	X	X	X	X	X	X		X
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	→	→	X	X
CCI											
Tape Strip Sub-study[n]											
CCI											

Atopic Dermatitis											
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13	**Screening**	**Treatment Phase** *All assessments/procedures are pre-dose, unless otherwise stated*								**Follow-Up (EOS)**	**ET**
		Day 1 (Baseline)	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 (EOT)**		
Visit Window	**Day -28 to -1**	**N/A**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**Day 57 ±2**	**Day 71 ±2**	**Day 85 ±2**	**28–35 days post-last dose**	**NA**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**NA**
Photography Sub-study[n]											
CCI [redacted]											
→= ongoing/continuous event											

a. Day relative to start of study intervention (Day 1). Except for Screening Visit and Day 1 Visit, Alternative Measures may be implemented in case of public emergencies. Refer to Appendix 9 for the details about the assessments that may be performed during a Telehealth Visit or a Home Health Visit.

b. Selected eligibility criteria should be met. Refer to Section 5.1 for details.

c. Following Day 1 visit, examination may be targeted to skin and previous findings, new/open AEs, or investigator discretion.

d. Site staff is to administer the C-SSRS to all participants at Screening and score immediately.

CCI [redacted]

f. A negative result from urine pregnancy test is required before receiving study intervention.

CCI [redacted]

j. Only for participants who do not meet eligibility criteria. If a participant hasn't withdrawn consent from participation from the study, e-diary may be collected at ET or EOS visits.

k. Local tolerability at a non-lesional site of study intervention application will be assessed immediately post-application. At ET, local tolerability assessment will be performed only if IP application was planned at that visit, but wasn't conducted due to tolerability assessment outcome of Grade 3 (severe) or Grade 4 (very severe), resulting in discontinuation of the study intervention as outlined in Section 7.1.4.

CCI [redacted]

1.3.2. Plaque Psoriasis

Plaque Psoriasis											
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13.	**Screening**	**Treatment Phase** *All assessments/procedures are pre-dose, unless otherwise stated.*								**Follow-Up (EOS)**	**ET**
		Day 1 (Baseline)	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 (EOT)**		
Visit Window	**Day -28 to -1**	**NA**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**Day 57 ±2**	**Day 71 ±2**	**Day 85 ±2**	**28–35 days post- last dose**	**NA**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**NA**
Enrollment Procedures											
Informed consent/assent	X										
General medical and PsO history	X	X									
Medication history	X	X									
Demography	X										
Eligibility assessment	X	X[b]									
Weight	X	X									
Height	X										
Clinical Assessments											
Physical examination[c]	X	X		X		X			X		X
ECG	X	X							X		X
Vital signs	X	X							X		X
C-SSRS[d]	X										
PsO-Related Clinical Assessments											
PGA	X	X	X	X	X	X	X	X	X	X	X
PASI		X	X	X	X	X	X	X	X	X	X
BSA	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments											
Hematology, Chemistry and Urinalysis	X	X		X		X			X		X
Serum FSH (WONCBP only)	X										
Serum Pregnancy Test (WOCBP only)	X										
Urine Pregnancy Test[e]		X	X	X	X	X	X	X	X	X	X
Pharmacokinetics											
CCI											

Plaque Psoriasis											
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13.	**Screening**	**Treatment Phase** *All assessments/procedures are pre-dose, unless otherwise stated.*								**Follow-Up (EOS)**	**ET**
		Day 1 (Baseline)	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 (EOT)**		
Visit Window	**Day-28 to -1**	**NA**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**Day 57 ±2**	**Day 71 ±2**	**Day 85 ±2**	**28–35 days post- last dose**	**NA**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**NA**
CCI											
Retained Research Samples											
CCI											
Prep B1.5 (plasma)		X				X			X		X
Prep B2.5 (serum)		X				X			X		X
e-diary											
Dispense e-diary and instruct on usage	X										
Complete assigned PROs and record study intervention application	X[h]	→	→	→	→	→	→	→	X		
Collect e-diary		X[i]								X	X
Study Intervention											
Calculate BSA for study intervention need	X	X	X	X	X	X	X	X			
Mark/update areas of application on body map		X	X	X	X	X	X	X			
Weigh and dispense study intervention tubes		X	X	X	X	X	X	X			
Study intervention application and observation		X	X	X	X	X	X	X	X		
Collect and weigh returned study intervention tubes			X	X	X	X	X	X	X		X
Review of e-diary for compliance		X	X	X	X	X	X	X	X		X
Safety Monitoring											
Concomitant Medication		X	X	X	X	X	X	X	X	X	X
Contraception usage confirmation	X	X	X	X	X	X	X	X	X	X	X
Local tolerability assessment[j]		X	X	X	X	X	X	X	X		X
Serious and non-serious AE monitoring	X	→	→	→	→	→	→	→	→	X	X

Plaque Psoriasis											
Visit Identifier[a] Abbreviations used in this table may be found in Appendix 13.	**Screening**	**Treatment Phase** *All assessments/procedures are pre-dose, unless otherwise stated.*								**Follow-Up (EOS)**	**ET**
		Day 1 (Baseline)	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 (EOT)**		
Visit Window	**Day-28 to -1**	**NA**	**Day 8 ±2**	**Day 15 ±2**	**Day 29 ±2**	**Day 43 ±2**	**Day 57 ±2**	**Day 71 ±2**	**Day 85 ±2**	**28–35 days post- last dose**	**NA**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**NA**
CCI											
Tape Strip Sub-study[n]											
CCI											
Photography Sub-study[n]											
CCI											
→= ongoing/continuous event											

a. Day relative to start of study intervention (Day 1). Except for Screening Visit and Day 1 Visit, Alternative Measures may be implemented in case of public emergencies. Refer to Appendix 9 for the details about the assessments that may be performed during a Telehealth Visit or a Home Health Visit.

b. Selected eligibility criteria should be met. Refer to Section 5.1 for details.

c. Following Day 1 visit, examinations may be targeted to skin and previous findings, new/open AEs, or investigator discretion.

d. Site staff is to administer the C-SSRS to all participants at Screening and score immediately.

e. A negative result from urine pregnancy tests is required before receiving study intervention.

CCI

i. Only for participants who do not meet eligibility criteria. If a participant hasn't withdrawn consent from participation from the study, e-diary may be collected at ET or EOS visits.

j. Local tolerability at a non-lesional site of study intervention application will be assessed immediately post-application. At ET, local tolerability assessment will be performed only if IP application was planned at that visit, but wasn't conducted due to tolerability assessment outcome of Grade 3 (severe) or Grade 4 (very severe), resulting in discontinuation of the study intervention as outlined in Section 7.1.4.

CCI [redacted]

l. To be completed using e-diary, weekly after Day 1 at home/residence or during site visit, if scheduled.

CCI [redacted]

2. INTRODUCTION

PF-07038124 is a topical PDE4 inhibitor that is currently being investigated in treatment of AD and PsO.

2.1. Study Rationale

The purpose of the study is to investigate the efficacy, safety, tolerability and pharmacokinetics of topical PF-07038124 in participants, 12 years and older and with mild-to-moderate AD or mild-to-severe PsO. Participants will apply either PF-07038124 ointment or a vehicle ointment for 12 weeks.

2.2. Background

Role of Proinflammatory Cytokines in AD and PsO

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. Although AD affects patients of all ages, it is one of the most common, chronic, relapsing childhood dermatoses affecting 15%-30% of all children in the US. There are a limited number of topical skin 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. There have been more recent topical treatments. Crisaborole, a PDE-4 inhibitor, has been used for treatment of mild-to-moderate AD. Topical JAK inhibitors have also been used for treatment of mild-to-moderate AD. Ruxolitinib, a recently approved JAK inhibitor for topical use in mild-to-moderate AD can be used only intermittently and short-term, due to its systemic effects. Delgocitinib has been shown to be modestly effective in treatment of mild-to-moderate AD. Additional treatments generally reserved for severe AD include phototherapy (eg, UVA light with or without psoralen) and systemic agents (eg, corticosteroids, cyclosporine, recombinant IFN-γ, mycophenolate mofetil, methotrexate). None of the currently available therapies offer a cure; therefore, the main aims of existing treatments are to reduce the occurrence of acute flares, increase the time between relapses, reduce pruritus and reduce the resulting sleep disturbances. For most AD patients not responding to topical therapies and phototherapy, off-label use of systemic agents, which includes both oral corticosteroids and oral immunosuppressants remain the last viable treatment option. More recently, there have been oral JAK inhibitors that have been approved for treatment of moderate-to-severe atopic dermatitis, such as Abrocitinib and Upadacitinib. Dupilumab injection, an IL-4 receptor alpha antagonist, was approved for use in patients with moderate-to-severe AD. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. Therefore, the prominent unmet medical need in AD is for an effective, safe topical agent for once-a-day dosing without restrictions on long-term or continuous use, and without local or systemic side effects.

