Protocol C3561001

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

Statistical Analysis Plan (SAP)

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

RORC2 is a transcription factor that controls the production of the cytokine IL-17A, which plays a central role in the pathogenesis of psoriasis. Psoriasis lesions contain prominent inflammatory cell infiltrates that include T cells that produce IL-17A. PF-06763809 inhibited the binding of purified recombinant human RORC2 ligand binding domain steroid receptor coactivator-1 (SRC-1) with an IC50 value of 3.1nM. In vivo studies *data suggest that topical PF-06763809 inhibited the production of IL-17A in mouse models to an extent that was sufficient to cause a reduction in inflammation which was similar to neutralization of IL-17A by anti-IL17A mAb.*

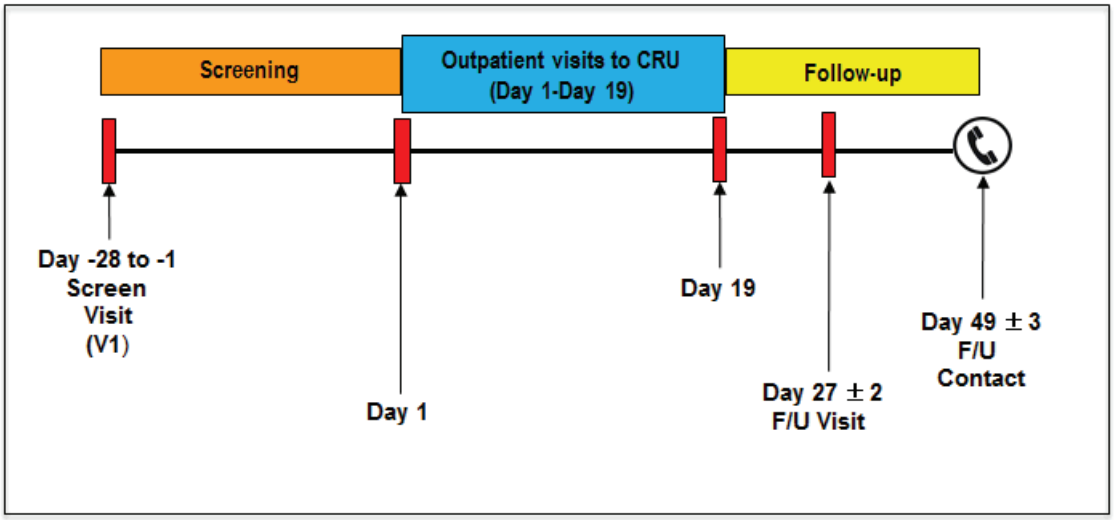
Inhibition of RORC2-mediated inflammation has the potential to provide a novel approach in the topical treatment of plaque psoriasis. This first-in-human study will evaluate PF-06763809 solution, applied topically to skin surface areas in subjects with chronic mild to moderate plaque psoriasis. The primary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

2.1. **Study Design**

The study is proposed as a randomized, double-blinded, vehicle and active comparator-controlled, multiple dose study in subjects with psoriasis. 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. Subjects will receive topical doses (2.3%, 0.8% and 0.23%) of PF-06763809, PF-06763809 vehicle, and two active comparators (calcipotriene/calcipotriol and betamethasone) *in this study. Each eligible subject will receive six treatments at six different test fields in a random order. 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.*

The overall study design is summarized in Figure 1.

Figure 1. Overall Study Design



2.2. Study Objectives

2.2.1. Primary Objectives

- *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.*

- *To determine the safety and tolerability of multiple dose topical administration of PF-06763809 in psoriasis subjects.*

2.2.2. Secondary Objectives

- *To evaluate the Area Under the Curve (AUC) of psoriatic skin infiltrate thickness/EPB for PF-06763809 compared to vehicle.*

- *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.*

- *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.*

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study.

This is a randomized double-blind study. *Subjects are blinded to the treatment sequence throughout the study. Investigators will be blinded to the treatment sequence, except exceptional circumstances when knowledge of the actual treatment code is absolutely essential for management of the subject. Blinded personnel performing the* CCI *ultrasound measurements should not be present during the treatment application procedures in order to remain blinded.*

It is anticipated that a limited number of site staff administering the treatments will be unblinded. Other *investigator site staff and Pfizer study team will be blinded to study treatment sequence. The blinded study monitor, if assigned, will remain blinded to treatment until all monitoring of the study has been completed.*

To minimize the potential for bias, treatment randomization information will be kept confidential will not be released to the blinded investigator or blinded investigator site staff until the study database has been locked or the investigator requests unblinding of individual subjects for safety reasons.

Study unblinding will not be performed until the final database has been locked for all subjects. Final analysis will follow the official database release.

4. HYPOTHESES AND DECISION RULES

4.1. **Statistical Hypotheses**

This study is designed to show that PF-06763809 has a superior effect against vehicle in the primary endpoint of relative change from baseline in infiltrate thickness at Day 19. The following hypotheses will be formally tested first under a significance level of 5% (two-sided):

- The null hypothesis (H_{01}): PF-06763809 has no greater reduction from baseline in infiltrate thickness at Day 19 than vehicle.
- The alternative hypothesis (H_{11}) is that PF-06763809 has a greater reduction from baseline in infiltrate thickness at Day 19 than vehicle.

