

# Efficacy and safety of the histamine H<sub>4</sub> receptor antagonist ZPL-3893787 in patients with atopic dermatitis



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**Background:** H<sub>4</sub> receptor antagonists are potential novel treatments for inflammatory skin diseases, including atopic dermatitis (AD).

**Objective:** We sought to study the efficacy and safety of ZPL-3893787 (a selective H<sub>4</sub> receptor antagonist) in patients with moderate-to-severe AD.

**Methods:** A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate ZPL-3893787 (30 mg) once-daily oral therapy in adults with moderate-to-severe AD. Patients were randomized (2:1) to ZPL-3893787 (n = 65) or placebo (n = 33) for 8 weeks. Patients had a history of AD for more than 12 months, Eczema Area and Severity Index (EASI) scores of 12 or greater and 48 or less, Investigator's Global Assessment (IGA) scores of 3 or greater, pruritus scores of 5 or greater (0- to 10-point scale), and AD on 10% or greater of body surface area. Efficacy parameters included EASI, IGA, SCORAD, and pruritus assessment. **Results:** Treatment with oral ZPL-3893787 showed a 50% reduction in EASI score compared with 27% for placebo. The placebo-adjusted reduction in EASI score at week 8 was 5.1 (1-sided *P* = .01). Clear or almost-clear IGA scores were 18.5% with ZPL-3893787 versus 9.1% with placebo. SCORAD scores exhibited 41% reduction with ZPL-3893787 versus 26% with placebo (placebo-adjusted reduction of 10.0, *P* = .004). There was a 3-point reduction (scale, 1-10) in pruritus with ZPL-3893787, but there was a similar reduction with placebo, resulting in a nonsignificant difference (*P* = .249). Patient-reported pruritus subscores obtained from SCORAD were reduced with ZPL-3893787 compared with

placebo at week 8 (nonsignificant). ZPL-3893787 was well tolerated.

**Conclusion:** For the first time, these results showed that ZPL-3893787 improved inflammatory skin lesions in patients with AD, confirming H<sub>4</sub> receptor antagonism as a novel therapeutic option. (*J Allergy Clin Immunol* 2019;143:1830-7.)

**Key words:** Atopic dermatitis, atopic eczema, eczema, histamine 4 receptor antagonist, Eczema Area and Severity Index, SCORAD, Investigator's Global Assessment, pruritus

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin condition. It is characterized by poorly defined erythema, with edema, vesiculation, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage.<sup>1,2</sup> These symptoms result in severely reduced quality of life. In particular, pruritus that continues throughout the day and worsens at night causes sleep loss and has an effect on everyday activities, as well as psychosocial well-being.<sup>3</sup> AD is commonly associated with other atopic and inflammatory disorders, such as asthma and allergic rhinitis.

The prevalence of AD has at least doubled in industrial countries during the last 3 decades. Between 15% and 30% of children and 2% to 10% of adults are affected by AD.<sup>4</sup>

Current anti-inflammatory treatments for moderate-to-severe AD include topical corticosteroids, topical calcineurin inhibitors, phototherapy, and oral agents, such as systemic steroids or cyclosporine. In addition, antiseptic (eg, bleach baths) therapies

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Pharma and had private investments in the Ziarcopharma Group at the time of the study. W. Liu was an employee of Ziarcopharma and was a stockholder of the Ziarcopharma Group at the time of the study, was cited on a patent that was held by Ziarcopharma at the time of the study, and received a grant to partially fund the phase 2a study from Innovate UK. A. Tsianakas's institution received fees for trial visits during the phase 2a study. L. Purkins was an employee of Ziarcopharma Ltd at the time of the study, was a stockholder of the Ziarcopharma Group at the time of the study, and was also cited on a patent that was held by Ziarcopharma at the time of the study. The rest of the authors declare that they have no relevant conflicts of interest.