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

PSORIASIS: The most common variant of psoriasis, PsO (psoriasis vulgaris), is a chronic inflammatory skin disease characterized by red, scaly, raised plaques. Chronic PsO is a common skin disorder with a worldwide prevalence of 2%. Although psoriasis primarily affects the skin and is not a life-threatening disease, it can profoundly impact the patient's QoL resulting in an impairment akin to other major diseases, such as type 2 diabetes, myocardial infarction, and arthritis. Current treatments for psoriasis include topicals, phototherapy, systemic non-biological therapies (methotrexate, cyclosporin, acitretin, apremilast [Otezla®]) and biologics. Proinflammatory cytokines such as TNF-α, IFN-γ and IL-23/T-helper-17 response cytokines play an important role in the pathogenesis of psoriasis.[3] Several biologic monoclonal antibodies that target these proinflammatory cytokines have been shown to be effective for the treatment of psoriasis in clinical trials.[4] Biologic agents used in the treatment of psoriasis include multiple anti-TNF agents (such as infliximab, adalimumab, etanercept), anti-IL-12/IL-23 antibodies and anti-IL-17 antibodies. PDE4 inhibitors such as apremilast (Otezla®) may reduce production of pro-inflammatory TNF-α and IFN-γ by increasing cAMP levels.

Description of Investigational Product: Mechanism of Action

Phosphodiaesterases are a family of enzymes that breakdown the ubiquitous second messengers, cAMP and cGMP, that regulate various cellular processes. PDE4 is a subfamily that includes the 4 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 PsO 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 CCI [redacted]

PF-07038124 is a potent and selective PDE4 inhibitor intended to be used for topical administration for the treatment of AD and PsO. CCI [redacted]

CCI

[redacted]

Preclinical Safety Data

CCI

[redacted]

CCI [redacted]

2.2.1. Clinical Overview

To date, clinical experience with PF-07038124 ointment comprises 3 studies:

1. A Phase 1, multiple ascending dose study in adult healthy participants (C3941001, completed). CCI [redacted]

2. A Phase 2a randomized, double-blind study in participants with mild-to-moderate AD or PsO, treated with 0.01% PF-07038124 ointment or vehicle ointment QD for 6 weeks (C3941002, completed). The total duration of study participation was approximately 17 weeks, including a screening period of up to 6 weeks, a double-blind, vehicle-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.

   In this study, there were no deaths or SAEs. All treatment-related (all-causality and treatment-related) severe AEs (4 participants) occurred in the vehicle group. There were no treatment-related AEs in the 0.01% PF-07038124 ointment group. The number of TEAEs (all-causality) and participants reporting TEAEs were higher in the vehicle group (15 [29.4%] participants with 26 events) compared to the PF-07038124 group (12 [22.6%] participants with 16 events).

   The most common all-causality TEAEs by SOC in the 0.01% PF-07038124 ointment groups was Infections and Infestations (11.3%), and in vehicle group was Skin and Subcutaneous Tissue Disorders (13.7%). There were no participants with application site pain or other skin reaction at application site in the 0.01% PF-07038124 ointment groups.

   There were 3 (5.9%) participants in the vehicle group with 3 TEAEs related to COVID-19, and 1 (2.0%) participant had a temporary discontinuation due to COVID-19. No participants in the 0.01% PF-07038124 ointment groups experienced AE related to COVID-19.

The study met the statistical significance for the primary endpoint for both indications.

AD

PF-07038124 (0.01% ointment QD) met the primary efficacy endpoint in the C3941002 study for AD: PF-07038124 (0.01% ointment QD) was statistically significantly different from vehicle in percentage change from baseline in EASI score at Week 6.

There was a statistically significant difference in the key secondary endpoint: response rate for IGA (clear = 0 or almost clear = 1 and a reduction from baseline of ≥2 points) at Week 6 between PF-07038124 (0.01% ointment QD) group and vehicle group, which supported the findings of the primary endpoint analysis.

The results from other important secondary endpoints including EASI-75 and PP-NRS response at Week 6 were consistent with the primary and key secondary endpoint findings.

PsO

PF-07038124 (0.01% ointment QD) met the primary efficacy endpoint in the C3941002 study for PsO: PF-07038124 (0.01% ointment QD) was statistically significantly different from vehicle in change from baseline in PASI score at Week 6.

There was no statistically significant difference in the key secondary endpoint: response rate for PGA (clear = 0 or almost clear = 1 and a reduction from baseline of ≥2 points) at Week 6 between PF-07038124 (0.01% ointment QD) group and vehicle group, although observed response rate was higher in PF-07038124 (0.01% ointment QD) group than vehicle group.

The results from PASI-75 at Week 6 were consistent with the primary findings.

3. A Phase 1, randomized, double-blind, vehicle-controlled, parallel cohort study to evaluate the safety, tolerability, skin irritation potential and pharmacokinetics of multiple-dose, topical administration of PF-07038124 to Japanese healthy participants (C3941003, enrollment complete, CSR pending). Preliminary data suggest that 0.01% PF-07038124 ointment is generally safe and well tolerated in Japanese healthy participants.

Table 1. PF-07038124 CCI [redacted] – Completed Studies as of January 2022

Study ID	Description	PF-07038124 Dose/Regimen	Number of Participants
C3941001 (completed)	Part A: Part A evaluated the skin irritation potential of 0.06% PF-07038124 (Cohort 1; 0.06%) and vehicle (placebo) applied to normal skin with a small surface area of 0.1% BSA (20 cm^2). Part B: Part B evaluated the safety, tolerability, skin irritation potential and PK following application of PF-07038124 at increasing concentrations (Cohorts 1-4; 0.01%, 0.03%, and 0.06%) and vehicle (placebo) to 10% BSA (2000 cm^2).	CCI [redacted]	
C3941002 (completed)	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 AD and PsO.	0.01% QD applied to 2000-4000 cm^2 (5-20% for AD; 5-15% PsO) for 6 weeks. CCI [redacted]	104 AD: 36 active; 34 vehicle PsO: 17 active; 17 vehicle
C3941003 (enrollment complete, CSR pending)	Randomized, double-blind, vehicle-controlled, parallel cohort study to evaluate the safety, tolerability, skin irritation potential and PK	0.01% QD applied to 2000 (10% BSA) or 4000 cm^2 (20% BSA) for 10 days. CCI [redacted]	12 4 active; 2 vehicle applied at 2000 cm^2, 4 active; 2 vehicle applied at 4000 cm^2
CCI [redacted]			

Clinical data for completed studies, C3941001 and C3941002, are provided in the current version of the IB.

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 IB, which is the SRSD for this study.

CCI [redacted]

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07038124		
Skin Sensitization - non-clinical findings	CCI [redacted]	Participants will be assessed for safety at regular intervals throughout the study, including assessment of the administration site. Participants with any history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products will be excluded from the study. Study treatment may be temporarily discontinued if severe or very severe application site reaction occur.
PDE4-related nervous system and gastrointestinal effect (a class effect of AEs observed with PDE4 inhibitors) – non-clinical findings	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.	IP application will be up to 40% BSA reducing the risk of systemic exposure. Systemic exposure will be assessed in the study. Participants will be assessed for safety at regular intervals throughout the study.
Worsening of disease (AD or PsO)	1. Participants in vehicle (or in lower dose arm) may experience a worsening of disease. 2. Participants may experience a worsening of disease during washout and/or follow-up periods.	AD and PsO are not life-threatening diseases. Participants may discontinue treatment or withdraw from the study at any time for any reason. Participants meeting withdrawal/discontinuation criteria may be able to use alternative treatments after withdrawal from the study. Participants will be assessed for safety at regular intervals throughout the study.

Other		
Risk of SARS-CoV-2 infection	Participants attending site visit may be exposed.	Use of telehealth, home health, etc and appropriate local and global restrictions guidelines will be utilized and followed to minimize potential exposure of trial participants to SARS-CoV-2 (see Appendix 9).

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 CCI [redacted] and in the treatment of PsO CCI [redacted]. Other PDE4 inhibitors, such as crisaborole (Eucrisa®, Staquis®), apremilast (Otezla®), and roflumilast (ARQ-151)[6] have demonstrated efficacy in the treatment of AD or PsO. In addition, in clinical Study C3941002 with participants with AD and PsO, signal of efficacy was noted. 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 PsO.

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 was selected for its emollient properties and favorable tolerability profile. The use of topical emollients is an essential element of AD and PsO treatment and is recommended by published guidelines.

2.3.3. Overall Benefit/Risk Conclusion

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

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

- The satisfactory safety and local tolerability profile on PF-07038124 to date based on non-clinical studies and clinical Studies C3941001, C3941002, and C3941003.
- The expected efficacy of PF-07038124 for the treatment of AD and PsO based on pre-clinical data generated with PF-07038124, signal of efficacy in clinical Study C3941002, and 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 mild-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 PsO supporting the initiation of Phase 2b Study C3941005.

Additional background information on PF-07038124 can be found in the current version of the IB (version 3.0, 2022), especially the Summary of Data and Guidance for the Investigator (Section 7 of the IB).

