A PHASE 1, RANDOMIZED, DOUBLE-BLIND, VEHICLE AND ACTIVE COMPARATOR-CONTROLLED, PSORIASIS PLAQUE TEST STUDY TO ASSESS SAFETY, TOLERABILITY, AND PSORIATIC SKIN INFILTRATE THICKNESS FOLLOWING REPEATED, TOPICAL DOSES OF PF-06763809 SOLUTION IN SUBJECTS WITH MILD TO MODERATE CHRONIC PLAQUE PSORIASIS

Investigational Product Number:	PF-06763809
Investigational Product Name:	Not applicable
United States (US) Investigational New Drug (IND) Number:	Not applicable
European Clinical Trials Database (EudraCT) Number:	2017-002684-18
Protocol Number:	C3561001
Phase:	1

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	8 February 2018	1. Added blood pressure measurements on Day 1 for sentinel subjects (Schedule of Activities). *Rationale: To monitor vitals after IP administration in sentinel subjects.* 2. Added hematology blood tests for sentinel subjects daily on Days 2-8. *Rationale: To monitor hematologic parameters after IP administration in sentinel subjects.* 3. Added sentinel dosing (Section 3.1). *Rationale: In accordance with Ethics Committee request, to minimize risk given first in human study.* 4. Added a limit on the number of subjects replaced for non-safety reasons and clarified that this is at sponsor's discretion (Sections 3.1 and 6.4). *Rationale: To clarify the maximum number of subjects in the study.* 5. Added to inclusion criterion # 1 that subjects have to be ≥18 years at the time of consent (Section 4.1). *Rationale: To comply with country (Germany) specific requirements.* 6. Decreased allowed alcohol consumption within 6 months before Screening (Exclusion

		criterion # 4, Section 4.2). *Rationale: To minimize potential confounding of efficacy & safety assessments.* 7. Decreased maximum values for systolic and diastolic blood pressure and added minimum value for systolic blood pressure (Exclusion criterion # 6, Section 4.2). *Rationale: To minimize risk factors and potential confounding of cardiovascular safety assessments.* 8. Decreased allowed AST, ALT and total bilirubin (Exclusion criterion # 8, Section 4.2), excluded subjects with history of Gilbert syndrome. *Rationale: To minimize risk factors and potential confounding of hepatic safety assessments.* 9. Excluded more than occasional consumption of tobacco-or nicotine-containing products and/or in excess of 5 cigarettes per day (Exclusion criterion # 13 in Section 4.2, Section 4.4.1). *Rationale: To minimize risk factors and potential confounding of safety assessments.* 10. Added exclusion criterion for known hypersensitivity against active comparators, any of its excipients or dressing material and for subjects who consent to biopsy, known hypersensitivity to local anesthesia (Exclusion criterion #25, Section 4.2). *Rationale: To minimize risk to*

		study participants. 11. Added a restriction on biologics to 5 half-lives (whichever is longer) (Exclusion criterion #20, Section 4.2). *Rationale: To accommodate prior use of investigational biologics with an appropriate period since dosing.* 12. Allowed site staff administering IP to be unblinded in Sections 5.1, 5.2 and 5.3. *Rationale: To ensure appropriate dosing but without bias in assessments.* 13. Clarified how subjects will be assigned to treatment (Section 5.1). *Rationale: To clarify treatment assignment.* 14. Administrative clarifications in Section 4.2 (exclusion criterion # 10), Sections 3.2, 5.2, 5.4.1, 5.4.2, 5.6 and Appendix 1. *Rationale: To incorporate protocol administrative letters and to provide additional administrative clarifications.*
Original protocol	19 September 2017	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale:

PF-06763809 is a retinoid acid-related orphan receptor 2 (RORC2; also referred to as RORγt) inhibitor. Inhibition of RORC2-mediated inflammation has the potential to provide a novel approach in the topical treatment of plaque psoriasis. The aim of this first-in-human study is to assess the antipsoriatic activity of PF-06763809 solutions in subjects with chronic mild to moderate plaque psoriasis in a psoriasis plaque test (PPT).

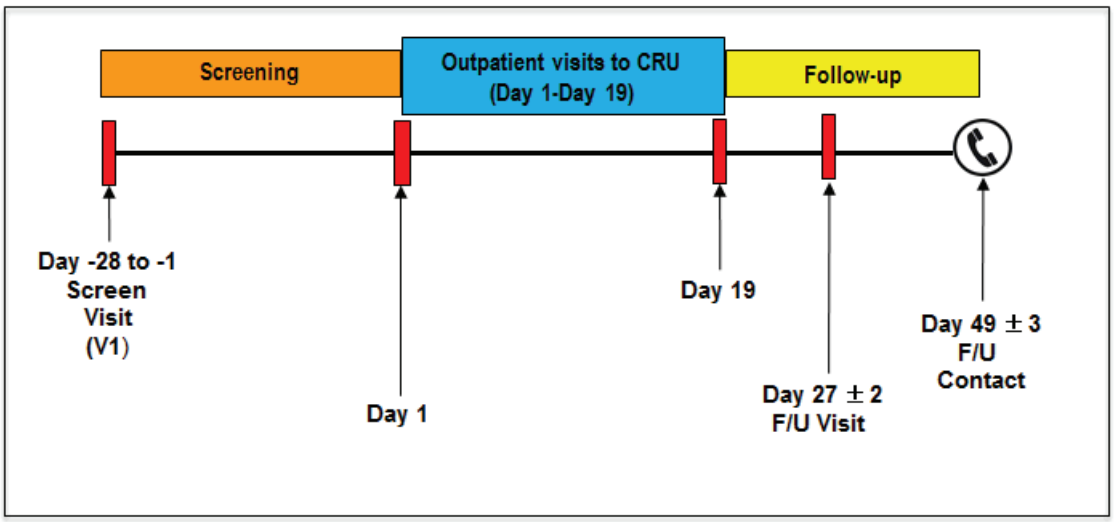
Objectives and Endpoints:

Primary Objective(s):	Primary Endpoint(s):
• To assess the changes in psoriatic skin infiltrate thickness/echo poor band (EPB) in response to PF-06763809 2.3%, 0.8% and 0.23% applied topically for 18 consecutive days as compared to the vehicle control.	• Change relative to baseline at Day 19 in psoriatic skin infiltrate thickness/EPB.
• To determine the safety and tolerability of multiple dose topical administration of PF-06763809 in psoriasis subjects.	• Assessment of adverse events (AEs), clinical laboratory tests, vital signs (including blood pressure and pulse rate), and cardiac conduction intervals as assessed via 12-lead electrocardiogram (ECG).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the Area Under the Curve (AUC) of psoriatic skin infiltrate thickness/EPB for PF-06763809 compared to vehicle.	• AUC of the psoriatic skin infiltrate thickness/EPB from Day 1 to Day 19.
• To assess the effect of PF-06763809 compared to calcipotriene/calcipotriol solution in the change of psoriatic skin infiltrate thickness/EPB both within and following 18 days of treatment.	• Change relative to baseline in psoriatic skin infiltrate thickness/EPB.
• To assess the effect of PF-06763809 compared to betamethasone solution in the change of psoriatic skin infiltrate thickness/EPB both within and following 18 days of treatment.	• Change relative to baseline in psoriatic skin infiltrate thickness/EPB.
CCI [redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Study Design:

The study is proposed as a randomized, double-blinded, vehicle and active comparator-controlled, multiple dose study in subjects with psoriasis. Subjects will receive topical doses (2.3%, 0.8% and 0.23%) of PF-06763809, PF-06763809 vehicle, and two active comparators.