If the null hypothesis H_{01} is rejected statistically, then the following hypotheses will be formally tested next under a significance level of 5% (two-sided):

- The null hypothesis (H_{02}): PF-06763809 has no greater reduction from baseline in infiltrate thickness at Day 19 than calcipotriene/calcipotriol.
- The alternative hypothesis (H_{12}) is that PF-06763809 has a greater reduction from baseline in infiltrate thickness at Day 19 than calcipotriene/calcipotriol.

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 C
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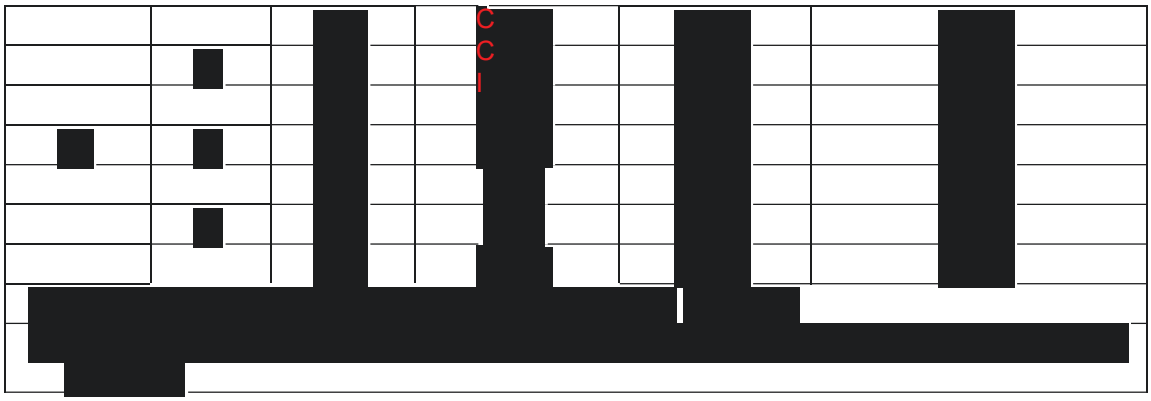

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4.2. **Statistical Decision Rules**

The primary endpoint for this study is the change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19 CCI *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 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.*

5. ANALYSIS SETS

5.1. **Full Analysis Set**

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).

5.2. **Per Protocol Set**

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 key protocol violators will follow the procedure outlined in Section 5.7 below.

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5.5. **Safety Analysis Set**

Safety analysis will be performed for all subjects who had any investigational product dispensed. Subjects will be analyzed according to the treatment they are actually received.

5.6. **Treatment Misallocations**

If a subject takes a treatment that is not consistent with the treatment they are randomized to, then they will be reported under their randomized treatment group for efficacy analyses, but will be reported under treatment they actually received for all other analyses.

5.7. **Protocol Deviations**

Different protocol deviations may have different impact on the analyses. A full list of protocol deviations will be compiled and reviewed prior to database closure. In protocol deviation review meetings, the classification of major and minor protocol deviations will be carried out by the clinician and statistician prior to unblinding and a decision will be made for each subject's eligibility for PPS analysis set.

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5.7.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.7.2. Deviations Assessed Post-Randomization

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

6.1.1. Primary Efficacy Endpoint

- *Change relative to baseline at Day 19 in psoriatic skin infiltrate thickness/EPB.*

6.1.2. Secondary Efficacy Endpoint

- *AUC of the psoriatic skin psoriatic thickness/EPB from Day 1 to Day 19.*
- *Change relative to baseline in psoriatic skin infiltrate thickness/EPB* at visit other than Day 19.

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6.2. Safety Endpoints

Safety endpoints of this study include 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). These safety data will be analyzed in standard safety summaries.

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6.4. **Covariates**

Baseline values of psoriatic skin infiltrate thickness/EPB will be included as a covariate in the longitudinal and landmark analysis of covariance (ANCOVA) analysis of the primary endpoint.

7. HANDLING OF MISSING VALUES

In this primary longitudinal ANCOVA analysis of psoriatic skin infiltrate thickness/EPB, the missing data will be assumed as missing at random and no imputation will be made for missing data. In the landmark ANCOVA analysis the missing assessment of psoriatic skin infiltrate thickness/EPB 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.*

Any data displays using last observation carried forward will be labeled 'LOCF'. For other data displays LOCF will not be used and subjects with missing values of a particular endpoint will not contribute to the analysis.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

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

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.

In additional to the model-based analyses described below, all study endpoints will be summarized using descriptive statistics. For binary endpoints, summary statistics including

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the numbers and percentages will be presented. For continuous endpoints, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented, by each planned measurement time point and treatment group if applicable. Inter-quarter ranges and 95% confidence intervals may be provided where meaningful.

8.1. **Analysis of Primary Efficacy Endpoint**

The primary endpoint for this study is the change relative to baseline in psoriatic skin infiltrate thickness/EPB at Day 19 CCI *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 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.

8.2. **Safety Analysis**

The safety endpoints described in Section 6.2 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set.

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

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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.

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