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

ATOPIC DERMATITIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA success as the 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 12.	• Estimand E1: the difference in proportions of the binary endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle using EASI-75 as an endpoint in participants with mild or moderate AD.	• Proportion of participants achieving EASI-75 (75% improvement from baseline) at all study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA success as the 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 all study visit time points specified in the SoA, except at Week 12.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using percent CFB in EASI as the endpoint in participants with mild or moderate AD.	• Percent CFB in EASI total score at all study visit time points specified in the SoA.	• Estimand E2: the difference in mean of the continuous endpoint between IP treated (0.01% or 0.03% PF-07038124 ointment) and vehicle in participants with mild or moderate AD without the benefit of additional prohibited medications and regardless of treatment compliance.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using IGA clear or almost clear as the endpoint in participants with mild or moderate AD.	• Proportion of participants achieving IGA score of clear (0) or almost clear (1) at all study visit time points specified in the SoA.	• Estimand E1 described above.

• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using measures of PP-NRS PRO, in participants with mild or moderate AD.	• Proportion of participants having ≥4 points of reduction from baseline in weekly averages of PP-NRS at study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of 2 dose levels of PF-07038124 ointment versus vehicle, using BSA as the endpoint in participants with mild or moderate AD.	• Percent CFB in affected BSA at all study visit time points specified in the SoA.	• Estimand E2 described above.
• To characterize the safety and tolerability of 2 dose levels of PF-07038124 ointment versus vehicle in participants with mild or moderate AD.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests. • Incidence of increase in local tolerability severity grades at times indicated in the SoA.	• Not Applicable.
CCI [redacted]		

Tape Stripping Sub-study • To evaluate pharmacological effects of applying multiple doses of PF-07038124 ointment versus vehicle ointment using tape stripping method that is used to collect upper part of epidermis.	CCI [redacted]
Photography Sub-study • To compare the efficacy of two dose levels of PF-07038124 ointment versus vehicle CCI [redacted] • To document effects of applying multiple doses of PF-07038124 ointment versus vehicle ointment using photographic images.	

PLAQUE PSORIASIS		
Objectives	**Endpoints**	**Estimands**
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA success as the endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12.	Estimand E1: the difference in proportions of the binary endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild-to-severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle using PASI-75 as an endpoint, in participants with mild-to-severe PsO.	• Proportion of participants achieving PASI-75 (75% improvement from baseline) at times indicated in the SoA.	• Estimand E1 described above.

• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA success as endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at times indicated in the SoA, except at Week 12.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using CFB PASI as the endpoint in participants with mild-to-severe PsO.	• Change from baseline in PASI at times indicated in the SoA.	Estimand E2: the difference in mean of the continuous endpoint between IP treated (0.01%, 0.03%, or 0.06% PF-07038124 ointment) and vehicle in participants with mild-to-severe PsO without the benefit of additional prohibited medications and regardless of treatment compliance.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using PGA clear or almost clear as the endpoint in participants with mild-to-severe PsO.	• Proportion of participants achieving PGA score of clear (0) or almost clear (1) at all study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using measures of PP-NRS PRO, in adult (18-75 years old) participants with mild-to-severe PsO.	• Proportion of adult (18-75 years old) participants having ≥4 points of reduction from baseline in weekly averages of PP-NRS at study visit time points specified in the SoA.	• Estimand E1 described above.
• To compare the efficacy of multiple dose levels of PF-07038124 ointment versus vehicle, using BSA as the endpoint in participants with mild-to-severe PsO.	• Percent CFB in affected BSA at all study visit time points specified in the SoA.	• Estimand E2 described above.
• To characterize the safety and tolerability of multiple dose levels of PF-07038124 ointment versus vehicle in participants with mild-to-severe PsO.	• Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests. • Incidence of increase in local tolerability severity grades at times indicated in the SoA.	• Not Applicable.

CCI

[redacted]

CCI

Tape Stripping Sub-study

- To evaluate pharmacological effects of applying multiple doses of PF-07038124 ointment versus vehicle ointment using tape stripping method that is used to collect upper part of epidermis.

Photography Sub-study

- To document effects of applying multiple doses of PF-07038124 ointment versus vehicle ointment using photographic images.

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2b, randomized, double blind, vehicle controlled, parallel group, multicenter study to assess the efficacy, safety and tolerability, and PK of multiple doses of PF-07038124 ointment versus vehicle in treatment of participants, 12 years and older, and with AD or PsO.

In this study, a total of approximately 240 participants with AD or PsO will be randomly assigned to study intervention (PF-07038124 or vehicle).

Participants will be screened for eligibility to participate in the trial within 4 weeks of randomization, on Day 1. During Screening period, participants will begin documenting their disease symptoms in the e-diary, at least 7 days prior to randomization. After confirming eligibility on Day 1, as outlined in Section 1.3.1 and Section 1.3.2 for AD and PsO respectively, randomization will occur and treatment with the study intervention will begin. Treatment with study intervention (PF-07038124 ointment or vehicle ointment) will be once daily for 12 weeks followed by a safety follow-up period of 4-5 weeks from last application of study drug to last study visit. The total duration of study participation is approximately 21 weeks.

- For AD, approximately 120 participants will be randomly assigned 1:1:1 to receive either 0.01% PF-07038124 ointment, 0.03% PF-07038124 ointment or a vehicle ointment.
    - Randomization will be stratified by baseline disease severity (mild [IGA = 2] vs moderate [IGA = 3]) and by tape stripping sub-study participation. CCI [redacted]
- For PsO, approximately 120 participants will be randomly assigned 1:1:1:1 to receive either 0.01% PF-07038124 ointment, 0.03% PF-07038124 ointment, 0.06% PF-07038124 or a vehicle ointment.
    - Randomization will be stratified by baseline disease severity (mild [PGA = 2], moderate [PGA = 3], severe [PGA = 4]) and by tape stripping sub-study participation. CCI [redacted]

Table 2. Participant Distribution

Participant Population	Study Intervention	Approximate number of Participants Completing the Study
AD	0.01% PF-07038124	40
	0.03% PF-07038124	40
	Vehicle	40
PsO	0.01% PF-07038124	30
	0.03% PF-07038124	30
	0.06% PF-07038124	30
	Vehicle	30

Multiple safety, efficacy, PK and biomarker assessments will be performed during the treatment and follow-up period.

The study will include 2 sub-studies:

CCI [redacted]

4.2. Scientific Rationale for Study Design

A single, primary endpoint based on regulatory precedence is planned for both AD and PsO. FDA requires primary endpoint for AD and PsO to be IGA and PGA, respectively and secondary endpoints to be EASI and PASI. Since IGA and EASI in AD and PGA and PASI in PsO are not independent variables and should track in parallel, there is a high probability that these will be consistent. These are well-validated endpoints and have been used as regulatory and clinical endpoints in AD/PsO studies for many years, therefore, for AD, IGA is chosen to be the primary endpoint and EASI as secondary. Similarly, for PsO, PGA is chosen as the primary endpoint and PASI as secondary.

CCI [redacted]

CCI [redacted]

4.2.1. Diversity of Study Population

Reasonable attempts will be made to enroll participants with the distribution of characteristics with respect to race, ethnicity, and age to ensure the study population is representative of the patient population that will use study intervention in clinical practice.

4.2.2. Choice of Contraception/Barrier Requirements

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. Therefore, the use of a highly effective method of contraception is required (see Appendix 4).

4.2.3. Collection of Retained Research Samples

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

4.3. Justification for Dose

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 doses proposed for this study were determined considering all relevant information obtained from nonclinical safety studies, incorporating the NOAEL from 3-month studies in minipigs, together with the systemic exposure and tolerability observed following topical application of PF-07038124 to healthy participants in Study C3941001 (Table 3) and Study C3941003 (preliminary data), and in participants with AD or PsO in 6-week Study C3941002.

In Study C3941002, at Week 6, up to 6 hours post-dose, greater than 86% and 98% of plasma PK samples of PF-07038124 were BLQ of 10 pg/mL in AD and PsO participants, respectively. CCI [redacted] In addition, the updated formulation CCI [redacted] was also investigated in healthy Japanese participants (C3941003) and the findings were consistent with the exposure observed in AD and PsO patients (C3941002).

CCI [redacted]

Dose strengths selected for this study are 0.01%, 0.03% and 0.06% PF-07038124. CCI [redacted]
The clinical translation of these in vitro systems is unknown.

Based on the findings from the Phase 2a study (C3941002), the clinical efficacy criterion for %change from baseline in EASI and %IGA responders in AD were met using the 0.01% dose strength following QD application, and comparable to efficacy with other topical agents approved for mild-to-moderate AD. The dose strengths of PF-07038124 selected for this study are 0.01% and a higher dose of 0.03% in participants with AD to investigate the ability to achieve greater efficacy compared to other topical agents, while still minimizing systemic exposure. For PsO, even though the clinical efficacy criterion of change from baseline in PASI score was met with the 0.01% QD regimen, the efficacy criterion for %PGA responders was not achieved. As a result, the intent of this Phase 2b study is to establish maximum efficacy and safety in this indication with exploration of the largest possible dose range (eg, 0.01%, 0.03%, and 0.06%) is required.

CCI [redacted]

CCI

[redacted]

4.4. End of Study Definition

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

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

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 PsO 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 PsO, respectively.