Study Treatment:

For this study, the investigational products are:

- PF-06763809 (2.3%, 0.8% and 0.23%);

- Matching vehicle.

The comparator agents are:

- calcipotriene/calcipotriol 50 µg/mL solution;
- betamethasone 1 mg/g solution.

Subjects with chronic plaque type psoriasis and with a treatment area sufficient for 6 treatment fields on 1 to 3 comparable plaques defined as having treatment fields with psoriatic skin infiltrate thickness/EPB of at least 200 µm will be enrolled in this study. All subjects will receive each study treatment once daily. All study treatments will be applied by way of Duhring® chambers seated in holes punched in a hydrocolloid dressing (eg, Varihesive® E [Convatec], Munich, Germany). The hydrocolloid dressing will be fixed on the skin with adhesive patches (eg, BSN Medical, Hamburg, Germany, or comparable) containing the same holes for the chambers as the hydrocolloid dressing. PPD [redacted] After each test chamber is filled with the appropriate volume, the test chambers will be subsequently applied to the test fields.

The chambers will be fixed in place with Leukosilk® (eg, BSN, Hamburg, Germany or comparable) and will be removed before each new application. The distance between the chambers must be at least 1.5 cm. This distance is sufficient to exclude interactions with neighboring fields. The fields will be treated with occlusion for a treatment period of 18 days.

Statistical Method:

The sample size determination is based on the primary endpoint of change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19. The log-scale of infiltrate thickness is used for a more stable variability over the assessed efficacy range and a better approximation to normal distribution.

A sample size of 15 completers was selected based on the power analysis results and enrollment should ensure approximately 15 completers.

All subjects who have at least one application of the investigational products and have at least one post-baseline assessment of the primary efficacy variable will be included into the Full Analysis Set (FAS) which will be the primary analysis set.

The primary endpoint for this study is the change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19 PPD [redacted] for PF-06763809 in comparison to vehicle. The efficacy assessment of PF-06763809 will be performed for the change from baseline in log of the psoriatic skin infiltrate thickness/EPB on Day 19 using a longitudinal analysis of covariance model, with treatment, visit, treatment by visit interaction as main effects and the log of the psoriatic skin infiltrate thickness/EPB at

baseline as covariate. The CS@UN covariance structure will be assumed to adequately model the two within-subject factors (treatment, visit), where the compound symmetric (CS) correlation is for repeated measures from different treatments within each visit and the unstructured (UN) correlation is for longitudinal measures from different visits. The point estimate and 95% confidence interval (CI) for the difference in log transformed means at Day 19 visit between treatment groups will be constructed using least square means and appropriate standard errors.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections 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 schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Activities

[for a list of abbreviations refer to Appendix 1]	Screen	Treatment Phase (activities at 0 hr before dosing unless otherwise specified)																		FU Visit	
Visit Identifier/Study Day	**-28 to -3**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**27±2[a]**	**49±3**
Informed consent & demography	x																				
Outpatient visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Review inclusion/exclusion criteria	x	x																				
Medical history	x	x																				
Review alcohol/tobacco/contraception use	x	x																			x	x[b]
Review prior or concomitant treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination[c]	x	x																		x		
Height + body weight	x																					
Descaling if necessary	x[d]																					
Serious and non-serious adverse event monitoring	x	x	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	x	x	x
Single 12-lead ECG	x	x									x									x		
Single, supine vital sign assessment	x	x[k]									x									x		
Blood sampling for –																						
FSH in females amenorrheic ≥12 consecutive months, ***only***	x																					
CCI																						
Clinical laboratory tests (see Section 7.1.1)	x	x	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]	x[l]		x									x		
Urine sampling for –																						
Urine drug test	x																					
Urinalysis (and microscopy, if needed)	x	x									x									x		
Randomization		x																				
Determination of test fields		x																				
Removal of chambers and IMP residues			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Investigational product administration[f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
CCI																						
CCI																						

Table 1. Schedule of Activities

[for a list of abbreviations refer to Appendix 1]	Screen	Treatment Phase (activities at 0 hr before dosing unless otherwise specified)																		FU Visit	
Visit Identifier/Study Day	**-28 to -3**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**27±2[a]**	**49±3**
CCI [redacted]																						

NOTE: Where applicable, all activities are to be conducted pre-dose unless otherwise noted.

a. This follow-up visit is only mandatory for subject who have consent to the optional biopsy or who have an open AE following completion of Day 19.
b. Confirmation of appropriate contraception use, *only*.
c. A complete physical examination may be done at Screening or may be deferred to Day 1 at the discretion of the Investigator; at all other time points, limited PE for findings during previous PE or new/open AEs *only*, at Investigator discretion.
d. 5% salicylic acid in Vaseline provided to applicable subjects to apply at home until Day -2 for a maximum of five days.
CCI [redacted]
f. Investigational product administration will occur every day without regard to food or a meal.
CCI [redacted]
C [redacted]
CCI [redacted]
k. Blood pressure will be taken once pre-dose. For sentinel subjects only, blood pressure will be taken also every 30 min post-dose until 4 hours post-dose.
l. For sentinel subjects only, blood samples (for hematology only) will be taken on Days 2-8 inclusive.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06763809 is a retinoid acid-related orphan receptor 2 (RORC2; also referred to as RORγt) inhibitor that is being developed for topical treatment of adult subjects with mild or moderate psoriasis vulgaris (plaque psoriasis).

1.2. Background and Rationale

Plaque psoriasis is a chronic inflammatory skin disease of variable severity that is characterized by red, scaly, raised plaques. Chronic plaque psoriasis is a common skin disorder with a worldwide prevalence of 2%.[1] Psoriasis had been viewed as primarily a disease of epidermal hyperplasia, but more recently has come to be regarded as an immune-mediated disease.[2] Cutaneous and systemic overexpression of T cells, as well as type 1 cytokines such as interleukin (IL)-2, IL-6, IL-8, IL-12, IL-23, IL- 17, have been implicated in the pathophysiology of chronic plaque psoriasis.[3] T-cell infiltration and associated pro-inflammatory cytokines drive epidermal hyperplasia, which is characterized by increased cell division and aberrant differentiation that result in the psoriatic phenotype.[2,4,5]

Although psoriasis is not a life-threatening disease, it can profoundly impact the individual's quality of life causing disability (eg, physical and mental functioning) akin to other major diseases such as type 2 diabetes, myocardial infarction, and arthritis.[6] It is also associated with serious co-morbidities, including psoriatic arthritis, depression, malignancy, metabolic syndrome, cardiovascular morbidity and mortality.[4,7-11,]

Nearly all patients with mild psoriasis are treated topically. Patients with moderate to severe disease, who receive systemic therapies or phototherapy, often also apply topical agents to recalcitrant areas. Topical treatment of psoriasis is dominated by corticosteroids and vitamin D analogs. However, to be effective in this disease, corticosteroids must be high potency (eg, fluocinonide) or ultra-high potency (eg, clobetasol). These agents can cause skin atrophy and striae with chronic use and hypophyseal-pituitary axis suppression when applied over large body surfaces. Vitamin D analogs are less effective and often irritating, but may be used in combination with corticosteroids. Consequently, there remains an unmet medical need for a topical therapy that will provide symptomatic relief with a high degree of safety and minimize required doses of systemic medications, ultimately reducing the burden of the disease.