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#### Abbreviations used

|         |                                                            |
|---------|------------------------------------------------------------|
| AD:     | Atopic dermatitis                                          |
| ANCOVA: | Analysis of covariance                                     |
| EASI:   | Eczema Area and Severity Index                             |
| EASI50: | Fifty percent reduction from baseline in EASI score        |
| EASI75: | Seventy-five percent reduction from baseline in EASI score |
| ECG:    | Electrocardiogram                                          |
| FAS:    | Full analysis set                                          |
| IGA:    | Investigator's Global Assessment                           |
| NRS:    | Numeric rating scale                                       |
| PGIC:   | Patient's Global Impression of Change                      |
| VRS:    | Verbal rating scale                                        |

and approaches improving the disturbed skin barrier in lesional skin (eg, wet wraps with emollients) have been shown to be efficient in some clinical studies.<sup>1,2</sup> However, there are concerns with lack of efficacy and side effects with some of these treatments. Importantly, there are no orally administered treatments that are safe, effective, and suitable for chronic use. A number of biological therapies under development, as well as the anti-IL-4 receptor  $\alpha$  mAb dupilumab,<sup>5,6</sup> which has recently been approved in the United States and the European Union,<sup>7</sup> are likely to be used by more severely affected patients. This poses a significant health care challenge in treating patients with moderate-to-severe disease whose symptoms are not adequately controlled with topical agents only. This underscores the need for a new oral AD treatment that safely and effectively targets both the inflammatory and pruritic components of this condition.

H<sub>4</sub> is the most recently discovered histamine receptor subtype, and its role in mediating histamine-induced inflammation and pruritus is well documented.<sup>8,9</sup> H<sub>4</sub> mediates proinflammatory functions in a number of cell types involved in allergic inflammation, including T cells, mast cells, eosinophils, and dendritic cells. Selective H<sub>4</sub> receptor antagonists have shown anti-inflammatory and antipruritic efficacy in various preclinical animal models, supporting the concept that they might represent a novel treatment for inflammatory skin diseases, including AD. The recent demonstration of clinical efficacy by the selective H<sub>4</sub> antagonist JNJ-39758979 in patients with moderate AD has added weight to this therapeutic potential.<sup>10</sup> Indeed, H<sub>4</sub> antagonism might also be a useful therapeutic in patients with other inflammatory indications, such as asthma, allergic rhinitis, rheumatoid arthritis, and inflammatory bowel disease.<sup>11,12</sup>

ZPL-3893787 (formerly PF-3893787) is a very potent and highly selective histamine H<sub>4</sub> receptor antagonist, which is more than 100-fold selective for the H<sub>4</sub> receptor over the H<sub>1</sub>, H<sub>2</sub>, and H<sub>3</sub> receptors.<sup>13</sup> Functional antagonism has been observed with native human H<sub>4</sub> receptors against a variety of end points associated with the chemotactic and inflammatory responses in primary human eosinophils.<sup>13</sup> ZPL-3893787 is a small molecule with pharmacokinetic properties appropriate for once-daily dosing. The aim of this study was to investigate the efficacy and safety of ZPL-3893787 in adults with moderate-to-severe AD.

## METHODS

### Study design

This was a randomized, double-blind, placebo-controlled, parallel-group study in adult patients with moderate-to-severe AD ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)

registration NCT02424253). The study was conducted in 17 centers in 4 countries (the United Kingdom, Poland, Germany, and Belgium) and in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. The study was approved by independent ethics committees appropriate to each site/country.

After screening, patients were given an electronic diary (eDiary) to capture pruritus end points and emollient use over a 1-week run-in period (days –7 to –1). Pruritus was scored by using 0- to 10-point numeric rating scales (NRSs). At the baseline visit (day 0), eligibility was confirmed, and patients were randomized and received their first dose of study medication. Patients were randomized by using a 2:1 allocation to receive oral ZPL-3893783 (30 mg) or placebo once daily for 8 weeks. The randomization was stratified according to baseline mean pruritus NRS score ( $\leq 7.5$  and  $>7.5$ ). A computer-generated pseudorandom code generated by using the method of permuted blocks was used to assign patients to treatment within each stratum. Randomization occurred through an interactive Web-based system.