5.1.1. General Inclusion Criteria Applicable for both AD and PsO

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

Age and Sex:

1. Participants ages 12 years (inclusive) and above, at Screening.

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

Type of Participant and Disease Characteristics:

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

Informed Consent/assent:

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

    The investigator, or a person designated by the investigator, will obtain written/electronically signed informed consent from each study participant's legal guardian (as defined in Appendix 1) and the participant's assent, when applicable,

before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/EC. All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

5.1.2. Disease-Specific Inclusion Criteria:

5.1.2.1. AD Specific Inclusion Criteria

4. Have been diagnosed with AD for at least 3 months prior to Screening.

   Note: The clinical diagnosis of AD will be confirmed according to the criteria of Hanifin and Rajka[7] (Appendix 10).

5. Have an IGA score of 2 (mild), or 3 (moderate) at Screening and Day 1, prior to randomization. Refer to Section 8.1.1.1.1 and Appendix 12 for the assessment of 5-point IGA.

6. Have AD covering 5% and up to 40% of BSA (excluding the hair-bearing scalp) at Screening and Day 1, prior to randomization. Refer to Section 10.12.1.3 (Appendix 12) for detailed methods of calculating treatable % BSA.

7. Have a PP-NRS average score of ≥2 assessed at Day 1, prior to randomization.

5.1.2.2. PsO Specific Inclusion Criteria

8. Have a diagnosis of PsO (psoriasis vulgaris) for at least 6 months prior to Screening.

9. Have a PGA score of 2 (mild), 3 (moderate), or 4 (severe) at Screening and Day 1, prior to randomization. Refer to Section 8.1.2.1.1 and Appendix 12 for the assessment of 5-point PGA.

10. Have PsO covering 2% to 20% (inclusive) of BSA (excluding the hair-bearing scalp, palms, soles, finger nails and toe nails) at Screening and Day 1, prior to randomization. Refer to Section 10.12.2.3 (Appendix 12) for detailed methods of calculating treatable BSA.

5.2. Exclusion Criteria

The exclusion criteria for AD and PsO population 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 criteria in Appendix 11, at Screening.

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 (within approximately 3 months prior to Day 1) of systemic, 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. Undergone significant trauma or major surgery within 1 month prior to Screening.

6. 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.

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

8. 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:

9. Current use of any prohibited concomitant medication(s) or those unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.8 and Section 10.8 for guidance on permitted and prohibited concomitant medications.

Prior/Concurrent Clinical Study Experience:

10. 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, PsO, PsA or RA in the previous 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:

11. Participants with ANY of the following abnormalities in clinical laboratory tests at Screening, as assessed by the sponsor defined laboratory and confirmed by a single repeat (the last value will be used to determine eligibility), if deemed necessary:

    - Renal impairment as defined by an eGFR of <40 mL/min/1.73m^2 calculated using the serum creatinine-based CKD-EPI formula for adults and serum creatinine >1.5 x ULN in adolescents (12-18 years old).

    - Hepatic dysfunction defined as total bilirubin ≥2x ULN (≥3 x ULN for Gilbert's disease), AST ≥2.5 x ULN, ALT ≥2.5 x ULN.

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

Other Exclusions:

13. 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.

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

5.3. Lifestyle Considerations

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 selected methods of contraception) considering that their risk for pregnancy may have

changed since the last visit. In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.3.2. 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). Herbal 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 Appendix 8.

- All topical medications and treatments that could affect AD or PsO skin areas must be discontinued prior to Day 1, as specified in Appendix 8, if the skin areas are to be treated with study intervention.
- Unless specified in Appendix 8, any other concomitant medication for AD or PsO will be considered on a case-by-case basis by the investigator in consultation with the sponsor medical monitor.
- Participants will stop applying bland (non-medicated, urea- and lactic acid free-) emollients and sunscreen on AD/PsO affected skin 24 hours prior to Day 1.
    - After Day 1 Visit, use of non-medicated bland emollient(s) is permitted during the study to manage dry skin in areas surrounding but not on or overlapping the treatable AD/PsO affected skin areas, normal skin or areas which were never treated with study intervention (ie palms, soles or nails for PsO). Any non-medicated emollient used by the participant during the study should be documented in study records and the CRF.
- Due to the potential to affect AD and PsO 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 8 for details on prohibited light therapy.
- 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, and finger and toenails [PsO only]). Scalp tar preparations, salicylic acid preparations and shampoos free of corticosteroids are permitted for the treatment of scalp.

5.3.4. Other Lifestyle Requirements

- Participants should not apply occlusive dressing(s) to the areas treated with study intervention.
- Participants should not swim, bathe, be bathed or have treatment areas washed for at least 4 hours after application of the study intervention.
- The participant should avoid wiping the study intervention off the skin and the study intervention 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.
- 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 12 visit.
- When applying the study intervention, 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 study intervention on hard-to-reach areas (eg, back), this person must wear gloves to avoid accidental exposure to the study intervention.

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. As an exception, a participant who otherwise qualified for this study but did not enroll due to positive COVID-19 test, due to recent vaccination, or due to exhibiting COVID-19-related symptoms or potential exposure, may be rescreened after an appropriate interval, if judged appropriate by the investigator. In such cases, all screening procedures must be repeated. Rescreened participants should be assigned a new participant number.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

For the purposes of this protocol, study intervention refers to:

- PF-07038124 0.01% ointment;
- PF-07038124 0.03% ointment;
- PF-07038124 0.06% ointment;
- Vehicle ointment (placebo).

6.1. Study Intervention(s) Administered

	Study Interventions(s)			
Intervention Name	PF-07038124 0.01% ointment	PF-07038124 0.03% ointment	PF-07038124 0.06% ointment	PF-07038124 vehicle ointment
ARM Name (group of patients receiving a specific treatment (or no treatment)	Participants with mild or moderate AD, and mild, moderate, or severe PsO	Participants with mild or moderate AD, and mild, moderate, or severe PsO	Participants with mild, moderate, or severe PsO	Participants with mild or moderate AD, and mild, moderate, or severe PsO
Type	Drug	Drug	Drug	Drug

	Study Interventions(s)			
Dose Formulation	Ointment	Ointment	Ointment	Ointment
Unit Dose Strength(s)	0.1 mg/g ointment in 60-gram tube	0.3 mg/g ointment in 60-gram tube	0.6 mg/g ointment in 60-gram tube	0 mg/g ointment in 60-gram tube
Dosage Level(s)	0.01% (wt/wt), QD	0.03% (wt/wt), QD	0.06% (wt/wt), QD	0% (wt/wt), QD
Route of Administration	Topical	Topical	Topical	Topical
Use	Experimental	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.	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.	Study intervention will be provided in cartons. Each carton will contain one tube. Both the carton and tube will be labeled in a blinded format as required per country requirement.	Study intervention will be provided in cartons. Each carton will contain one tube. Both the carton and tube will be labeled in a blinded format as required per country requirement.

PF-07038124 ointment, 0.1 mg/g, 0.3 mg/g and 0.6 mg/g will be provided as the active ingredient with CCI [redacted]

Vehicle (placebo, no active drug in the formulation) ointment will be provided as the CCI [redacted]

6.1.1. Administration

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

PsO treatable areas will be all areas affected by PsO, except hair-bearing scalp, palms, soles, fingernails, and toenails.

A layer of study intervention ointment will be applied at a target application rate of approximately 3 mg/cm^2 by using a fingertip unit method.

Day 1 Visit

At the Day 1 visit, before the Day 1 initial study intervention 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.

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

Post Day 1

Following Day 1 visit through the final dose at Week 12 visit, the study intervention should be applied **once daily** (around same time of the day), to all treatable AD or PsO involved areas identified at the Day 1 visit as well as to new areas identified as "treatable" during the course of 12 weeks. All participants will be supplied with instructions on application.

- Note: Any new AD or PsO areas identified by the participant or caregiver(s) should also be treated with the study intervention ***after 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. If the new lesion is identified as treatable, then body map will be updated, and study intervention need will be re-assessed.

The study intervention will be applied at home/residence except on the days of in-clinic visits. **On the days of scheduled in-clinic visit, participants will be instructed to refrain from applying the study intervention at home/residence**. The last dose of study intervention will be applied during the Week 12 in-clinic visit (EOT visit) as specified in the SoA.

- Note: If due to public emergency, local regulations don't allow participant to visit the clinic on scheduled visit days, the participant will refrain from applying the study intervention until selected assessments can be completed using televisit or home health visit.

The participant and/or caregiver will be instructed to complete the dosing diary section of the e-diary, starting with the first dose applied in the clinic on Day 1 through Week 12 (each time study intervention is 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 continue to be treated even if substantial improvement or clearing of AD or PsO occurs.

The reason for maintaining study intervention 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 12 weeks in participants with AD or PsO.

Under no circumstances will the study intervention 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 study intervention 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 the study intervention.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation, Handling, Storage, and Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

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

5. Study interventions should be stored in their original containers.

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 IP manual.

6.2.1. Preparation and Dispensing

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

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

The study intervention will be dispensed in a blinded fashion using an IRT system at Day 1/Baseline, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10 visits. A qualified staff member will dispense the study intervention 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.

Study intervention 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 study intervention dispensing visits to enter information including, but not limited to, % affected BSA, height, and weight to receive correct tube numbers to be dispensed to the participant. Alternatively,

the tool to standardize the study intervention need calculation across participants and study sites may be provided by the sponsor.