RORC2 is a transcription factor that controls the production of the cytokine IL-17A, which plays a central role in the pathogenesis of psoriasis.[12,13] Psoriasis lesions contain prominent inflammatory cell infiltrates that include T cells that produce IL-17A.[14] The evidence that RORC2 controls IL-17A production in humans is provided by the observation that human subjects who are homozygotes for a loss-of-function mutation in RORC gene lack IL-17A+ cells in peripheral blood.[15] Naïve T cells differentiate into T helper 17 (Th17) cells upon antigen presentation in the presence of appropriate cytokines including IL-1β, IL-23, TGFβ, and IL-6. TH17 cells are elevated in psoriatic lesions, along with levels of proinflammatory cytokines, including IL-17A, IL-17F, IL-17C, which are expressed by TH17 cells and are

likely mediators of inflammation and tissue damage.[16,17] RORC2 is barely detectable in normal naïve T cells and its expression is dramatically increased during the Th17 differentiation process.[18]

In addition to genetic evidence, several effective psoriasis therapies target TH17 cytokine production, suggesting a central role of TH17 and IL-17 in the disease. Secukinumab selectively targets IL-17A and has been shown to be effective in the treatment of psoriasis, and other therapies such as cyclosporine, phototherapy, and infliximab inhibit the TH17 pathway.[19-22] The monoclonal antibody Ustekinumab, disrupts IL-23 activation of TH17 cells by blocking the IL-23 receptor, and has proven to be effective in treating psoriasis.[23] Collectively, there is strong rationale for targeting RORC2, which is implicated in the TH17 pathway and IL-17A in the treatment of psoriasis. As such, it is hypothesized that administration of a RORC2 inhibitor should block its activity in infiltrating T cells in psoriatic lesions, thereby reducing the production of pathogenic IT-17A, and ultimately improving the clinical signs and symptoms for patients with psoriasis.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure for PF-06763809. The SRSD for the comparator agents calcipotriene/calcipotriol solution (related to a synthetic form of vitamin D) and betamethasone solution are the approved product labels.

1.2.1. Nonclinical Primary Pharmacology

1.2.1.1. In Vitro Assays

PF-06763809 inhibited the binding of purified recombinant human RORC2 ligand binding domain to steroid receptor coactivator-1 (SRC-1) with an IC_{50} value of 3.1 nM which demonstrates direct interaction of PF-06763809 with RORC2.

Because RORC2 is a transcription factor that directly controls IL-17A expression in lymphocytes, the effect of PF-06763809 on IL-17A production was examined. In human lymphocytes subjected to Th17 differentiation, PF-06763809 inhibited IL-17A protein production and gene expression with IC_{50} values of 2.2 and 1.6 nM, respectively, which are consistent with the potency of PF-06763809 on RORC2 activation as described above. This effect of PF-06763809 on Th17 lymphocytes was specific because PF-06763809 had minimal effect on IFNγ and IL-13 production by human Th1 and Th2 cells, respectively, and no effect on cell viability. Topical administration of PF-06763809 to human skin in vitro with the formulation that will be used in this clinical study caused a dose-dependent inhibition of IL-17A gene expression relative to vehicle alone which demonstrates that PF-06763809 has IL-17A inhibitory activity in the target organ of psoriasis.

PF-06763809 inhibited IL-17A production in mouse and rat lymphocytes, and minipig peripheral mononuclear cells subjected to Th17 differentiation with IC_{50} of 4.2, 3.2 and 90 nM, respectively.

1.2.1.2. In Vivo Studies

The efficacy of topically applied PF-06763809 was evaluated in two mouse models of ear skin inflammation, namely the imiquimod-induced model and the IL-23-induced model. These models partially respond to neutralizing anti-IL-17 mAb which is a highly efficacious mechanism in human psoriasis. In both models, topical PF-06763809 inhibited the increase in ear thickness, which is a readout of inflammation, to a similar maximum extent as anti-IL-17A neutralizing mAb. A dose-dependent effect of PF-06763809 in ear swelling was observed in the IL-23-induced model. In addition, 5% topical PF-06763809 statistically significantly inhibited IL-17A gene expression in both models, and also inhibited IL-17A protein production in imiquimod-induced model. IL-17A protein determinations in IL-23-induced model were very low and close to the limit of detection of the assay so the results were inconclusive. The effect of PF-06763809 on IL-17A gene expression and protein levels is consistent with its inhibitory action on RORC2. Taken together, these data suggest that topical PF-06763809 inhibited the production of IL-17A in these mouse models to an extent that was sufficient to cause a reduction in inflammation which was similar to neutralization of IL-17A by anti-IL-17A mAb. Systemic exposure of PF-06763809 was below its IC_{50} for inhibition of IL-17A production by mouse lymphocytes in vitro, which suggests that the observed effects of PF-06763809 were due to its local action in the skin.

1.2.2. Nonclinical Pharmacokinetics and Metabolism

Following intravenous administration, PF-06763809 exhibited a plasma clearance (CL) in rats of 33 mL/min/kg (hepatic blood flow value 70 mL/min/kg) and in mini-pigs of 22.6 mL/min/kg (hepatic blood flow value 39 mL/min/kg). The steady state volume of distribution (Vss) values in rats and mini-pigs were 1.8 and 3 L/kg, respectively with half-life values of 1.4 and 2.6 hours, respectively.

Following topical administration to mini-pigs as part of the topical toxicology study, the Day 28 estimated topical bioavailability was approximately 1%.

PF-06763809 was highly bound in rat, mini-pig, and human plasma with fraction unbound values of 0.00887, 0.0225, and 0.0268, respectively. The blood to plasma ratios were 0.62, 0.83, and 0.8, respectively.

The major route of metabolism of PF-06763809 in human hepatocytes was oxidation in the cyclopentane ring. All metabolites observed in human hepatocytes were present in hepatocytes from preclinical species. Following topical administration to min-pigs, only parent PF-06763809 was observed circulating in plasma.

CYP3A4 is the major cytochrome P450 (CYP) responsible for the metabolism of PF-06763809, with minor contributions from CYP2C8, 2C9, 2C19, and 3A5.

Based on the relatively low predicted systemic exposure following topical administration, PF-06763809 is not expected to cause a CYP mediated drug interaction by inhibition or induction. It is possible that CYP3A4 inhibitors will significantly increase the exposure of PF-06763809 on co-administration. However, based on the large potential safety margins, this interaction is highly unlikely to have clinical consequences.

Further details of the nonclinical pharmacokinetic profile of PF-06763809 are provided in the current Investigator Brochure.

