Efficacy and Safety of PF-07038124 in Patients With Atopic Dermatitis and Plaque Psoriasis
A Randomized Clinical Trial

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IMPORANCE
Atopic dermatitis (AD) and plaque psoriasis are inflammatory skin diseases with unmet need for effective topical treatments with few application site reactions.

OBJECTIVE
To assess the efficacy and safety of the topical phosphodiesterase 4 inhibitor PF-07038124 in patients with AD and plaque psoriasis.

DESIGN, SETTING, AND PARTICIPANTS
This phase 2a, randomized, double-blind clinical trial was conducted from December 21, 2020, to August 18, 2021, at 34 sites across 4 countries. Eligible patients (aged 18-70 years) had mild to moderate AD (covering 5%-20% body surface area) or plaque psoriasis (covering 5%-15% body surface area). Data were analyzed until December 15, 2021.

INTERVENTIONS
Patients were randomized (1:1) to PF-07038124, 0.01%, topical ointment or vehicle once daily for 6 weeks.

MAIN OUTCOMES AND MEASURES
The primary end point was the percent change from baseline (CFB) in the Eczema Area and Severity Index (EASI) total score among patients with AD and in the Psoriasis Area and Severity Index (PASI) score among patients with plaque psoriasis at week 6. Safety measures included treatment-emergent adverse events, including application site reactions.

RESULTS
Overall, 104 patients were randomized (mean [SD] age, 43.0 [15.4] years; 55 [52.9%] women; 4 [3.8%] Asian, 13 [12.5%] Black, and 87 [83.7%] White), including 70 with AD (41 women [58.6%]; mean [SD] ages, 41.4 [16.6] years in the PF-07038124 group and 36.1 [13.9] years in the vehicle group) and 34 with plaque psoriasis (20 men [58.8%]; mean [SD] ages, 51.8 [12.3] years in the PF-07038124 group and 51.2 [10.8] years in the vehicle group). Baseline characteristics were generally balanced. At week 6, the PF-07038124 groups showed significantly greater improvements compared with vehicle groups in EASI (least-squares mean CFB, −74.9% vs −35.5%; difference, −39.4% [90% CI, −58.8% to −20.1%]; P < .001) and PASI scores (CFB, −4.8 vs 0.1; difference, −4.9 [90% CI, −7.0 to −2.8]; P < .001). The number of patients with treatment-emergent adverse events was comparable between treatment groups in patients with AD (PF-07038124, 9 [25.0%]; vehicle, 9 [26.5%]) and plaque psoriasis (PF-07038124, 3 [17.6%]; vehicle, 6 [35.3%]). There were no application site reactions with PF-07038124 treatment.

CONCLUSIONS AND RELEVANCE
Topical PF-07038124 was well tolerated and demonstrated superior efficacy compared with vehicle in patients with mild to moderate AD and plaque psoriasis.

TRIAL REGISTRATION
ClinicalTrials.gov Identifier: NCT04664153

Published online December 20, 2023.
A topic dermatitis (AD) and plaque psoriasis are chronic, inflammatory skin diseases associated with substantial health-related and socioeconomic burden.\textsuperscript{1,2} Topical treatments, such as daily emollients and corticosteroids, are first-line therapies for mild to moderate AD and plaque psoriasis\textsuperscript{3,4}; however, corticosteroids are associated with systemic adverse events (AEs) and application site reactions, such as burning and stinging.\textsuperscript{5,6} As such, new treatments are needed for AD and plaque psoriasis with robust efficacy and fewer adverse reactions.

Atopic dermatitis is primarily mediated by type 2 helper T-cell–driven inflammation, which involves cytokines such as interleukin 4 (IL-4) and IL-13,\textsuperscript{7} while plaque psoriasis typically involves tumor necrosis factor α, IL-17, and IL-23.\textsuperscript{8} Phosphodiesterase-4 (PDE4) inhibitors represent a promising therapeutic target for inflammatory diseases as they can increase cyclic adenosine monophosphate levels and subsequently reduce the production of proinflammatory cytokines.\textsuperscript{9} Topical roflumilast is a PDE4 inhibitor that was approved by the US Food and Drug Administration for plaque psoriasis in 2022.\textsuperscript{10} Apremilast is an oral PDE4 inhibitor that has shown efficacy as a treatment for plaque psoriasis and is well tolerated, yet it has been associated with gastrointestinal AEs such as nausea and diarrhea.\textsuperscript{11} For AD, crisaborole is currently the only topical PDE4 inhibitor approved as a treatment.\textsuperscript{12}

Topical PF-07038124 is designed to be a potent, oxaborole-based PDE4 inhibitor with immunomodulatory activity in T-cell–based assays, contributing to inhibition of IL-4 and IL-13; thus, it could provide therapeutic benefit in the treatment of AD and plaque psoriasis. The aim of this study was to assess the efficacy, safety, tolerability, and pharmacokinetics of topical PF-07038124 in patients with mild to moderate AD or plaque psoriasis.