The calculation of treatable %BSA is described in Section 10.12.1.3 and Section 10.12.2.3 for AD and PsO, respectively.

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

6.2.2. Study Intervention Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the study intervention supplies. All study intervention will be accounted for using a drug accountability form/record. All tubes of the study intervention 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 study intervention (including empty, partially used and unused tubes) at every visit; participants will be asked to bring e-diary to the clinic at every clinic visit. All previously dispensed study intervention tubes will be retained by the site. For each participant, study intervention tubes with caps will be weighed individually 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 study intervention label is a nominal weight and not an exact weight of the study intervention and tube. Detailed drug accountability records, including tube weights measured in the clinic, will be maintained by study staff for each participant.

The original study intervention 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 Study Intervention Supplies

For all study intervention 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 study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

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 re-dispensed 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. 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

Participants will be instructed to bring to the clinic all used, partially used and empty study intervention tubes in their original containers for weighing, at each visit.

Participant compliance with study intervention will be assessed on visits identified in the SoA. Compliance will be assessed by review of the participant/caregiver completed dosing diary section of the e-diary and thorough review of dosing instructions at every visit. The difference in weight(s) of the returned study intervention tubes will be used to estimate the doses applied at the end of the study. 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 12 visit, non-compliance is defined as application of study intervention less than 80% in a week or more than 120% of study intervention applications. If non-compliance is identified, or even if a few dose applications are missed or over-applied (as informed by the participant to the site staff), then, participants will be re-trained on the importance and the process of proper study intervention 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 study intervention 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. Dose Modification

Not applicable.

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

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

6.7. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose within a 12-hour time period will be considered an overdose.

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 Pfizer 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.

6.8. Concomitant Therapy

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 8 for the list of prohibited 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).

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 participation in study. Vaccines used in the event of a disease outbreak or pandemic are allowed.

6.8.1. 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.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following: 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 permanently discontinued, the participant will remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.1.1. Liver Injury

Please refer to Section 10.6 for Potential Cases of Drug-Induced Liver Injury (DILI; Hy's law).

7.1.2. ECG Changes

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

- QTcF >500 msec.
- Change from baseline: QTcF >60 msec and QTcF >450 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.

7.1.3. 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 or sponsor medical monitor notified immediately.

7.1.4. 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 study intervention for up to 48 hours without consulting the sponsor. If in the clinical judgment of the investigator study intervention interruption beyond 48 hours is advisable, the investigator must obtain agreement from the Pfizer medical monitor to continue withholding study intervention. If temporary study intervention 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.

7.1.5. 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.

7.1.6. Temporary Discontinuation

Temporary discontinuations of study intervention:

- 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 of 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 the sponsor prior to temporary discontinuation.

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 may include the following:

- Refused further study procedures;
- 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.

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.

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. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD/assent 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.

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 140 mL for participants with AD and 120 mL for participants with PsO. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

8.1. Efficacy Assessments

8.1.1. Efficacy Assessments for AD

All efficacy assessments will be based on areas treated with study intervention.

8.1.1.1. Physician Assessments

8.1.1.1.1. 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 in Section 10.12.1.1 (Appendix 12). The assessment will be a static evaluation without regard to the score at a previous visit.

8.1.1.1.2. 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] The clinical evaluator of AD will perform an assessment of severity and area involved as described in Section 10.12.1.2 (Appendix 12).

8.1.1.1.3. BSA

Assessment of BSA for efficacy is performed separately for four areas of the body:

- Head, *including* neck and face but *excluding* hair-bearing scalp;
- Trunk, *including* axillae and groin;
- Upper limbs;
- 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.

The clinical evaluator of AD will perform an assessment of the %BSA as described in Section 10.12.1.3 (Appendix 12).

CCI [redacted]

CCI

[redacted]

8.1.1.2.1. PP-NRS

The PP-NRS is a daily patient-reported assessment of intensity of pruritus on an 11-point numerical rating scale, with a 24-hour recall period.[2] The PP-NRS will be completed QD, starting at least 7 days prior to Day 1 and then, completed QD every day from Day 1 to Week 12 before study intervention dose is applied, preferably at the same time of each day, as noted in the SoA. All participants will complete the questionnaire at the follow-up visit in clinic.

Note that the average of 7 days (minimum of 4 days) of PP-NRS scores immediately preceding randomization will be used to calculate the baseline average score and assess eligibility, as in Section 5.1.

CCI

[redacted]

CCI

CCI

CCI [redacted]

CCI [redacted]

- The PP-NRS and CCI questionnaires will be completed at the participants' home/residence, using the e-diary provided by sponsor. The PP-NRS will be completed only by participants 18 to 75 years old at Screening, starting from at least 7 days prior to Day 1.

CCI [redacted]

8.1.2.2.1. PP-NRS

The PP-NRS is a daily patient-reported assessment of intensity of pruritus on an 11-point numerical rating scale, with a 24 hour recall period.[2] The PP-NRS will be completed QD, starting at least 7 days prior to Day 1 and then, completed QD every day from Day 1 to Week 12 before study intervention dose is applied, preferably at the same time of each day, as noted in the SoA. All adult (18-75 years old at Screening) participants will complete the questionnaire at the follow-up visit in-clinic.

CCI

[redacted]

8.1.3. 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 or Rater Qualification Plan. 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.

To assure consistency and reduce variability, the same evaluator should assess all dermatological clinical evaluations for any individual participant throughout the study whenever possible.

- A backup experienced and qualified protocol-trained evaluator will only be allowed and documented in case of emergency or special situations when the designated evaluator is unable to perform the evaluation.

- The rater(s) must become certified to perform selected study assessments before he or she can participate in the conduct of the study.

For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8.2. 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 and Medication 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 PsO disease history, medications and non-medication therapies history, and alcohol and tobacco use status/history.

- Complete AD or PsO disease history includes collection of details of AD or PsO: AD or PsO diagnosis, the use of topical treatments, systemic treatments and other treatments (eg, use of biologic drugs) for AD or PsO taken during the 90 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.

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 the Baseline Day 1 visit for 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.

- It is recommended that weight be measured in kg to the nearest 0.1 kg and that height be measured in 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.

- A complete physical examination will include, at a minimum, assessments of the general appearance, skin (presence of rash), HEENT, 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.

- Disease focused physical examination: includes all AD or PsO involved skin (in treatable and non-treatable areas) and evaluation of any current or reported symptoms for clinically significant changes.

Any clinically significant changes from the most recent physical examination should be recorded as AEs. Lack of efficacy is generally not considered an AE.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Please see Section 8.2.7 for skin Local Tolerability Assessment.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar)

should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

- During screening, if participants have initial screening value QTcF >450 msec, ECG should be repeated two more times and the average of the 3 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 2 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 post-dose QTcF interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QT 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 criteria 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 QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

When the timing of these measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection.

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

8.2.4. Vital Signs

Temperature, pulse rate, and blood pressure will be assessed.

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

- Blood pressure and pulse rate measurements will be assessed with the participant in a supine or seated position using a completely automated device. Manual techniques will be used only if an automated device is not available. Appropriately sized cuff should be used and it is preferred that the same arm (preferably the dominant arm)

and same position be used throughout the study for an individual participant. 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.

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 - C-SSRS

The C-SSRS is a validated tool for investigative staff to use to evaluate suicidal ideation and behavior.[12] 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 (See Appendix 11 for details). 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 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 study intervention application, **immediately post-application of the study intervention**. This assessment[13] will focus on the **non-lesional** skin using the scale in Table 5. 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.

Table 5. Skin Tolerability Grading System for Non-lesional Skin

Grade	Severity	Description
0	None	No evidence of local intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but needs no adaptation of posology
3	Severe (to be reported as an AE)	Erythema, edema glazing with fissures, few vesicles or papules: consider removing topical agent (if still in place)
4	Very severe (to be reported as an AE)	Strong reaction spreading beyond the treated area, bullous reaction, erosions: removal of topical agent (if still in place)

8.2.8. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

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

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, Serious Adverse Events, and Other Safety Reporting

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

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

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

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian 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/assent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

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

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then exposes his female partner prior to or around the time of conception.

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

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 calendar 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 pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion;

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

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

the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

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

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

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action 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.
- The administration of an incorrect study intervention.
- The administration of an incorrect dosage.