1.2.3. Summary of Toxicology Studies

In nonclinical safety studies with PF-06763809 in rats (oral) and mini-pigs (dermal) of up to 1-month in duration, the cardiovascular and immune systems have been identified as potential key systemic targets and vehicle-related mild to moderate skin irritation by the topical route of administration. The no observed adverse effect levels (NOAELs) in the pivotal toxicity studies were 200 mg/kg in rats (Cmax, 6280 ng/mL and AUC_{24}, 71,000 ng•h/mL) and the maximum feasible dose, 2.3% formulation applied at 0.02 mL/cm^2/dose to ~10% body surface area, twice daily (BID), in minipigs (C_{max}, 41.3 ng/mL and AUC_{24}, 309 ng·h/mL). PF- 06763809 was not identified with mutagenic or clastogenic potential from in vitro and in vivo studies. PF-06763809 did not demonstrate phototoxicity potential and did not demonstrate a sensitization potential in the in vitro sensitivity assays. Details of the nonclinical safety program are provided in the current Investigator's Brochure.

1.2.4. Calcipotriene/calcipotriol Solution

PF-06763809's anti-psoriatic activity will be benchmarked against that of calcipotriene solution. In a similar designed study, Daivonex® solution reduced the skin inflammatory infiltrate by 38% relative to vehicle with a within standard deviation (SD) of 0.435 (data on file; bioskin®).

1.2.5. Betamethasone Solution

PF-06763809's anti-psoriatic activity will be benchmarked against that of betamethasone solution. In a similar designed study, Betnesol® solution reduced the skin inflammatory infiltrate by 79% relative to vehicle (data on file; bioskin®).

While betamethasone solution is approved for scalp psoriasis, the proposed use being highly limited on other skin surfaces in this study, does not significantly increase the risks (or decrease acceptability of risks) associated with the use of this product. As noted earlier, the SRSD is the approved product label.

1.2.6. Benefit Risk Assessment Summary

There is no known benefit for the subjects with plaque psoriasis participating in this study since only small test fields will be treated. Based on the clinical safety profile as well as the projected low systemic availability of PF-06763809, the risk to the subjects with plaque psoriasis is deemed to be minimal.

1.3. Study Rationale

Inhibition of RORC2-mediated inflammation has the potential to provide a novel approach in the topical treatment of plaque psoriasis. This first-in-human study will evaluate PF-06763809 solution, applied topically to skin surface areas in subjects with chronic mild to moderate plaque psoriasis. The primary study objective using the psoriasis plaque test is to

assess the reduction in psoriatic skin infiltrate thickness/ echo poor band (EPB) as a measure of disease activity in response to study treatment; appropriate vehicle and active controls (calcipotriene/calcipotriol and betamethasone) will also be included. Safety and tolerability of PF-06763809 solution applied topically will also be assessed. Evidence of short-term clinical activity with PF-06763809 will systematically inform subsequent development of a formulation more suitable for topical use.

1.3.1. Design Rationale

1.3.1.1. Rationale for Design

The psoriasis plaque test (PPT) is a commonly employed methodology in the early assessment of topical agents for the treatment of psoriasis. Indeed, the skin infiltrate thickness/EPB thickness is considered an important indicator of disease activity in psoriasis and has been shown to correspond with increased inflammatory cell infiltrates, capillary congestion, and/or edema in the superficial dermis as identified by histopathology.[24,25] Given that the extent of the psoriatic infiltrate is an important clinical endpoint in psoriasis, the PPT relies on an objective biophysical measurement of psoriatic skin infiltrate thickness/EPB CCI to support traditional clinical endpoints in psoriasis.

Testing is conducted under optimized conditions using small skin surface areas located on stable psoriatic plaques in subjects with plaque psoriasis. The reduction in psoriatic skin infiltrate thickness/EPB in response to PF-06763809 solution (2.3%, 0.8%, and 0.23%), when applied topically at 180 µL to 1.1 cm^2 skin surface areas (a volume of 180 µL applied to a 1.1 cm^2 surface, equivalent to 164 $\mu L/cm^2$), will be measured in subjects with stable chronic plaque psoriasis. At the end of study treatment, the change relative to baseline in psoriatic skin infiltrate thickness of treated areas with PF-06763809's will be compared with vehicle as well as two active controls, calcipotriene/calcipotriol solution (50 µg/mL) and betamethasone (1 mg/g). The treated areas will be clinically assessed throughout the study. The study will also assess the safety and tolerability of topically applied PF-06763809 solution (2.3%, 0.8%, and 0.23%) in subjects with stable chronic plaque psoriasis.

CCI

This first-in-human study will enroll subjects with psoriasis and body mass index (BMI) of ≥17.5 and ≤35.5 kg/m^2. Use of this increased BMI range is justified to balance the need for an otherwise healthy subject population in this first study with PF-06763809 and permit recruitment of subjects with psoriasis who have higher prevalence for obesity.[26]

CCI [redacted]

1.3.2. Dose Rationale

The nonclinical safety profile of PF-06763809 has been adequately characterized in rat and mini-pig to support progression into human clinical studies up to 4 weeks in duration (See Section 1.2.3). Dose strengths selected for this are 2.3%, 0.8%, and 0.23%. The highest strength was selected based on the maximum solubility of the PF-06763809 in the vehicle and the results from the animal studies.

CCI [redacted] The doses applied in the study, are unlikely to be associated with clinically relevant systemic pharmacology based on the integration of the in vitro pharmacology and predicted exposure levels and as such, the safety monitoring implemented is reduced from what would be evaluated following oral administration in a first-in-human study. The proposed doses in this study showed efficacy in various animal efficacy models.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To assess the changes in psoriatic skin infiltrate thickness/EPB in response to PF-06763809 2.3%, 0.8% and 0.23% applied topically for 18 consecutive days as compared to the vehicle control.	• Change relative to baseline at Day 19 in psoriatic skin infiltrate thickness/EPB.
• To determine the safety and tolerability of multiple dose topical administration of PF-06763809 in psoriasis subjects.	• Assessment of adverse events (AEs), clinical laboratory tests, vital signs (including blood pressure and pulse rate), and cardiac conduction intervals as assessed via 12-lead electrocardiogram (ECG).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the Area Under the Curve (AUC) of psoriatic skin infiltrate thickness/EPB for PF-06763809 compared to vehicle .	• AUC of the psoriatic skin infiltrate thickness/EPB from Day 1 to Day 19.
• To assess the effect of PF-06763809 compared to calcipotriene/calcipotriol solution in the change of psoriatic skin infiltrate thickness/EPB both within and following 18 days of treatment.	• Change relative to baseline in psoriatic skin infiltrate thickness/EPB.
• To assess the effect of PF-06763809 compared to betamethasone solution in the change of psoriatic skin infiltrate thickness/EPB both within and following 18 days of treatment.	• Change relative to baseline in psoriatic skin infiltrate thickness/EPB.
CCI [redacted]	[redacted]

CCI [redacted]

3. STUDY DESIGN

3.1. Study Overview

The study is proposed as a randomized, double-blinded, vehicle and active comparator-controlled, multiple dose study in subjects with psoriasis. Subjects will receive topical doses (2.3%, 0.8% and 0.23%) of PF-06763809, PF-06763809 vehicle, and two active comparators in this study. In order to mitigate any unanticipated safety risks, sentinel dosing approach will be employed for this study. Two sentinel subjects will be dosed first for 18 days with all six treatments. The sponsor medical monitor will communicate with the investigator as soon as sentinel subjects complete Day 19, in order to determine whether it is safe to proceed with dosing of remaining subjects.