Further visits were performed at weeks 1, 2, 4, and 8. The last dose of study medication was taken the day before the week 8 visit. A final follow-up visit was conducted 21 to 28 days after the last dose. Patients continued their usual emollient skin care routine (ie, twice-daily application) from before the run-in period through the final visit. Rescue medication (0.1% mometasone furoate cream) was provided from day 0 through the final visit. Patients completed the eDiary throughout the study to capture study data, including adherence to investigational product dosing, emollient use, rescue medication use, and twice-daily worst pruritus NRS scores. Eczema Area and Severity Index (EASI), SCORAD, and Investigator Global Assessment (IGA) scores were assessed at all visits. Safety assessments and blood sampling for pharmacokinetic analysis were also conducted throughout the study.

### Patients

Eligible patients were male or female subjects (of nonchildbearing potential) aged 18 to 65 years with a physician-documented history or diagnosis of AD for at least 12 months before screening. Chronic AD was diagnosed by using the Eichenfield revised criteria of Hanifin and Rajka.<sup>1</sup> Patients had an EASI score of 12 or greater and less than 48, an IGA score of 3 or greater at both screening and day 0, a mean worst pruritus NRS score of 5 or greater over the 7-day run-in period, and AD affecting 10% or more of body surface area. All patients provided written informed consent before participation in the study. Key exclusion criteria included AD of such severity (EASI score  $>48$ ) that the patient could not comply with the demands of the study and/or the patient was not a suitable candidate for a placebo-controlled study, concurrent skin disease that might have interfered with study assessments, an active skin infection, or any other clinically apparent infections. Patients were not to have received phototherapy or systemic therapy known or suspected to have an effect on AD or systemic corticosteroids within 4 weeks of the start of the run-in period. Biologics were not to be used within 3 months of the start of the run-in period.

### Assessments and end points

Efficacy was assessed by using EASI, SCORAD, IGA, and Patient's Global Impression of Change (PGIC). Efficacy was also assessed by using the NRS and a verbal rating scale (VRS) for pruritus and the amount of rescue medication used. The NRS scores ranged from 0 (no itching) to 10 (itching as bad as can be imagined). The VRS included the following adjectives: "no itch," "mild," "moderate," and "severe." Worst daily itch for both the NRS and VRS was calculated as the mean of the worst scores from each day over a 7-day period. Use of rescue medication was assessed by weight used. The IGA was a 6-point scale from 0 (clear, with no inflammatory signs of AD) to 5 (very severe disease; severe erythema and severe papulation/infiltration with oozing/crusting). EASI and SCORAD (an alternative clinical score to depict the clinical severity in AD, including objective signs of dermatitis) are validated tools commonly used in AD studies and are described in the literature.<sup>14,15</sup>

The primary end point was change from baseline to week 8 in NRS score for pruritus (worst itch). Secondary end points included change from baseline for the following parameters: EASI, SCORAD, and daytime and nighttime NRS