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

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

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

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

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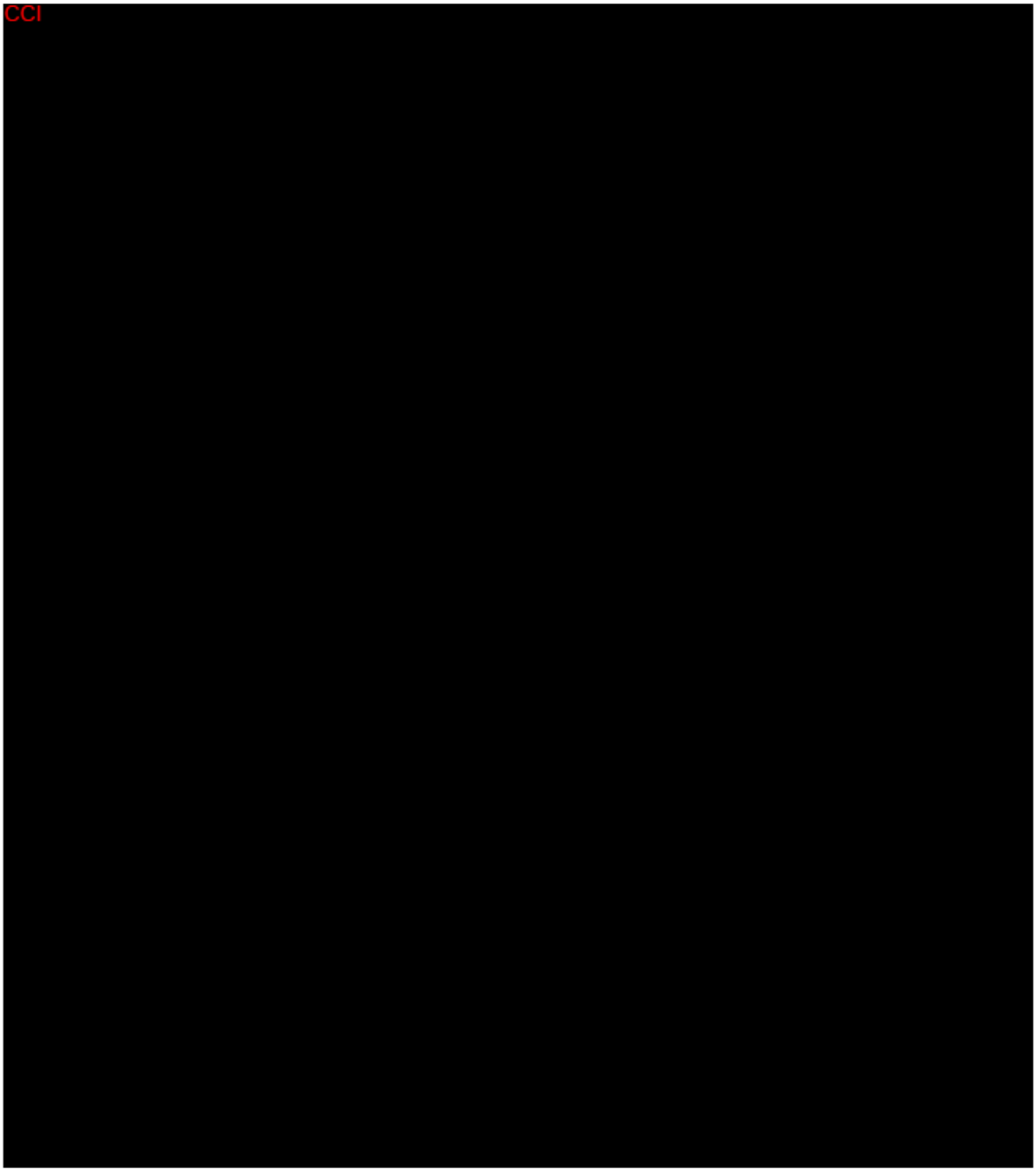

CCI [redacted]

8.5. Genetics

8.5.1. Specified Genetics

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

8.5.2. Retained Research Samples for Genetics

CCI [redacted]

Retained Research Samples may be used for research related to the study intervention, AD, PsO, and/or related inflammatory diseases. CCI [redacted]

CCI [redacted]. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.6. Biomarkers

8.6.1. Specified Gene Expression (RNA) Research

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

8.6.2. Specified Protein Research

Specified protein research is included in this study. The samples will be analyzed for exploratory research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

Samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

CCI [redacted]

CCI [redacted]

8.6.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.6.4. Retained Research Samples for Biomarkers

These Retained Research Samples will be collected in this study:

CCI [redacted]

- A 6-mL whole blood Prep B2.5 optimized for serum;
- A 6-mL whole blood Prep B1.5 optimized for plasma.

Retained Research Samples will be collected as local regulations and IRB/ECs allow according to the SoA.

Retained Research Samples may be used for research related to the study intervention, AD, psoriasis, and or related inflammatory diseases. CCI [redacted]

CCI [redacted] Details on processes for collection and shipment of these samples can be found in laboratory manual.

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.9. BSA for Study Intervention Need (Treatable BSA)

Evaluation of %BSA for study intervention need is the total BSA across all body locations being treated with the study intervention. The %BSA for study intervention need evaluation method will be the same as the BSA with AD or PsO for efficacy assessment.

Post Day 1, if any new AD or PsO areas become eligible for treatment, those should be included in the %BSA for study intervention need. The %BSA at subsequent visits should be equal to or greater than the value at Day 1.

8.10. Exploratory Assessments

8.10.1. Tape Strip Sub-study

CCI

[redacted]

8.10.2. Photography Sub-study

CCI

[redacted]

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

Statistical inference will be made on the primary endpoints: IGA/PGA response at Week 12. The null hypothesis is that there is no difference between each PF-07038124 dose level and the vehicle arm for each indication. The alternative hypothesis is that the PF-07038124 dose level is superior to the vehicle arm for each indication.

9.1.1. Estimands

9.1.1.1. Primary Estimand

The estimand is defined by the following attributes:

Atopic Dermatitis:

Treatment condition: received treatment: PF-07038124 ointment 0.01%, 0.03% or vehicle, without the benefit of additional prohibited medications and regardless of treatment compliance.

Population: Participants with mild or moderate AD as defined by the inclusion and exclusion criteria.

Variables: Proportion of participants achieving IGA score of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 12 and other binary endpoints.

Psoriasis:

Treatment condition: received treatment: PF-07038124 ointment 0.01%, 0.03%, 0.06% or vehicle, without the benefit of additional prohibited medications and regardless of treatment compliance.

Population: Participants with mild, moderate, or severe PsO as defined by the inclusion and exclusion criteria.

Variables: Proportion of participants with PGA score clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 12 and other binary endpoints.

Inter-current Events: A) Prohibited medication – response will be considered as failure for time points after start date of the event for participants who receive prohibited medication post-randomization. B) Withdrawal and all other events, except COVID-19 pandemic, leading to missing data will be treated similarly assuming that participants no longer receive

benefit from the study intervention and hence will be considered as failure. C) COVID-19 pandemic: if a participant misses a visit due to COVID-19, he/she will be excluded from the analysis for that visit; If a participant discontinues treatment or withdraws from the study due to COVID-19, he/she will be excluded from the analyses after the treatment discontinuation visit or study withdrawal visit, respectively. D) Inadequate compliance – participants data will be used as recorded.

Population level summary: The difference in success rates between each dose level and vehicle.

9.1.1.2. Secondary Estimand

All binary secondary endpoints estimands are similar to the primary endpoint.

The continuous endpoint estimand is defined by the following attributes:

Atopic Dermatitis:

Treatment condition: received treatment: PF-07038124 ointment 0.01%, 0.03% or vehicle, without the benefit of additional prohibited medications and regardless of treatment compliance.

Population: Participants with mild or moderate AD as defined by inclusion and exclusion criteria.

Variables: Percent change from baseline in EASI total score at all study visit time points specified in SoA.

Psoriasis:

Treatment condition: received treatment: PF-07038124 ointment 0.01%, 0.03%, 0.06% or vehicle, without the benefit of additional prohibited medications and regardless of treatment compliance.

Population: Participants with mild, moderate, or severe PsO as defined by the inclusion and exclusion criteria.

Variables: Change from baseline in PASI total score at all study visit time points specified in SoA.

Intercurrent events: A) Prohibited medication – all scores measured at time points after start date of the event for participants who receive prohibited medication post randomization will be excluded from the analysis and treated as missing scores. Missing scores will be imputed based on the assumption that participants do not benefit from the IP treatment.
B) Withdrawal and all other events leading to missing data, except COVID-19 pandemic, will be treated similarly assuming participants have efficacy values similar to control participants. C) COVID-19 pandemic: if a participant misses a visit due to COVID-19,

he/she will be excluded from the analysis for that visit; If a participant discontinues treatment or withdraws from the study due to COVID-19, he/she will be excluded from the analyses after the treatment discontinuation visit or study withdrawal visit, respectively. D) Inadequate compliance – participants data will be used as recorded.

Population-level summary: The mean difference between each dose level and vehicle.

9.1.2. Multiplicity Adjustment

For each indication, the overall family wise Type I error rate will be controlled at the 1-sided 0.025 level using the Hochberg step up procedure.

9.2. Analysis Sets

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

Participant Analysis Set	Description
Full Analysis Set	All participants randomly assigned to study intervention who take at least 1 dose of study intervention.
Safety Analysis Set	All participants randomly assigned to study intervention who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

Defined Analysis Set	Description
CCI	[redacted]

9.3. Statistical Analyses

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

9.3.1. General Considerations

Indication will be summarized separately by treatment.

9.3.2. Analyses for Binary Endpoints

Analysis of primary binary endpoints is specified in Section 9.3.4. Other binary endpoints at time points specified in the SoA will be analyzed similarly. No adjustments for multiplicity will be made for these endpoints.