A total of approximately 15 subjects with chronic plaque type psoriasis and with a treatment area sufficient for 6 treatment fields on 1 to 3 comparable plaques defined as having treatment fields with psoriatic skin infiltrate thickness/EPB of at least 200 µm will be randomized to achieve approximately 15 evaluable subjects. The effect of the PF-06763809 solutions will be assessed in comparison to the corresponding vehicle, calcipotriene/calcipotriol and betamethasone solutions using the PPT, which also allows within subject comparison of treatments. Subjects will be screened within 28 days prior to application of investigational product to confirm that they meet the subject selection criteria for the study. The total duration of participation in the study will be approximately 7-weeks (minimum) to approximately 11-weeks (maximum), including the interval from Screening to the Follow-up phone call visit (Day 49). The six test fields will be selected on Day 1. A visual examination of the skin will be completed including measurement of psoriatic skin infiltrate thickness/EPB CCI [redacted] and clinical assessment. CCI [redacted]

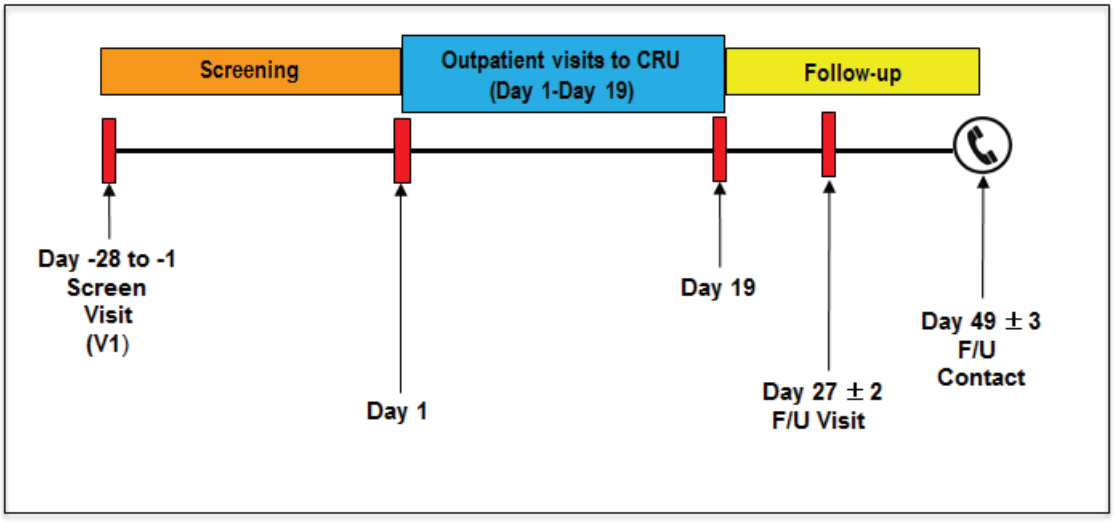
Approximately 180 µL of each liquid preparation and 180 µL of each comparator will be applied CCI [redacted] under Duhring® chambers (12 mm inside diameter, 14 mm outside diameter) seated in holes punched in hydrocolloid dressing (eg, Varihesive®, Bristol-Myers Squibb Gruppe, Munich, Germany). The fields will be treated under occlusion for 18 days. Subjects will return daily to the center for re-application of the test substances daily during the 18-day treatment period. Before each new application any remaining residue of the previously applied preparation will be removed gently by cleansing each test field with a clean soft tissue. Following this regimen, each preparation will be left in contact with lesional skin under a Duhring® chamber until removal for inspection at the next visit. This ensures that there is exposure to each preparation almost continually for the 18 days of the treatment phase of the study.

CCI [redacted]

Safety will be assessed by monitoring of vital signs, safety laboratory tests (see Section 7.1.4 and 7.1.1 respectively) and by recording of adverse events (AEs) and serious adverse events (SAEs) (see Section 8). Special attention will be given to local safety (ie, signs of skin irritation at the application sites). Skin reactions will be recorded as AEs.

The overall study design is summarized in Figure 1.

Figure 1. Overall Study Design



In this study, subjects who prematurely discontinue for non-safety related reasons ***may*** be replaced, at the discretion of the Sponsor. Up to 5 subjects may be replaced.

3.2. Stopping Rules for Dosing in Individual Subjects

At investigator discretion, ***for subjects' safety,*** dosing with any or all double-blinded investigational product/s, may be stopped in an individual subject – either temporarily **or** permanently. In such cases, any open TEAEs (treatment emergent adverse events) must be followed to resolution or until such time that the event is viewed to have stabilized – refer to Section 8 for details.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Healthy female subjects of non-childbearing potential and/or male subjects with psoriasis who, at the time of consent and Screening, are ≥18 years. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead electrocardiogram (ECG) or clinical laboratory tests, as assessed by the investigator.

2. Female subjects must be of non-childbearing potential to enroll into this study and as such, must meet at least ***one*** of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; **and** have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state (with a single repeat permitted if deemed necessary by Investigator);

   b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   c. Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

3. Body mass index (BMI) of ≥17.5 and ≤35.5 kg/m^2; and a total body weight >50 kg (110 lbs).

4. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

5. Subjects who are willing and able to comply with all scheduled visits, treatment plans, laboratory tests, and other study procedures.

6. Subjects with psoriasis vulgaris in a chronic stable phase and with a plaque area of mild to moderate severity sufficient for six treatment fields located in up to three plaque areas.

7. The target lesion(s) should be on the trunk or extremities (excluding palms/soles).

   a. Psoriatic lesions on the knees or elbows are not to be used as a target lesion.

   b. Test areas to be treated should have a comparable psoriatic skin infiltrate thickness/EPB of at least 200 μm.

c. The visual examination of the skin must be without disease findings unless the investigator considers an abnormality to be irrelevant to the outcome of the clinical trial.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

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

2. Subject-reported history of skin sensitivity to topical prescription or non-prescription products such as creams, lotions and cosmetics.

3. A positive urine drug test at Screening.

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

    - Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

5. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).

6. Screening supine blood pressure (BP) >140 mm Hg (systolic) or >90 mm Hg (diastolic) or <100 mm Hg (systolic), following at least 5 minutes of supine rest. If BP is >140 mm Hg (systolic) or >90 mm Hg (diastolic) or <100 mm Hg (systolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the subject's eligibility.

7. Screening supine 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTc or QRS values should be used to determine the subject's eligibility.

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

    - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level >1.0x upper limit of normal (ULN);

- Total bilirubin level >1.0x ULN;
    - **NOTE:** Subjects with a history of Gilbert syndrome are not eligible.

9. Subjects with history of hepatitis, or positive result at screening for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb):
    - As an exception, a positive HepBsAb result due to vaccination or healed hepatitis B, is permissible.
10. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; fertile male subjects who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol (Section 4.4.3) for the duration of the study and for **at least 28 days** after the last dose of investigational product.
11. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within **60 days** prior to first dose of investigational product.
12. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol described in Section 4.4.
13. Use of tobacco-or nicotine-containing products if consumed more than occasionally and/or in excess of 5 cigarettes per day (see Section 4.4).
14. Subjects who are investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
15. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
16. Other skin disease noted on physical examination that is considered by the investigator to be relevant to the outcome of the trial.
17. Subjects with psoriasis guttata, psoriasis punctata, psoriasis erythrodermatica, and pustular psoriasis.

18. Treatment with any locally acting medications (including anti-psoriasis medications like topical corticosteroids, vitamin D analogues, dithranol) which in the opinion of the investigator might counter or influence the trial aim within 4 weeks preceding the treatment phase of the trial and during the trial.