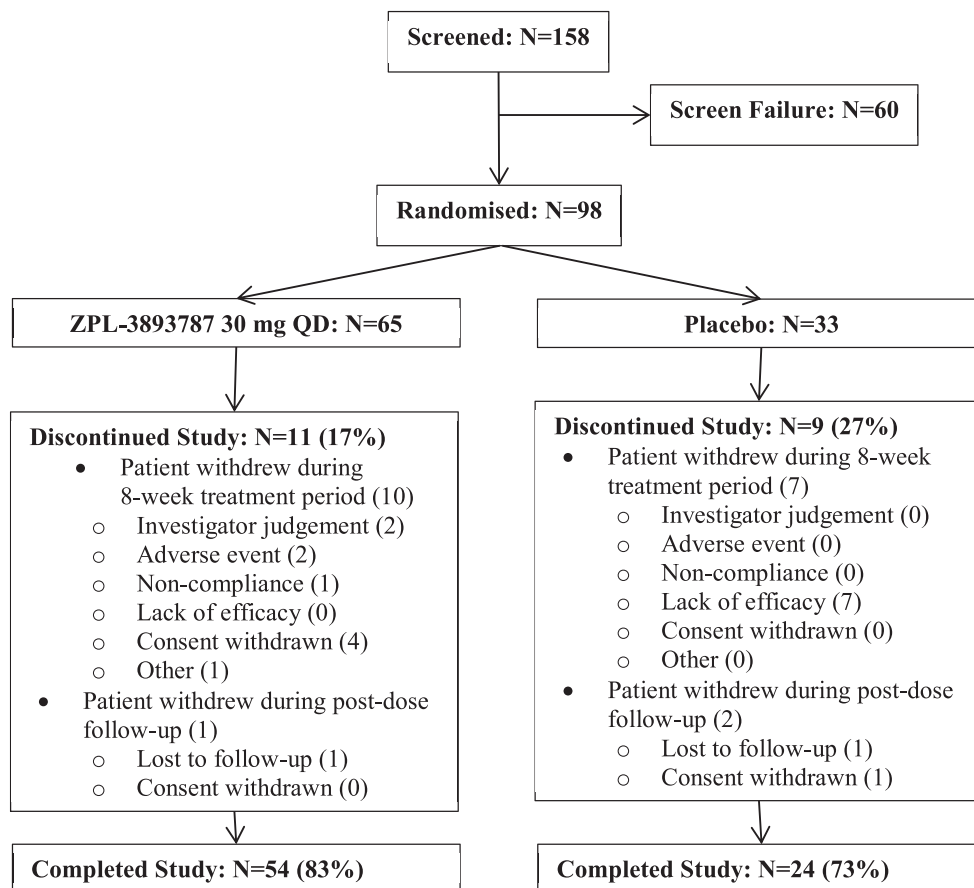


FIG 1. Patient disposition.

for pruritus (worst itch). The number of patients with a 50% or 75% reduction from baseline in EASI score (EASI50 and EASI75, respectively) were also calculated. Week 8 IGA end points included success (“clear” or “almost clear,” which implies a reduction of  $\geq 2$  from baseline).

Subsequent to the protocol-defined efficacy analyses, several *post hoc* analyses were conducted to further evaluate the data in this study. These analyses included change from baseline in EASI excoriation, lichenification, erythema and edema/induration/papulation subscores, and SCORAD sleep and pruritus subscores over time.

Safety was assessed based on reported adverse events, results of clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital signs (systolic and diastolic blood pressure, pulse rate, and body temperature), 12-lead electrocardiograms (ECGs), concomitant medications, and results of physical examinations. Blood was drawn for analysis of ZPL-3893787 at each visit (baseline to week 8 only).

## Statistical analysis

With 60 patients in the ZPL-3893787 group and 30 patients in the placebo group, there was more than 80% power for obtaining a statistically significant result with the primary end point, assuming there was an improvement of 1.5 points with ZPL-3893787 compared with placebo and an SD for the changes from baseline between patients of 2.5. This was based on the analyses described and a 1-sided test at the 5% level of significance. No adjustments were made for multiple comparisons.

For derivation of the primary end point, the mean of the worst daily itch scores collected over the last 7 days was calculated. If there were fewer than 4 measurements in the 7-day period, the overall score was not calculated. Changes from baseline to week 8 of the score were analyzed by using an analysis of covariance (ANCOVA) model that included baseline score as a

covariate and treatment group (ZPL-3893787 or placebo). The influence of missing data was assessed by using alternative analyses based on the assumption of the data being missing at random (multiple imputation) or possibly informative (with the use of worst-case values; ie, score of 10). The primary analysis included all randomized patients who received at least 1 dose of study medication (full analysis set [FAS]) and was based on multiple imputation data. The robustness of the primary analysis was also evaluated by an analysis using a per-protocol population.

For secondary end points, change from baseline was also analyzed by means of ANCOVA, with multiple imputation techniques to account for missing data. ANCOVA models included the relevant baseline score and stratification variable (actual worst pruritus over 24 hours; NRS score,  $\leq 7.5$  or  $> 7.5$ ) as covariates, as well as treatment group.