Methods

Study Design

This phase 2a, randomized, double-blind, vehicle-controlled, parallel-group, multicenter clinical basket study was conducted across 34 sites in 4 countries from December 21, 2020, to August 18, 2021, in patients with mild to moderate AD or plaque psoriasis. The trial protocol and statistical analysis plan are provided in Supplement 1. Following a 6-week or shorter screening period, eligible patients were randomized (1:1) using a web-based interactive response with a computer-generated randomization list to receive a once-daily dose of PF-07038124 or a vehicle control for 6 weeks with a safety follow-up period of 4 to 5 weeks (Figure 1). Qualified staff supplied PF-07038124 as a 0.01% weight/weight ointment with a corresponding vehicle control. Patients, investigators, and the sponsor study team were blinded until the end of the study. The basket study design allowed the efficacy of topical PF-07038124 vs vehicle to be assessed in 2 different indications (AD and plaque psoriasis), with a separate vehicle control for each indication. A thin layer (approximately 3 mg/cm²) of the ointment was applied to all affected areas around the same time each day, excluding the scalp in patients with AD and the scalp and nails in patients with plaque psoriasis. Patients were instructed to maintain treatment for the duration of the study, even if substantial improvements or clearing of AD or psoriasis occurred.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki\textsuperscript{13} and all International Council for Harmonisation Good Clinical Practice Guidelines.\textsuperscript{14} A signed and dated informed consent form was required from all patients before any study-specific activity was performed. The final protocol and informed consent documentation were reviewed and approved by each investigational center’s institutional review board or ethics committee.

Patients

Eligible patients were aged 18 to 70 years at screening with a body weight of at least 50 kg and a body mass index (calculated as weight in kilograms divided by height in meters squared) ranging from 17.5 to 40.0. Study patients were asked to self-report ethnicity first and race second. If the patient refused to provide this information or where local laws prohibit collection of this information, the record was marked as not reported. Patients with AD had a clinical diagnosis at least 3 months prior to day 1, with AD covering 5% to 20% body surface area (BSA) excluding the scalp, an Investigator’s Global Assessment (IGA) score of 2 (mild) or 3 (moderate), an Eczema Area

Key Points

**Question** Is topical PF-07038124 a safe and effective treatment for atopic dermatitis (AD) and plaque psoriasis?

**Findings** This phase 2a randomized clinical trial of 104 patients, 70 with AD and 34 with plaque psoriasis, found that PF-07038124, 0.01%, administered once daily was more effective than vehicle after 6 weeks of treatment. Treatment with PF-07038124 was generally well tolerated, with no application site reactions.

**Meaning** Topical PF-07038124 is an effective and well-tolerated treatment for AD and plaque psoriasis.
and Severity Index (EASI) total score ranging from 3 to 21 at screening and randomization (overall scores range from 0-72, with higher scores indicating worse severity), and a Peak Pruritus Numerical Rating Scale (PP-NRS) score of at least 2 at randomization (scores range from 0-10, with higher scores indicating worse itch). Patients with plaque psoriasis had a diagnosis at least 6 months prior to day 1, with plaque psoriasis covering 5% to 15% BSA excluding the scalp and a Physician’s Global Assessment (PGA) score of 2 (mild) or 3 (moderate) at screening and day 1. Exclusion criteria are detailed in the eMethods in Supplement 2.

**Efficacy Parameters**

In patients with AD, the primary end point was the percentage change from baseline (CFB) in EASI total score at week 6. Secondary end points were the CFB in EASI total score, the proportion of patients achieving 75% improvement in EASI from baseline (EASI-75) and at least a 4-point reduction from baseline in PP-NRS at each study visit, and the proportion of patients achieving an IGA score of clear (0) or almost clear (1) and a reduction from baseline of at least 2 points at week 6 and at each study visit.

For plaque psoriasis, the primary end point was the CFB in Psoriasis Area and Severity Index (PASI) score at week 6. Secondary end points were the CFB in PASI scores at each study visit, the proportion of patients achieving 75% improvement from baseline in PASI (PASI-75) at each study visit, and the proportion of patients with a PGA score of clear (0) or almost clear (1) and at least a 2-point improvement from baseline at week 6 and at each study visit. The CFB in affected BSA at each study visit was assessed in both patients with AD and plaque psoriasis.