19. Treatment with any systemic medications which in the opinion of the investigator might counter or influence the trial aim (including anti-psoriasis medications, eg, corticosteroids, cytostatics or retinoids) or medications which are known to provoke or aggravate psoriasis (eg, beta-blocker, anti-malarial drugs, lithium [unless on a stable dose for 3 months before dosing is initiated]) or phototherapy/psoralen+UVA (PUVA) within 8 weeks preceding the treatment phase of the trial and during the trial.

20. Treatment with any biologics (eg, tumor necrosis factor (TNF) blockers, apremilast, ustekinumab, and anti-IL17 agents) within 3 months or five half-lives (whichever is longer) prior to Day 1 of the trial and during the trial.

21. Ultraviolet (UV)-therapy within 8 weeks before first treatment and during the study.

22. Current treatment with anticoagulant drugs (applicable for subjects consenting to the biopsy procedures).

23. Contraindications according to summary of product characteristics of the active comparators (see also Summary of Product Characteristics).

24. Subject is institutionalized because of legal or regulatory order.

25. Known hypersensitivity against active comparators, any of its excipients or dressing material. In addition, subjects who consent to biopsy must not have known hypersensitivity to local anesthesia.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

4.4. Lifestyle Requirements

The following guidelines are provided:

4.4.1. Alcohol, Caffeine, and Tobacco

- Nicotine-containing products are permitted during participation in the study only if consumed occasionally and not in excess of 5 cigarettes per day.

- Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

4.4.2. Activity

- The dressings are not to be soaked through (swimming, bathing, sauna not allowed). Short showering is allowed as long as the treated plaques are shielded from water.

- In case of accidental contact with the test fields, it is recommended to wash the hands.

- The application of any lotions or creams to the area of assessment other than those provided by site staff is prohibited from Day 1 until the on-site Follow-up visit.

- As additional precautionary measure, the subjects should avoid natural or artificial UV irradiation (solarium) during the treatment with the study treatments.

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.4.3. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), by the male subject's female partner(s) and the female partner(s) plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

Females of child-bearing potential are **not** eligible for this study.

4.5. 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 supporting study documentation.

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

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or vehicle being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or

packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are:

- PF-06763809 (2.3%, 0.8%, and 0.23%);
- Matching vehicle.

The comparator agents are:

- calcipotriene/calcipotriol 50 μg/mL solution;
- betamethasone 1 mg/g solution.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Each eligible subject will receive six treatments at six different test fields in a random order. There will be no subdivision into treatment groups.

The test fields will be numbered 1-6. As far as possible the following procedure for numbering will be followed: The numbering should begin with the uppermost or most proximal site on the left from the investigator's view. Fields along the same line should be numbered from left to right. If more than one plaque is included, numbers for the fields on the next plaque will be assigned likewise starting with the next free number. The exact location of each test field in relation to the outline of the plaque(s) will be traced on a transparent plastic sheet which will be kept with the subject's source data. The location of the test fields will be documented in the Case Report Form (CRF) as:

Upper/lower left/right arm,

Upper/lower left/right leg,

Front/back trunk.

At screening, a subject will be assigned a subject number. Once the subject meets all eligibility criteria, the subject will be randomized into the study according to the randomization schedule, which is generated through the Pfizer randomization system. Randomization will be performed by permutation of the six treatments. At randomization, each eligible subject will be assigned a randomization number, which corresponds to a random permutation of six treatments. The treatment listed first in the respective treatment sequence will be assigned to test field number 1, the second treatment to test field number 2, etc.

Subjects are blinded to the treatment sequence throughout the study. Investigators will be blinded to the treatment sequence except exceptional circumstances described in Section 5.2. Limited site staff who administer the treatments will be unblinded.

5.2. Breaking the Blind

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be a manual process. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that unblinding is necessary. When the blinding code is broken, the reason must be fully documented and entered on the case report form (CRF).

The investigator site staff, blinded study monitor, if assigned, and Pfizer study team will be blinded to study treatment. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring for the study has been completed. To minimize the potential for bias, treatment randomization information will be kept confidential and will not be released to the blinded investigator or blinded investigator site personnel until the study database has been locked or the investigator requests unblinding of individual subjects for safety reasons. However, it is anticipated that a limited number of site staff administering the IP (Investigational Product) will be unblinded. The blinded and unblinded site personnel will be documented at the site.

5.3. Subject Compliance

Investigational product will be administered by unblinded investigator site personnel.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

CCI [redacted]

PF-06763809 and vehicle will be packaged in open-label dosing vials and provided to the site for topical application by site personnel.

Active comparators calcipotriene/calcipotriol (50 µg/mL) solution and betamethasone 1 mg/g solution will be sourced by a pharmacy and used as marketed materials without repackaging and relabeling.

All study treatments will be labeled according to the requirements of local law and legislation.

5.4.2. Preparation and Dispensing

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

CCI [redacted] Prepared doses will be provided in containers labeled in accordance with Pfizer regulations and the investigator site's labeling requirements.

Calcipotriene/calcipotriol (50 µg/mL) solution and betamethasone (1 mg/g) solution will be dispensed from bulk materials as described in Section 5.5.

At the clinical site, an unblinded administrator will dispense the study drugs according to a randomization schedule into Duhring® chambers. A second unblinded site staff member will observe the correct dispensing and administration of study drugs.

CCI [redacted] The site will take all necessary precautions to maintain the Investigator and site personnel blind (except for the unblinded administrators). All subjects in the study will be blinded to the study treatments.

5.5. Administration

The dosing volume for all study treatments is 180 µL (164 µL/cm^2), applied topically once daily to 1.1 cm^2 skin surface area during an 18 day treatment period. Hence, subjects will be exposed to:

Study Treatment 1:

2.3% PF-06763809 solution
Daily dosage: approximately 4.1 mg PF-06763809
CCI [redacted]

Study Treatment 2:

0.8% PF-06763809 solution.
Daily dosage: approximately 1.4 mg PF-06763809
CCI [redacted]

Study Treatment 3:

0.23% PF-06763809
Daily dosage: approximately 0.41 mg PF-06763809
CCI [redacted]

Study Treatment 4 (vehicle):

Active ingredient-free vehicle to PF-06763809 treatments

Study Treatment 5 (positive control):

Calcipotriene/ calcipotriol (50 µg/mL)
Daily dosage of calcipotriol**:** approximately 0.01 mg
CCI [redacted]

Study Treatment 6 (positive control):

Betamethasone (1 mg/g)

Daily dosage of approximately 0.18 mg
CCI [redacted]

All subjects will receive each study treatment once daily. All study treatments will be applied by way of Duhring® chambers seated in holes punched in a hydrocolloid dressing (eg, Varihesive® E [Convatec], Munich, Germany). The hydrocolloid dressing will be fixed on the skin with adhesive patches (eg, BSN Medical, Hamburg, Germany, or comparable) containing the same holes for the chambers as the hydrocolloid dressing. CCI [redacted] The filled chamber will then be placed on the skin at the location of the relevant test fields. After each test chamber is filled with the appropriate volume, the test chambers will be subsequently applied to the test fields.