Responder end points (EASI50, EASI75, IGA success, IGA response, and PGIC) were summarized and analyzed by using logistic regression, with missing responses counted as nonresponders. Baseline scores (all end points, except PGIC), stratification variable, and treatment group were included in the models as factors.

The total amount of rescue medication used during the study adjusted for study duration (mean daily use) was analyzed by using the Van Elteren test.

Safety and pharmacokinetic data were summarized descriptively.

*Post hoc* analyses of end points at times other than week 8 were also conducted. In these *post hoc* analyses, the FAS was used, and values were averaged across multiple imputations before summarizing across patients.

## RESULTS

The study was conducted between May 18, 2015, and February 3, 2016. A total of 98 patients were randomized, and 78 (80%)

**TABLE I.** Demographics and baseline characteristics

|                                                                 | ZPL-3893787 (n = 65) | Placebo (n = 33)  |
|-----------------------------------------------------------------|----------------------|-------------------|
| Age (y), median (minimum-maximum)                               | 31.0 (19-61)         | 35.0 (18-64)      |
| Body mass index (kg/m <sup>2</sup> ), median (minimum-maximum)  | 24.70 (17.3-34.6)    | 25.30 (20.7-34.2) |
| Sex, no. (%)                                                    |                      |                   |
| Male                                                            | 29 (44.6)            | 13 (39.4)         |
| Female                                                          | 36 (55.4)            | 20 (60.6)         |
| Race, no. (%)                                                   |                      |                   |
| White                                                           | 61 (93.8)            | 31 (93.9)         |
| Asian                                                           | 3 (4.6)              | 1 (3.0)           |
| Black                                                           | 0                    | 1 (3.0)           |
| Other                                                           | 1 (1.5)              | 0                 |
| Fitzpatrick skin type, no. (%)                                  |                      |                   |
| I                                                               | 2 (3.1)              | 4 (12.1)          |
| II                                                              | 24 (36.9)            | 11 (33.3)         |
| III                                                             | 32 (49.2)            | 14 (42.4)         |
| IV                                                              | 3 (4.6)              | 2 (6.1)           |
| V                                                               | 3 (4.6)              | 1 (3.0)           |
| VI                                                              | 1 (1.5)              | 1 (3.0)           |
| Duration of AD (y), median (minimum-maximum)                    | 22.0 (1-56)          | 25.0 (2-47)       |
| NRS worst pruritus score over 24 h, median (minimum-maximum)    | 7.29 (5.0-9.6)       | 7.26 (5.0-9.0)    |
| VRS worst rating for pruritus over 24 h, no. (%)                |                      |                   |
| No itch                                                         | 0                    | 0                 |
| Mild                                                            | 3 (4.6)              | 1 (3.0)           |
| Moderate                                                        | 35 (53.8)            | 23 (69.7)         |
| Severe                                                          | 27 (41.5)            | 9 (27.3)          |
| EASI score, median (minimum-maximum)                            | 19.00 (12.5-45.0)    | 18.70 (12.4-36.3) |
| SCORAD score, median (minimum-maximum)                          | 54.50 (34.8-80.0)    | 55.60 (37.5-75.7) |
| Percentage body surface area affected, median (minimum-maximum) | 40.00 (11.0-96.0)    | 38.0 (11.0-92.0)  |
| IGA score, no. (%)                                              |                      |                   |
| Moderate disease                                                | 48 (73.8)            | 24 (72.7)         |
| Severe disease                                                  | 15 (23.1)            | 9 (27.3)          |
| Very severe disease                                             | 2 (3.1)              | 0                 |

VRS, Verbal rating score.

completed the study. All 98 patients were included in the FAS. A greater proportion of patients who received ZPL-3893787 completed the study than patients who received placebo (Fig 1). Notably, all 7 patients who withdrew because of a lack of efficacy were in the placebo group. Demographics and baseline characteristics were similar across the 2 treatment groups (Table I).