**Safety and Pharmacokinetics**

In all patients with AD and plaque psoriasis who applied at least 1 dose of the study treatment, the incidence of treatment-emergent AEs (TEAEs), serious AEs, and clinically significant changes in vital signs, electrocardiography (ECG), and laboratory tests were assessed. Plasma PF-07038124 concentrations after topical administration were determined using a liquid chromatography with tandem mass spectrometric assay validated in patients with AD and plaque psoriasis. The lower limit of quantification (LLQ) was 10 pg/mL.

**Statistical Analysis**

Data were analyzed until December 15, 2021. A planned 56 patients with AD (28 per treatment group) provided approximately 90% power to detect a 50% difference in CFB and allowed for a 25% dropout rate. A planned 32 patients with plaque psoriasis (16 per treatment group) provided approximately 80% power to detect a treatment difference of 4.5 in PASI score for the comparison of PF-07038124 vs vehicle and allowed for a 25% dropout rate. Further details regarding sample size calculations are provided in the eMethods in Supplement 2.

Data for all randomized patients who received at least 1 dose were used for analyses. The CFBs in EASI and in PASI at week 6 were analyzed using analysis of covariance, including treatment effect and baseline score as covariates. A control-based method imputed vehicle group missing data under a missing-at-random assumption and imputed missing data in the active treatment group, assuming it was similar to the vehicle group. The CFB in BSA, EASI, and PASI were analyzed using similar analysis of covariance with no imputation of missing data. The EASI-75, PASI-75, IGA, PGA, and PP-NRS scores were analyzed using the method of Chan and Zhang, with data presented as proportions and risk differences with 90% CIs and 1-sided P values, and missing values imputed as nonresponders. The 90% CIs of binomial proportions were reported using the Blyth-Still-Casella method. P < .05 indicated statistical significance.

The full analysis set and safety analysis sets were defined as all patients randomly assigned to treatment who applied at least 1 dose. The pharmacokinetics concentration set was defined as all patients who applied at least 1 dose of PF-07038124 and in whom at least 1 concentration value was reported. Safety and pharmacokinetics data were summarized descriptively. We used SAS Studio, version 3.8 (SAS Institute, Inc), for all data analyses.

**Results**

**Patients**

A total of 152 patients were screened, of whom 104 were randomized and treated (49 [47.1%] men and 55 [52.9%] women; 4 [3.8%] Asian, 13 [12.5%] Black, and 87 [83.7%] White; mean [SD] age, 43.0 [15.4] years). Seventy patients had AD (29 men [41.4%] and 41 women [58.6%]; mean [SD] age, 41.4 [16.6] in the PF-07038124 group and 36.1 [13.9] years in the vehicle group). Thirty-four patients had plaque psoriasis (20 men [58.8%] and 14 women [41.2%]; mean [SD] age, 51.8 [12.3] years in the PF-07038124 group and 51.2 [10.8] years in the vehicle group). Thirty-three patients (91.7%) with AD and plaque psoriasis completed the treatment period, while 15 (88.2%) in the PF-07038124 group and 14 (91.2%) in the vehicle group had moderate disease (per IGA score). Among patients with plaque psoriasis, 16 each receiving vehicle and PF-07038124 (94.1%) had moderate disease (per PGA score).

**Efficacy Outcomes**

**Atopic Dermatitis**

At week 6, the PF-07038124 group had statistically significantly greater LSM CFB in EASI total score compared with the vehicle group (−74.9% vs −35.5%; LSM difference, −39.4% [90% CI, −58.8% to −20.1%]; P < .001) (Figure 3A). In both the PF-07038124 and vehicle groups, there was a trend toward improvement in EASI total score from week 1, with the maximum mean decrease observed at week 6 (LSM CFB, −8.0 [90% CI, −9.2 to −6.8] vs −4.2 [90% CI, −5.5 to −2.8]; LSM difference, −3.9 [90% CI, −5.6 to −2.1]; P < .001) (eFigure 1A in eMethods).
The proportion of patients achieving EASI-75 was significantly higher in the PF-07038124 group compared with the vehicle group from week 2 and maintained at week 6 (61.1% [90% CI, 47.0%-74.6%] vs 20.6% [90% CI, 11.3%-34.9%]; difference from vehicle, 40.5% [90% CI, 19.3%-58.0%]; P < .001) (eFigure 1B in Supplement 2).
A significantly greater proportion of patients achieved an IGA score of clear (0) or almost clear (1) and a reduction from baseline of at least 2 points in the PF-07038124 group compared with the vehicle group at week 6 (44.4% [90% CI, 30.2%-59.1%] vs 8.8% [90% CI, 3.3%-19.7%]). The PF-07038124 group was significantly different from the vehicle group from week 2; this was maintained over the treatment period to week 6 (difference from vehicle, 35.6% [90% CI, 15.8%-51.7%]; P < .001) (eFigure 1C in Supplement 2).