The chambers will be fixed in place with Leukosilk® (eg, BSN, Hamburg, Germany or comparable) and will be removed before each new application. In previous studies the hydrocolloid dressing has been shown to be well tolerated. The lack of a therapeutic influence of the dressing on the psoriasis has been verified by determination of the psoriatic skin infiltrate thickness/EPB before and after application. CCI [redacted] The fields will be treated with occlusion for a treatment period of 18 days (Day 1 through 18). Before each new application remaining preparation residues will be removed by gently cleansing each test field with a separate soft tissue. The hydrocolloid dressing will be renewed on Days 1 and all subsequent CCI [redacted] measurement days or as necessary.

In case of a missed day of treatment/evaluation, the subject is advised to keep the dressing on the plaques until he/she can return to the investigator site. The subject should return to the investigator site at the next occasion. Study procedures performed will be such that any procedures that were to be performed on the missed day are performed at the next scheduled visit if not already planned. Subjects who miss >1 dose may be discontinued and replaced at the discretion of the investigator or sponsor.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

CCI [redacted]

Any storage conditions stated in the single reference safety document (SRSD) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product-label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.7.1. Destruction of Investigational Product Supplies

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

5.8. Concomitant Treatment(s)

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment as defined in the Schedule of Activities (Table 1).

Treatments taken **within 28 days** before the dose of investigational product will be documented as a prior treatment. Treatments taken after dosing of investigational product will be documented as concomitant treatments.

Subjects are permitted to be on stable doses of background medications for the management of their concomitant medical condition(s). ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the on-site Follow-up visit (on Day 27).

6. STUDY PROCEDURES

6.1. Screening

Refer to Schedule of Activities Table 1 for the study procedures to be completed at the Screening visit.

Subjects will be screened **within 28 days** prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section (Section 12.3).

To prepare for study participation, subjects will be instructed on the Lifestyle Requirements (Section 4.4) and Concomitant Treatment(s) (Section 5.8) of the protocol.

6.2. Study Period

Refer to Schedule of Activities Table 1 for the study procedures to be completed. CCI [redacted]

[redacted]

If a subject has any clinically significant, study-related abnormalities, the Pfizer medical monitor (or designated representative) should be notified and an appropriate course of action will be determined.

6.3. Follow-up

6.3.1. Follow-up Visit

In this study, there are two Follow-up visits, as follows:

1st is an on-site visit where only subjects who have consented to the optional biopsy or who have an open AE following completion of Day 19 will return to the CRU on Day 27 (8 **±2 days** following Day 19);

2nd is a telephone contact to occur for all subjects who participated in the study, on Day 49 (**31 ± 3 days** following the last dose of investigational product);

Refer to Schedule of Activities—Table 1 for the study procedures to be completed at each of the two Follow-up visits.

6.4. Subject Withdrawal/Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal from the Study Due to Adverse Events section) or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to Follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and Follow-up with the subject regarding any unresolved adverse events (AEs).

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:

- Conduct an inquiry about any spontaneously reported AEs by asking the subject to respond to a non-leading question such as "how do you feel?";
- Perform a limited physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit at PI discretion;

- Obtain supine, single, standard, 12-lead ECG (refer to Section 7.1.5);
- Obtain supine, single set of blood pressure and pulse rate measurements (refer to Section 7.1.4);
- Collect blood and urine specimens, for clinical laboratory tests (refer to Section 7.1.1) and pregnancy test if applicable.

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

If the subject withdraws from the study and also withdraws consent 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.

Subjects who withdraw from the study for ***non-safety reasons*** may be replaced at the discretion of the sponsor. Up to 5 subjects may be replaced.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject 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.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

7. ASSESSMENTS

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 subject. 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.

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities Table 1 of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Any remaining serum/plasma/urine from samples collected for clinical safety laboratory measurements at baseline and at all times after dose administration may be retained and stored for the duration of the study. Upon completion of the study, these retained safety samples may be used for the assessment of exploratory safety biomarkers or unexpected safety findings. These data will not be included in the clinical study report (CSR). Samples to be used for this purpose will be shipped to either a Pfizer-approved Biospecimen Banking System (BBS) facility or other designated laboratory and retained for up to 1 year following the completion of the study.

Table 2. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Direct bilirubin[d,e] Indirect bilirubin[d,e] Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Other tests as part of clinical laboratory tests: • Serum FSH[b] • Urine drug test[c] • Blood[d] for HIV, HepBsAg, HepBcAb, HCVAb
Additional Tests (Needed for Hy's Law) – also refer to Section 8.4.1			
AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR Total bile acids Acetaminophen drug and/or protein adduct levels			

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening, and only in females who are amenorrheic for ≥12 consecutive months.
c. At Screening only; with minimum requirements including cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
d. At Screening ***ONLY***.
e. *After* Screening, direct and indirect bilirubin assessed when total bilirubin is >ULN, ***only.***

Subjects may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for subjects to receive investigational product.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects 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.

7.1.3. Temperature

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

7.1.4. Blood Pressure and Pulse Rate

BP and pulse rate (PR) will be measured at times specified in the Schedule of Activities section of this protocol. Additional collection times, or changes to collection times, of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

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

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for **≥30 seconds**.

7.1.5. Electrocardiogram

12-Lead ECGs should be collected at times specified in the Schedule of Activities section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for **≥10 minutes in a supine position**.

The ECG measurements collected at Day 1, 0H will serve as the baseline, *during study conduct*.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTc interval is increased by ≥45 msec from the baseline, or an absolute QTc value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the average of QTc values from the triplicate measurements remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then the subject will be transferred to their primary care physician or a cardiologist for additional monitoring.

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 are 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 QTc values are in the acceptable range.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

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

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

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result 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; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

  Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab 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 subject’s individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) 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.

8.4.2. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

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

8.4.2.2. Exposure During Breastfeeding

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

8.4.2.3. Occupational Exposure

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

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

8.4.3. Medication Errors

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

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

8.4.3.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor and finalized prior to the unblinding of the study. 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. Sample Size Determination

The sample size determination is based on the primary endpoint of change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19. The log-scale of infiltrate thickness is used for a more stable variability over the assessed efficacy range and a better approximation to normal distribution.

Data from three psoriasis plaque test (PPT) studies conducted at bioskin® GmbH were used to generate the assumption for sample size calculation. In these three studies, the calcipotriene/calcipotriol solution demonstrated 36% - 44% reduction in infiltrate thickness relative to vehicle. The observed within-subject standard deviation (SD) estimates for calcipotriene/calcipotriol solution relative to vehicle ranged from 0.331-0.435. Power analyses were performed for samples sizes of N=15 and N=20 under within-subject SDs of 0.38, 0.435 and 0.5 with 2-sided type-I error rate of 5% and results were summarized in

CCI

A sample size of 15 completers was selected based on the above results and enrollment should ensure approximately 15 completers.

9.2. Efficacy Analysis

All subjects who have at least one application of the investigational products and have at least one post-baseline assessment of the primary efficacy variable will be included in the Full Analysis Set (FAS). The Per Protocol Set (PPS) is a subset of the FAS. Subjects with major protocol deviations and subjects who discontinued the study prematurely will be excluded from the PPS. The PPS definition will be defined in the SAP and the subject assignment to the analysis sets will be carried out jointly by the medical advisor, the study manager and the statistician before breaking the blind during the blinded data review meeting. The intent-to-treat (ITT) analysis of efficacy based on the FAS will be considered as primary. The per-protocol (PP) analysis based on the PPS will be provided as a sensitivity analysis.