9.3.3. Analyses for Continuous Endpoints

Analysis of secondary continuous endpoints is specified in Section 9.3.5. Other continuous endpoints at time points specified in the SoA will be analyzed descriptively with no imputation. No adjustments for multiplicity will be made for these endpoints.

9.3.4. Primary Endpoint(s)/Estimand(s) Analysis

A landmark analysis of the composite IGA/PGA success endpoints at Week 12, defined in Section 9.1.1.1, will be performed using the full analysis set. The proportions responding and 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 95% confidence intervals will be computed using Chan and Zhang (1999)[14] method. The overall family wise Type I error rate will be controlled at the 1-sided 0.025 level using the Hochberg step up procedure.

In addition, Emax or other appropriate models may be used to characterize the dose response relationship. Details of the dose response model will be described in the SAP.

9.3.5. Secondary Endpoint(s)/Estimand(s) Analysis

Binary secondary endpoints will be analyzed similarly to the primary endpoints.

A landmark analysis of continuous endpoints including percent change from baseline in EASI and change from baseline in PASI at Week 12, defined in Section 9.1.1.2. will be performed by ANCOVA using the full analysis set with baseline as a covariate. Missing data, except missing due to COVID-19 pandemic, will be imputed using a control-based method, assuming participants have efficacy values similar to vehicle participants, and data are MAR. The imputation will utilize ANCOVA model including baseline as a covariate. The analysis will combine the results from the multiple imputations using Rubin's rule's as implemented in SAS PROC MIANALYZE. MMRM models may also be used on observed data at all time points as sensitivity analyses. The fixed effects of treatment, visit, and treatment by visit interaction will be included. Baseline value will be included as a covariate. No adjustments for multiplicity will be made.

9.3.6. Tertiary/Exploratory Endpoint(s)

Tertiary and exploratory endpoints will be analyzed descriptively. CCI [redacted]

9.3.7. Safety Analyses

The safety data will be summarized in accordance with Pfizer Data Standards. All safety analyses will be performed on the safety population. Safety endpoints include Incidence of treatment emergent AEs and SAEs, clinically significant changes in vital signs, ECG, and laboratory tests.

9.3.7.1. 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 post-dose 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

9.3.8. Other Analyses

CCI data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

CCI [redacted]

9.3.8.2. Interim Analyses

An interim analysis may be performed to assess efficacy and safety when approximately 60% of the planned participants, ie, approximately 25 participants per arm in AD and 18 participants per arm in PsO have completed or had the chance to complete Week 8 visit. Interim analysis results may be used for decisions regarding stopping for futility and internal program development. Additional interim analysis may be performed and will be detailed in the IRC charter.

Before any interim analysis is performed, the details of the objectives, decision criteria, dissemination plan, and method of maintaining the study blind as per Pfizer's SOPs will be documented and approved in an IRC charter. In addition, the analysis details will be documented and approved in the SAP.

9.4. Sample Size Determination

9.4.1. Sample Size Determination for AD

A sufficient number of participants will be screened to achieve approximately 120 participants randomly assigned to study intervention. The sample size calculation is based on the primary efficacy estimand IGA success at Week 12. Assuming 15% IGA

success rate for the vehicle arm, a sample size of 40 per arm will have 89% power to detect a treatment difference of 35% under a 1-sided Type 1 error 0.0125 for each of the 2 dose levels comparison to vehicle by the unconditional exact test, with an overall Type 1 error 0.025 1-sided. In addition, this sample size will provide 96% power to detect a 42% difference in EASI-75 between an active arm (62% EASI-75) and vehicle (20% EASI-75).

9.4.2. Sample Size Determination for PsO

A sufficient number of participants will be screened to achieve approximately 120 participants randomly assigned to study intervention. The sample size calculation is based on the primary efficacy estimand PGA success at Week 12. Assuming 8% PGA success rate for the vehicle arm, a sample size of 30 per arm will have 92% power to detect a treatment difference of 42% under a 1-sided Type 1 error 0.008 for each of the three dose levels comparison to vehicle by the unconditional exact test, with an overall Type 1 error 0.025 1-sided. In addition, this sample size will provide 96% power to detect a 44% difference in PASI-75 between an active arm (50% PASI-75) and vehicle (6% PASI-75).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations;
- For reporting cases of suspected child abuse and/or neglect according to local medical association (eg, AAP) or health department guidelines.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

10.1.2. Financial Disclosure

Investigators and sub-investigators 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/assent Process

The investigator or his/her representative will explain the nature of the study to the participant and his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, minor child), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, they must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. Participant's parent(s)/legal guardian 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's parent(s)/legal guardian and the study participant as applicable 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's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of his or her child's personal data keeping in mind the privacy rights that may restrict access of older adolescents medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

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

10.1.4. Data Protection

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

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of

disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will use an IRC. The IRC is independent of the study team and includes only internal members. The IRC charter describes the role of the IRC in more detail.

The IRC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the IRC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, investigators, as appropriate.

This study will not use a DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

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

Documents within marketing authorization packages/submissions

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

Data sharing

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

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

10.1.7. Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

10.1.8. Source Documents

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

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

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in study monitoring plan, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

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

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

10.1.9. Study and Site Start and Closure

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

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

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

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

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

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

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

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[redacted]

10.1.11. Sponsor's Qualified Medical Personnel

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

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an ECC) at the time of informed consent/assent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant. The Pfizer Call Center number should only be used when the investigator and site staff cannot be reached. The Pfizer Call Center number is not intended for use by the participant directly; if a participant calls that number directly, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

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

Table 6. Protocol Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN and creatinine	Protein (qual)	FSH[c]
Hematocrit	Creatinine Kinase	Blood (qual)	Pregnancy test (β-hCG)[d]
RBC count and indices	Glucose	Nitrites	
MCV	Calcium	Leukocyte esterase	
MCH	Sodium	Microscopy[b]	
MCHC	Potassium		
WBC count with differential	Chloride		
	Total CO_2 (bicarbonate)		
Total neutrophils (Abs)	AST, ALT		
Eosinophils (Abs)	Total bilirubin		
Monocytes (Abs)	Direct Bilirubin[a]		
Basophils (Abs)	Alkaline phosphatase		
Lymphocytes (Abs)	Uric acid		
Platelet count	Albumin		
	Total protein		

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. At Screening only.
d. Serum or urine β-hCG for female participants of childbearing potential per SoA. Serum pregnancy test must be performed at Screening.

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.

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

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

10.3.2. Definition of an SAE

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

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

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

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

g. Other situations:

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

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

AE and SAE Recording/Reporting

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

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

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

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

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

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

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

Assessment of Intensity

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

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 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 or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below.
    - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

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 agrees to use a highly effective contraceptive method (failure rate <1% per year) during the intervention period and for a minimum of 28 days after the last dose of study intervention. If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

For a female participant who becomes pregnant, this information will be shared with the study participant's parent/guardian if the participant's age is 12-17 years old or as required by local regulations.

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. Premenarchal.
2. 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.

3. 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.

          Note: For women over 60 years of age, FSH may still be tested, but is left to the discretion of the PI.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.

The following contraceptive methods are appropriate for this study:

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

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

5. Vasectomized partner:

   - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the 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 + barrier*;
   - Intravaginal + barrier*;
   - Transdermal + barrier*.

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

   - Oral + barrier*;
   - Injectable + barrier*.

   * In addition, one of the following effective barrier methods must also be used when options 6 or 7 are chosen above:

   - Male or female condom, with or without spermicide;
   - Cervical cap, diaphragm, or sponge with spermicide;

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

8. Sexual abstinence:

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multi study assessment of genetic factors involved in the response to PF-07038124 or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Retained samples will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

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

Potential Cases of Drug-Induced Liver Injury

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

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free 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 SAEs

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

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

10.8. Appendix 8: Prohibited Prior and Concomitant Medications

10.8.1. Prohibited Prior and Concomitant Medications

The prohibited concomitant medications listed below should not be taken with PF-07038124 for the period of time at least equal to the required washout period listed in the table, and throughout the conduct of the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgement on the ongoing participation of any participant with prohibited medication use during the study.

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®), difamilast.	2 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).

Drug Category	Drugs (Examples below)	Required Washout Period Requirement Prior to Day 1/Randomization
Systemic immunosuppressive agents and other oral nonbiologic treatments	methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, mizoribine, tacrolimus, MMF, hydroxycarbamide (hydroxyurea), fumaric acid derivatives, acitretin.	4 weeks.
Oral JAK inhibitors	tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib, peficitinib, filgotinib, abrocitinib (Cibinqo®).	4 weeks.
Interferon gamma	interferon gamma-1b (Actimmune®).	4 weeks.
Light therapy etc.	sunbathing, tanning bed use, or light therapy (UV, UV-B, PUVA), excimer laser (308 nm).	4 weeks.
Topical retinoids, Vitamin D analogues, 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).
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.
TCI or JAK inhibitor, anywhere on the body	topical tacrolimus (Protopic®), topical pimecrolimus (Elidel®), delgocitinib.	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).

Drug Category	Drugs (Examples below)	Required Washout Period Requirement Prior to 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,
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, urea- and lactic acid- free) 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 10.8.2 below.	7 days or 5 half-lives (whichever is longer).