Regarding the PP-NRS score, the PF-07038124 group had a significantly greater proportion of patients achieving at least a 4-point reduction in weekly means from week 2; this reduction was maintained to week 6 (41.2% [90% CI, 26.9%-56.7%] vs 13.8% [90% CI, 6.2%-27.9%]; difference from vehicle, 27.4% [90% CI, 6.2%-45.3%]; P = .009) (eFigure 1D in Supplement 2).

### Plaque Psoriasis

At week 6, the PF-07038124 group demonstrated a statistically significantly greater CFB in PASI total score compared with the vehicle group (LSM, −4.8 [90% CI, −6.2 to −3.4] vs 0.1 [90% CI, −1.5 to 1.7]). The LSM difference from vehicle at week 6 was −4.9 (90% CI, −7.0 to −2.8; P < .001) (Figure 3B).

As early as week 1, and at all other time points, the PF-07038124 group had a significantly greater CFB in total PASI score compared with the vehicle group, with the maximum mean decrease observed at week 6 (LSM, −4.7 [90% CI, −6.3 to −3.2] vs 0.4 [90% CI, −1.2 to 2.0]). At week 6, the difference from vehicle was −5.2 (90% CI, −7.4 to −3.0; P < .001) (eFigure 2A in Supplement 2). A statistically significantly higher proportion of patients achieved PASI-75 at week 6 in the PF-07038124 group compared with the vehicle group (35.3% [90% CI, 17.5%-56.8%] vs 5.9% [90% CI, 0.6%-22.5%]). The proportion of patients achieving PASI-75 in the PF-07038124 group was significantly different from the vehicle group from week 4 until the end of the treatment period (difference from vehicle at week 6, 29.4% [90% CI, 4.7%-52.5%]; P = .02) (eFigure 2B in Supplement 2).

The proportion of patients achieving a PGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline in the PF-0703814 group was significantly different from that of the vehicle group at week 4 (17.6% [90% CI, 6.7%-36.4%] vs 0 [90% CI, 0-14.0%]; difference from vehicle, 17.6% [90% CI, 6.7%-36.4%]; P = .04). There was a numerically higher proportion of patients achieving a PGA response at week 6 compared with the vehicle group, but this did not reach statistical significance (17.6% [90% CI, 6.7%-36.4%] vs 5.9% [90% CI, 0.6%-22.5%]; difference, 11.8% [90% CI, −9.1% to 33.8%]; P = .18) (eFigure 2C in Supplement 2).

In both indications, from week 1, the PF-07038124 group had statistically significantly larger CFB in BSA, with the mean maximum CFB observed at week 6 compared with the vehicle group in patients with AD (LSM, −58.9% [90% CI, −75.5% to −42.3%] vs −8.4% [90% CI, −25.8% to 9.1%]; difference, −50.5% [90% CI, −74.6% to −26.5%]; P < .001) and plaque psoriasis (LSM, −28.9% [90% CI, −56.3% to −1.5%] vs 27.8% [90% CI, −9.7% to 65.2%]; difference, −56.7% [90% CI, −103.5% to −9.8%]; P = .02) (eFigure 3 in Supplement 2).

### Safety Outcomes

Overall, 27 patients (26.0%) experienced 42 all-cause TEAEs during the study (Table 2). The number of TEAEs were comparable across treatment groups in patients with AD, with 9 patients reporting 12 TEAEs in the PF-07038124 group and 5 patients reporting 10 TEAEs in the vehicle group. Infections and infestations were the most commonly reported TEAEs in the PF-07038124 group (n = 5), whereas skin and subcutaneous tissue disorders were the most common in the vehicle group (n = 5). In all patients with plaque psoriasis, the number of TEAEs was lower in the PF-07038124 group than the vehicle group (3 patients reporting 4 TEAEs vs 6 patients reporting 11 TEAEs). All TEAEs by system organ class occurred in individual patients in the PF-07038124 group. Skin and subcutaneous tissue disorders were the most common TEAEs in the vehicle group (n = 2).

Across indications, treatment-related TEAEs were only reported in the vehicle groups (6 of 34 patients [17.6%] with AD and 2 of 17 [11.8%] with plaque psoriasis) (Table 2). Permanent discontinuations due to nonserious AEs only occurred in the vehicle groups (4 of 34 [11.8%] with AD and 1 of 17 [5.9%] with plaque psoriasis). No patients in the PF-07038124 groups experienced application site pain or skin reactions at the
application sites. There were no deaths or serious AEs reported during the study. Additionally, there were no clinically significant laboratory abnormalities, changes from baseline in vital signs, or ECG findings in the study.

