A Phase 2b study to evaluate the efficacy and safety of the topical TYK2/JAK1 inhibitor brepocitinib for mild-to-moderate atopic dermatitis

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Introduction

Brepocitinib or PF-06700841 is a small molecule that selectively inhibits tyrosine kinase 2 (Tyk2) and Janus Kinase 1 (JAK1), modulating cytokines in Th1, Th2 and Th17 lymphocytes that are important mediators in atopic dermatitis (AD). This study aimed to evaluate the efficacy and safety of topical brepocitinib in participants with AD.

Material and Methods

In this 6-week, multicentre, double-blind, vehicle-controlled Phase 2b study (NCT03903822), participants (aged 12–75 years [males] and 18–75 years [females]) with mild-to-moderate AD were enrolled at 70 sites in 10 countries. To be eligible, participants had to have a clinical diagnosis of AD for ≥3 months, covering 2–≤20% of total body surface area, and an Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate) at screening and Day 1. They were randomised to 6 weeks of treatment (1:1:1:1:1:1:1:1) in one of 8 dosing arms: 4 arms with doses of brepocitinib once-daily (QD) (0.1%, 0.3%, 1% and 3%), 2 arms with brepocitinib twice-daily (BID) (0.3% and 1%), 1 vehicle cream arm QD (V-QD), or 1 vehicle cream arm BID (V-BID), followed by a 4-week follow-up period. Participants and investigators were blinded to concentration but not to dosing frequency. The primary endpoint was the percentage change from baseline in the eczema area and severity index (EASI) total score at Week 6. The key secondary endpoint was the proportion of participants achieving an IGA score of 0 (clear) or 1 (almost clear) and a reduction from baseline of ≥2 points at Week 6. Other efficacy endpoints and safety were assessed.

Results

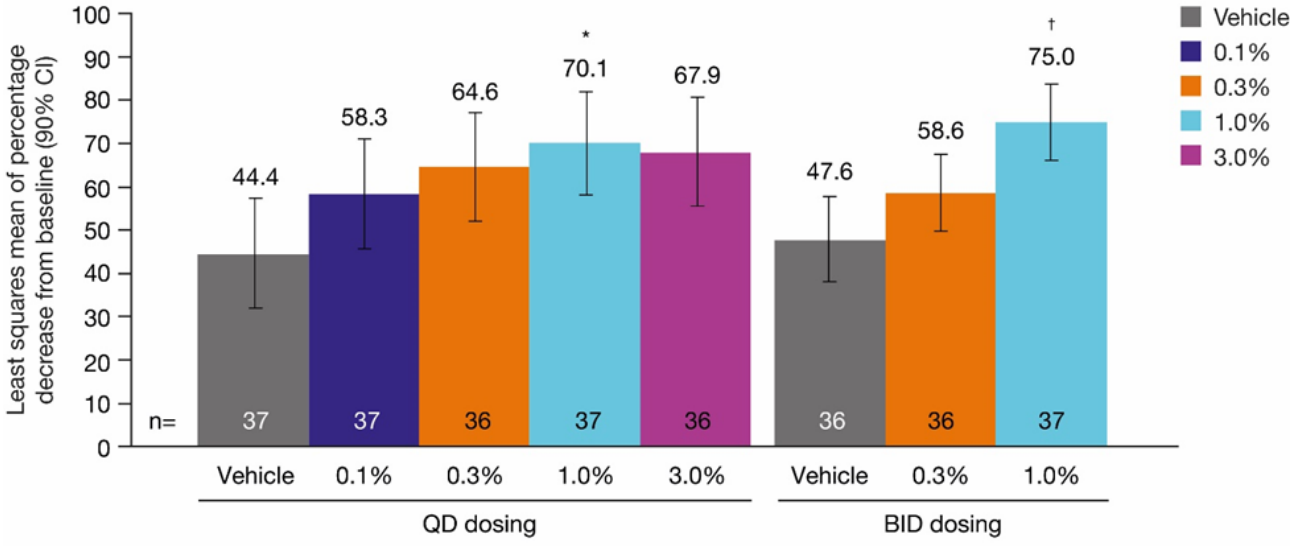
Overall, 292 participants were randomised and 240 completed the treatment period (mean age [range]: 40.2 [13–74] years; female: 53.4%; mean baseline EASI score: 7.3; IGA score mild/moderate: 51.7/47.9%). EASI score at Week 6 had decreased from baseline by 67.9% in the 3% QD arm, and had significantly decreased (with multiplicity adjustment) in the 1% QD (70.1%; p=0.0428) and the 1% BID arms (75.0%; p=0.0022) vs vehicle (V-QD: 44.4%; V-BID: 47.6%) (Figure). For IGA response rates, all QD doses (0.1–3%) and 1 BID dose (0.3%) showed significantly better responses vs vehicle at Week 6 (All QD doses: 29.7–44.4% vs V-QD: 10.8%; 0.3% BID: 33.3% vs V-BID: 13.9%, all p<0.05). Significantly more participants in the 0.3%, 1% and 3% QD arms (27.8–41.7%) and the 1% BID arm (27.0%) had a 90% improvement from baseline in EASI (EASI-90) vs vehicle (V-QD: 10.8%; V-BID: 8.3%) at Week 6 (all p<0.05). The proportion of participants with a ≥4 point improvement in the Peak Pruritis Numerical Rating Scale at Week 6 was statistically significant in the 1% QD arm (45.2%), the 3% QD arm (50.0%) and the 1% BID arm (40.7%), vs vehicle (V-QD: 18.2%; V-BID: 16.7%) (all p<0.05). In total, 108 (37.0%) participants had treatment-emergent adverse events (TEAEs), with more reported with vehicle (V-QD: 48.6%; V-BID: 47.2%) vs the brepocitinib arms (QD: 34.2%; BID: 31.5%).

The majority were mild and the most common were nasopharyngitis and worsening of AD. The number of participants with TEAEs did not increase with dose in the brepocitinib arms, and there were no serious TEAEs, deaths, cases of herpes zoster, malignancies, clinically relevant changes in ECG results or vital signs, or trends in laboratory parameters reported.

Discussion

Topical brepocitinib was effective in participants with mild-to-moderate AD, with reductions in EASI total score and improvement in IGA responder rate at Week 6. Treatment was generally well tolerated.

Percentage decrease from baseline in EASI score at Week 6 (primary endpoint; ANCOVA – FAS)



*p<0.05 vs vehicle QD; †p<0.05 vs vehicle BID.
ANCOVA contained fixed factors of treatment and baseline value.
ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; EASI, eczema area and severity index; FAS, full analysis set; QD, once daily.