## Efficacy

A reduction in EASI score from baseline was noted in both groups from week 1, with a separation of the treatment groups in favor of ZPL-3893787 occurring by week 2 and becoming statistically significant at week 6 (Fig 2). Absolute EASI scores are presented in Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). Treatment with oral ZPL-3893787 showed a 50% reduction in EASI score compared with 27% for placebo at week 8. After 8 weeks of treatment, ZPL-3893787 demonstrated a reduction in EASI score compared with placebo of 5.06 (1-sided  $P = .010$ , Table II). There was also a significant difference in EASI75 score at week 8 in favor of ZPL-3893787 (32%) compared with placebo (15%,  $P = .033$ ; Table II).

For the IGA, a greater percentage of patients were considered to be "clear/almost clear" (ie, success) in the ZPL-3893787 group (18.5%) compared with the placebo group (9.1%) at week 8 (odds ratio, 2.57; 1-sided  $P = .088$ ). When also including those with a reduction of at least 2 (ie, responders), the proportions

increased to 27.7% and 15.2% for the ZPL-3893787 and placebo groups, respectively (odds ratio, 2.75; 1-sided  $P = .049$ ).

Reductions in mean SCORAD scores were noted in both treatment groups at all weeks, with greater reductions from baseline being noted with ZPL-3893787 (−23.78) compared with placebo (−14.31) by week 1 (Fig 3 and Table II). Absolute SCORAD scores are presented in Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). A statistically significant improvement in SCORAD score was confirmed in the treatment group compared with the placebo group at weeks 4, 6, and 8. SCORAD scores exhibited a 41% reduction with ZPL-3893787 versus 26% placebo at week 8. At week 8, ZPL-3893787 demonstrated a reduction in SCORAD score compared with placebo of approximately 10.0 (1-sided  $P = .004$ ).

Assessment of changes from baseline in the worst daily pruritus scores (NRS; Fig 4, A), SCORAD pruritus subscore (Fig 4, B), and sleep subscores (Fig 4, C) suggested that ZPL-3893787 reduced pruritus.

There were large (>2.5) reductions in mean worst pruritus scores over 24 hours in both treatment groups. Although the reductions in the ZPL-3893787 group were greater at all time points compared with those in the placebo group, the difference (reduction of 0.35) was not statistically significant (1 sided  $P = .249$ ) at week 8 by using the FAS (primary end point, Table II). Results with the per-protocol population and sensitivity analyses with the FAS at week 8 were generally consistent with the primary analysis (see Table E1 in this article's

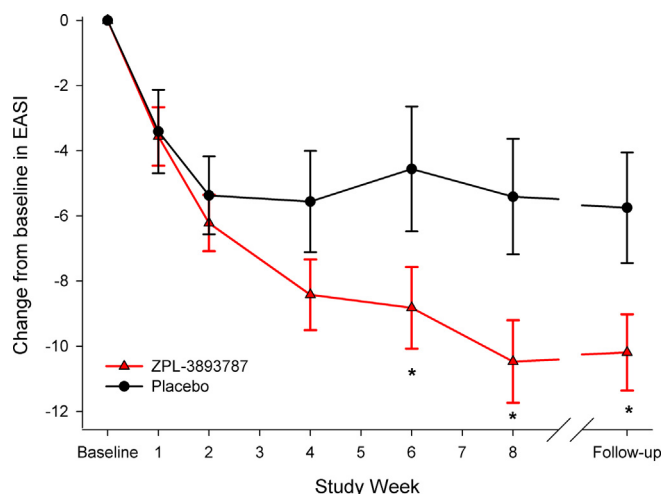


**FIG 2.** Least-squares means  $\pm$  SEs for change from baseline in EASI score. \* $P < .05$  versus placebo.

Online Repository at [www.jacionline.org](http://www.jacionline.org)); however, the analysis using worst-case imputation indicated a statistically significant difference between the treatment groups (reduction of 1.27, 1-sided  $P = .009$ ). This analysis imputed a score of 10 for missing data considered as informative; multiple imputation was used for other missing data. This worst-case imputation was only used for the 7 patients who withdrew because of lack of efficacy, who notably were all in the placebo group.