**Pharmacokinetics**

At week 6, up to 6 hours post dose, greater than 86% of plasma pharmacokinetics samples were below the LLQ of 10 pg/mL in patients with AD and less than 98% were below LLQ of 10 pg/mL in patients with plaque psoriasis. For pharmacokinetics samples that were above the LLQ, predose mean PF-07038124 concentrations were similar and appeared to reach a steady state following 1 to 2 weeks of treatment. Overall, PF-07038124 concentrations were generally low with a few outliers in patients with AD. Plasma PF-07038124 concentration-time profiles in patients with AD and plaque psoriasis can be seen in eFigure 4 in Supplement 2.

**Discussion**

In patients with AD and plaque psoriasis, PF-07038124 demonstrated superior efficacy compared with vehicle, as assessed by the investigator through multiple measures. Treatment with PF-07038124 was well tolerated in both study populations, as there were no application site AEs reported in the PF-07038124 groups, and all treatment-related TEAEs occurred in the vehicle group. There were also no deaths or clinically significant findings in laboratory values, ECGs, or vital signs throughout the study.

Our results are supported by those of previous studies investigating alternative topical inhibitors. In the present study, the proportion of patients achieving an IGA response following treatment with PF-07038124 for 6 weeks was significantly different from those receiving vehicle. These findings are similar to those from 2 identical phase 3 trials, whereby the proportion of patients with AD achieving success in IGA score after treatment with crisaborole for 4 weeks was also significantly different from placebo (32.8% vs 25.4% [P = .04] and 31.4% vs 18.0% [P < .001]). Unlike crisaborole, topical PF-07038124 was not associated with application site burning and stinging.

The topical PDE4 inhibitor roflumilast is approved for plaque psoriasis. In 2 phase 3 trials, the proportion of patients with plaque psoriasis who met the criterion for PASI-75 response following treatment with roflumilast for 8 weeks was significantly different from that of the vehicle group (trial 1: 41.6% vs 7.6% [P < .001]; trial 2: 39.0% vs 5.3% [P < .001]). Our results are consistent with these findings, as a statistically significant difference in the proportion of patients achieving a PASI-75 response in the PF-07038124 group, compared with the vehicle group, was observed at week 6. In addition, 1% of patients experienced application site pain following treatment with roflumilast, while no patients reported such AEs after treatment with PF-07038124 in the present study, although differences in trial design between the studies prevent direct comparison of the results. Roflumilast has also been assessed as a treatment for AD. In a proof-of-concept study in patients with mild to moderate AD, significant improvements in EASI score were observed following treatment with 0.15% roflumilast for 4 weeks, compared with vehicle (72.3% vs 55.8% [P = .049]), consistent with the 6-week findings of PF-07038124 in the present study.

Using a novel design, this study assessed efficacy and safety in 2 parallel patient populations, demonstrating PF-07038124 to be a promising treatment with no application site pain or reactions. In addition, the low systemic absorption of topical PF-07038124 may explain the minimal to no AEs that are typically associated with PDE4 inhibitors. Patients with mild to moderate AD and plaque psoriasis showed good clinical responses with no application site reactions and no treatment-related TEAEs with PF-07038124. Treatment with PF-07038124 was well tolerated and without the considerable systemic absorption that could lead to more serious AEs and changes in other chronic health conditions.

**Strengths and Limitations**

Strengths of this study included a good representation of moderate disease in patients with AD and plaque psoriasis and the
minimal AEs associated with PF-07038124. The basket study design was also an efficient way to assess PF-07038124 in 2 different indications, as comparisons can be drawn in a quicker, more cost-efficient way. In addition, only 1 topical PDE4 inhibitor, roflumilast, has currently been approved for plaque psoriasis, so PF-07038124 represents another potential therapeutic option with demonstrated efficacy in patients with plaque psoriasis. This study also has some limitations. The sample size was small, particularly for the population with plaque psoriasis, and the treatment period only lasted 6 weeks.

**Conclusions**

Treatment with PF-07038124 demonstrated superior efficacy, compared with vehicle, in patients with mild to moderate AD and plaque psoriasis. The study drug was well tolerated, with no treatment-related TEAEs or application site reactions reported in the PF-07038124 group. To confirm persistence of efficacy and the safety profile of PF-07038124, long-term data should be collected in larger studies.

**REFERENCES**