Change from baseline in the natural log-transformed psoriatic skin infiltrate thickness/EPB will be determined by subtraction of the baseline assessment from each post-baseline assessment.

The area under the curve (AUC) of the psoriatic skin infiltrate thickness/EPB from Day 1 to Day 19 will be determined using the linear trapezoidal rule. The log AUC will be performed by the natural logarithm of the AUC of the psoriatic skin infiltrate thickness/EPB.

9.2.1. Analysis of the Primary Endpoint

The primary endpoint for this study is the change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19 CCI [redacted] for PF-06763809 in comparison to vehicle. The efficacy assessment of PF-06763809 will be performed for the change from baseline in log of the psoriatic skin infiltrate thickness/EPB on Day 19 using a longitudinal analysis of covariance model, with treatment, visit, treatment by visit interaction as main effects and the log of the psoriatic skin infiltrate thickness/EPB at baseline as covariate. The CS@UN covariance structure will be assumed to adequately model the two within-subject factors (treatment, visit), where the compound symmetric (CS) correlation is for repeated measures from different treatments within each visit and the unstructured (UN) correlation is for longitudinal measures from different visits. If there are convergence issues, alternative covariance structure will be examined and adopted. The point estimate and 95% confidence interval (CI) for the difference in log transformed means at Day 19 visit between treatment groups will be constructed using least square means and appropriate standard errors. The assessment of the primary endpoint will be performed at a two-sided significance level of 0.05. In this primary analysis, the missing data will be assumed as missing at random and no imputation will be made for missing data.

In addition, a landmark analysis of covariance (ANCOVA) model analysis of the primary endpoint at Day 19 will be performed to examine the robustness of the conclusion drawn from the primary longitudinal analyses. The landmark ANCOVA model will include treatment as the main effect, log-transformed psoriatic skin infiltrate thickness/EPB at

baseline as covariate and a random subject effect to account for correlation among repeated measures from different treatments for each subject. Missing assessments of psoriatic skin infiltrate thickness/EPB at Day 19 will be imputed using the last observation carried forward (LOCF) procedure. In case of treatment discontinuation the last assessment prior to treatment discontinuation will be imputed for the following planned assessment of psoriatic skin infiltrate thickness/EPB.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

9.6. Safety Analysis

Safety analysis will be performed for all subjects who had any investigational product dispensed.

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

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

9.7. Interim Analysis

No formal interim analysis will be conducted for this study.

9.8. Data Monitoring Committee

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct for studies conducted at non-Pfizer investigator sites, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV) reflected by completion of the 2nd Follow-up visit for the last subject randomized in the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06763809 at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013; 133(2):377–85.

2. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007; 445(7130):866-73.

3. Asadullah K, Döcke WD, Volk HD, et al. The pathophysiological role of cytokines in psoriasis. Drugs Today 1999; 35(12):913-24.

4. Villadsen LS, Schuurman J, Beurskens F, et al. Resolution of psoriasis upon blockade of IL-15 biological activity in a xenograft mouse model. J Clin Invest 2003; 112(10):1571–80.

5. Schon MP, Boehncke WH. Psoriasis. New Engl J Med 2005; 352(18):1899-912.

6. Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. J Am Acad Dermatol 1999; 41(3 pt 1):401-7.

7. Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007; 143(12):1493–9.

8. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. J Invest Dermatol 2009; 129(10):2411–8.

9. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case–control study. Br J Dermatol 2007;157(1):68–73.

10. Mehta NN, Azfar RS, Shin DB, et al. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 2010; 31(8):1000-6.

11. Sterry W, Strober BE, Menter A. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. Br J Dermatol 2007; 157(4):649–55.

12. de Carvalho AV, Duquia RP, Horta BL, et al. Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Drugs R D 2017; 17(1):29-51.

13. Kim J, Krueger JG. The immunopathogenesis of psoriasis. Dermatol Clin **2015;** 33(1):13-23.

14. Kim J, Bissonnette R, Lee J, et al. The spectrum of mild to severe psoriasis vulgaris is defined by a common activation of IL-17 pathway genes, but with key differences in immune regulatory genes. J Invest Dermatol 2016; 136(11):2173-2182.

15. Okada S, Markle JG, Deenick EK, et al. IMMUNODEFICIENCIES. Impairment of immunity to Candida and Mycobacterium in humans with bi-allelic RORC mutations. Science 2015; 349(6248):606-13..

16. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Invest Dermatol 2013; 133(1):17-26.

17. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008; 128(5):1207-11.

18. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 2006; 126(6):1121-33.

19. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med 2014; 371(4):326-38.

20. Haider AS, Lowes MA, Suárez-Fariñas M, et al. Identification of cellular pathways of "type 1," Th17 T cells, and TNF- and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. J Immunol 2008; 180(3):1913-20.

21. Rácz E, Prens EP, Kurek D, et al. Effective treatment of psoriasis with narrow-band UVB phototherapy is linked to suppression of the IFN and Th17 pathways. J Invest Dermatol 2011; 131(7):1547-58.

22. Zaba LC, Suárez-Fariñas M, Fuentes-Duculan J, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. J Allergy Clin Immunol 2009; 124(5 Nov):1022-30.

23. Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 2015; 136(1):116-124.e7.

24. el Gammal S, Pieck C, Auer T, et al. [100 MHz ultrasound of psoriasis vulgaris plaque]. Ultraschall Med 1998; 19(6):270-4.

25. Gupta AK, Turnbull DH, Harasiewicz KA, et al. The use of high-frequency ultrasound as a method of assessing the severity of a plaque of psoriasis. Arch Dermatol 1996; 132(6):658-62.

26. Nutrition and Diabetes (2012) 2, e54; doi:10.1038/nutd.2012.26.

Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	absolute
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BBS	Biospecimen Banking System
BID	twice daily
BMI	body mass index
BP	blood pressure
CI	confidence interval
CL	Plasma clearance
Cmax	maximum observed concentration
CRF	case report form
CS	compound symmetric
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	data monitoring committee
CCI [redacted]	
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
CCI [redacted]	[redacted]
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EPB	echo poor band
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus

Abbreviation	Term
ICH	International Conference on Harmonisation
ID	identification
IL	interleukin
IND	investigational new drug application
INR	international normalized ratio
IP	Investigational Product
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LOCF	last observation carried forward
LSLV	last subject last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
N/A	not applicable
NOAEL	no observed adverse effect level
PCD	primary completion date
CCI [redacted]	
PE	physical examination
PI	principal investigator
PK	pharmacokinetics
PPS	per protocol set
PPT	psoriasis plaque test
PR	pulse rate
PT	prothrombin time
PUVA	phototherapy/psoralen+UVA
QTc	corrected QT
qual	qualitative
RBC	red blood cell
CCI [redacted]	
RORC2	retinoid acid-related orphan receptor 2
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SRC-1	steroid receptor coactivator-1
SRSD	single reference safety document
TEAE	treatment emergent adverse event
TBili	total bilirubin
Th17	T helper 17
THC	tetrahydrocannabinol

Abbreviation	Term
TNF	tumor necrosis factor
ULN	upper limit of normal
UN	unstructured
US	United States
UV	ultraviolet
V_{ss}	steady state volume of distribution
WBC	white blood cell