10.8.2. Prohibited Concomitant Medications which may Result in 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.

10.9. 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 Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (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.
- Confirmation that IP is applied to all treatment-eligible areas regularly.
- Administration of PROs, if applicable for that visit.
    - If administered, PRO assessment should occur at the beginning of the visit and to be conducted in a quiet, private area (ie, no one else around and/or able to provide input or influence their responses).
    - Document responses to CCI [redacted]
    - The site staff should read the instructions and questions to the participant and record the participant's responses in source documents.

- Questions should be read verbatim at clear and comfortable pace (re-read, if needed) with NO input from site staff or physicians.
- Do not interpret any part of the questionnaire for the participant. If the participant does not understand, please repeat the question and response choices verbatim and ask them to select the response that they feel best represents his/her experience.
- Confirm the patient's response selection before you record the answer (eg, you would like me to select "moderate pain", is that right?).

- Observation of application of study intervention on treatable area(s) (if feasible).
- Assessment of local tolerability, post application of IP on non-lesional areas.
- Assessment of efficacy outcome measures as described in 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:

- Laboratory Safety evaluations, including pregnancy testing (Table 6).

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.

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.

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. 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_Home_Health_Visits of this appendix regarding pregnancy tests;
- ECG;
- Vital signs;
- Physical assessment;
- Laboratory samples, CCI [redacted]
- Collect and weigh previous study intervention tubes;
- Dispensing of study intervention;

- Study intervention application and observation;
- Local Tolerability assessments;
- Other, as determined by the Investigator and/or sponsor.

10.9.5. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or serious 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 IGA, EASI, BSA, and severe lesion TSS (if applicable).
- Efficacy Assessments for PsO, including PGA, PASI, and BSA.

Only qualified raters will be allowed to evaluate participants remotely.

10.10. Appendix 10: Diagnosis Criteria for AD

Per AD-specific Inclusion Criteria as in Section 5.1.2.1, a participant is to have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka.[7]

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

10.11. Appendix 11: C-SSRS

Participants should be evaluated for any psychiatric condition including recent or active suicidal ideation or behavior and excluded from the study who meets any of the following criteria at Screening:

a. Suicidal ideation associated with actual intent and a method or plan in the past year: "Yes" answers on items 4 or 5 of the 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.

10.12. Appendix 12: Disease-Specific Assessments

10.12.1. AD-specific assessments

10.12.1.1. 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.

Table 7. Investigator's Global Assessment for AD

Score	Category	Description*
0	Clear	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 hair-bearing scalp from the assessment/scoring.

10.12.1.2. 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] The clinical evaluator of AD will perform an assessment of severity and area involved as described below.

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 4 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 8 below.

Table 8. 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 hair-bearing scalp from the assessment/scoring.

Area Score

The extent (% BSA) to which each of the four body regions ie head and neck, upper limbs, trunk and lower limbs is involved with AD is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 9). The %BSA is calculated as described in Section 10.12.1.3.

Table 9. EASI Area Score Criteria

Percent BSA* with AD in a Body Region	Area Score
0%	0
0 to <10%	1
10 to <30%	2
30 to <50%	3
50 to <70%	4
70 to <90%	5
90 to 100%	6
*based on handprint method	

Body Region Weighting

Each body region is weighted according to its approximate percentage of the whole body (Table 10).

Table 10. Body Region Weighting

Body Region	Total Number of Handprints in Body Region	Surface Area of Body Region Equivalent of One Handprint	Body Region Weighting
Head and Neck	10	10%	0.1
Upper Limbs	20	5%	0.2
Trunk (including axillae and groin)	30	3.33%	0.3
Lower Limbs (including buttocks)	40	2.5%	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 hair-bearing scalp will be excluded from the EASI assessment in this study, the maximum possible score will be less than 72.0.

10.12.1.3. BSA

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.

10.12.1.4. Severe Lesion TSS

The severe lesion TSS is an assessment of the Investigator-identified/selected severe lesion in each of the following: erythema, induration/papulation, excoriation, and lichenification. Each of these are rated using the 4-point severity scale described in Table 11. These ratings are then added to create a total score (12-point scale; ranging from 0 to 12 points).

Table 11. Severe Lesion TSS

Score		Description
Erythema (E; Redness)		
0	Absent	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
Induration/Papulation (I)		
0	Absent	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Excoriation (Ex; Evidence of Scratching)		
0	Absent	No evidence of excoriation
1	Mild	Mild excoriation present
2	Moderate	Definite excoriation present
3	Severe	Marked, deep, or extensive excoriation present
Lichenification (L; Epidermal Thickening)		
0	Absent	No epidermal thickening
1	Mild	Minor epidermal thickening
2	Moderate	Moderate epidermal thickening; accentuated skin lines
3	Severe	Severe epidermal thickening; deeply accentuated skin lines

10.12.2. Psoriasis-specific assessments

10.12.2.1. PGA

The PGA of psoriasis is scored on a descriptive 5-point scale.[9] The 5-point scale for PGA is: 0, "clear"; 1, "almost clear"; 2, "mild"; 3, "moderate"; 4 "severe". The assessment will be a static evaluation without regard to the score at a previous visit. The clinical evaluator of psoriasis will perform an assessment of the overall severity and assign an PGA score and category as described below.

Table 12. 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
* The PGA will exclude hair-bearing scalp, palms, soles, and finger and toe nails from the assessment/scoring		

10.12.2.2. PASI

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 13.

Table 13. 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 hair-bearing scalp, palms, soles, and finger and toe nails from the assessment/scoring		

Area Score

The extent (% BSA) to which each of the four body regions (ie head and neck, upper limbs, trunk, and lower limbs) is involved with psoriasis is categorized using a non-linear scaling method to a numerical area score according to the following BSA scoring criteria (Table 14). The %BSA is calculated as described in Section 8.1.2.1.3.

Table 14. PASI Area Score Criteria

Percent BSA* with Psoriasis in a Body Region	Area Score
0%	0
0 to <10%	1
10 to <30%	2
30 to <50%	3
50 to <70%	4
70 to <90%	5
90 to 100%	6
based on handprint method	

Body Region Weighting

Each body region is weighted according to its approximate percentage of the whole body (Table 15).

Table 15. Body Region Weighting

Body Region	Total Number of Handprints in Body Region	Surface Area of Body Region Equivalent of One Handprint	Body Region Weighting
Head and Neck	10	10%	0.1
Upper Limbs	20	5%	0.2
Trunk (including axillae and groin)	30	3.33%	0.3
Lower Limbs (including buttocks)	40	2.5%	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 hair-bearing scalp, palms, soles and nails will be excluded from the PASI assessment in this study, the maximum possible score will be less than 72.0.

10.12.2.3. BSA

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 PsO; h = head & neck; u = upper limbs; t = trunk; l = lower limbs.

10.13. Appendix 13: Abbreviations

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

Abbreviation	Term
AAP	American Academy of Pediatrics
Abs	absolute
AD	atopic dermatitis
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
β-hCG	beta-human chorionic gonadotropin
BAP	biomarker analysis plan
BPO	benzoyl peroxide
BID	twice daily
BLQ	below the limit of quantification
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
C_{av}	average concentrations
CCI [redacted]	
CFB	change from baseline
CFR	code of federal regulations
cGMP	cyclic guanosine monophosphate
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	clinical trial
CYP450	cytochrome p450
DDI	drug-drug interaction

Abbreviation	Term
DILI	drug-induced liver injury
CCI	[redacted]
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dispensable unit
EASI	Eczema Area and Severity Index
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
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
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
fup	fraction unbound plasma
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HEENT	head, eyes, ears, nose and throat
HRQoL	health-related quality of life
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitive concentration
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IGA	Investigator's Global Assessment
IgE	immunoglobulin e
IL	interleukin
IMP	investigational medicinal product

Abbreviation	Term
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
LLOQ	lower limit of quantification
LPS	lipopolysaccharide
MAR	missing at random
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MMF	mycophenolate mofetil
MMRM	mixed model repeated measures
msec	millisecond
MW	molecular weight
NA	not applicable
NIMP	non-investigational medicinal product
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PASI	Psoriasis Area and Severity Index
PBMC	peripheral blood mononuclear cell
PCP	primary care provider
PD	pharmacodynamic(s)
PDE	phosphodiesterase
PDE4	phosphodiesterase 4
PGA	Physician Global Assessment
CCI [redacted]	
PI	principal investigator
PK	pharmacokinetic(s)
CCI [redacted]	
PP-NRS	Peak Pruritus Numerical Rating Scale
PRN	as needed
PRO	patient reported outcomes
CCI [redacted]	
PsO	plaque psoriasis

Abbreviation	Term
PT	prothrombin time
PUVA	psoralen – ultraviolet a
PVC	premature ventricular contraction/complex
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	QTC corrected using Fridericia's formula
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOC	System organ class
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SSID	single subject identification
SUSAR	Suspected Unexpected Serious Adverse Reaction
CCI	[redacted]
TBili	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
TEAE	treatment emergent adverse events
Th2	type 2 helper T cell
TNF	tumor necrosis factor
TSS	Total Sign Score
uCav	unbound average concentrations
UGT	uridine glucuronyl transferases
ULN	upper limit of normal
US	United States
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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