The EASI excoriation subscore as an indicator of pruritus in patients with AD also demonstrated improvements from baseline in the ZPL-3893787 compared with placebo groups, with the separation between treatment groups already apparent by week 1 (see Fig E1).

The median amount of rescue medication used was 0.05 g/d for patients in the ZPL-3893787 group and 0.15 g/d for patients in the placebo group (1-sided  $P = .057$ ). Overall, the majority of patients in both treatment groups used rescue medication at some point during the double-blind treatment period: 75.4% in the ZPL-3893787 group and 84.8% in the placebo group.

## Pharmacokinetics

Starting with week 1, median predose (trough) ZPL-3893787 concentrations ranged from 5.7 to 7.0 ng/mL over the course of the study, and median postdose concentrations ranged from 13.8 to 14.7 ng/mL.

## Safety

The incidence of treatment-emergent adverse events was similar in both treatment groups (66% in the ZPL-3893787 group and 64% in the placebo group, Table III). A greater percentage of patients in the placebo group reported adverse events (30%) considered at least possibly related to the study medication by the investigator compared with the ZPL-3893787 group (23%). The only adverse events reported by at least 5% of patients in the ZPL-3893787 group were nasopharyngitis (18%), headache (11%), and eczema (6%), all of which were reported with a similar incidence in the placebo group. One patient reported a serious adverse event (ulcerative keratitis) in the placebo group, but no patients in the ZPL-3893787 group had a serious adverse

**TABLE II.** Analyses of primary and secondary efficacy end points

|                                           | ZPL-3893787<br>(n = 65) | Placebo<br>(n = 33) |
|-------------------------------------------|-------------------------|---------------------|
| Worst pruritus score (NRS)                |                         |                     |
| Change from baseline to week 8, mean (SD) | -3.03 (2.186)           | -2.66 (2.057)       |
| LS difference (90% CI)                    | -0.35 (-1.21 to 0.51)   |                     |
| One-sided <i>P</i> value                  | .249                    |                     |
| Worst pruritus score (VRS)                |                         |                     |
| Improvement from baseline, no. (%)        | 35 (53.8)               | 16 (48.5)           |
| Worsening from baseline, no. (%)          | 2 (3.1)                 | 0                   |
| EASI score                                |                         |                     |
| Change from baseline to week 8, mean (SD) | -10.72 (9.679)          | -5.38 (9.922)       |
| LS difference (90% CI)                    | -5.06 (-8.66 to -1.46)  |                     |
| One-sided <i>P</i> value                  | .010                    |                     |
| Responders (EASI50) at week 8, no. (%)    | 34 (52.3)               | 13 (39.4)           |
| Odds ratio (Wald 90% CI)                  | 1.82 (0.88 to 3.77)     |                     |
| One-sided <i>P</i> value                  | .089                    |                     |
| Responders (EASI75) at week 8, no. (%)    | 21 (32.3)               | 5 (15.2)            |
| Odds ratio (Wald 90% CI)                  | 2.80 (1.12 to 7.04)     |                     |
| One-sided <i>P</i> value                  | .033                    |                     |
| SCORAD score                              |                         |                     |
| Change from baseline to week 8, mean (SD) | -23.78 (17.278)         | -14.31 (16.090)     |
| LS difference (90% CI)                    | -9.99 (-16.16 to -3.84) |                     |
| One-sided <i>P</i> value                  | .004                    |                     |
| IGA score                                 |                         |                     |
| Success* at week 8, no. (%)               | 12 (18.5)               | 3 (9.1)             |
| Odds ratio (Wald 90% CI)                  | 2.57 (0.82 to 8.11)     |                     |
| One-sided <i>P</i> value                  | .088                    |                     |
| Responders† at week 8, no. (%)            | 18 (27.7)               | 5 (15.2)            |
| Odds ratio (Wald 90% CI)                  | 2.75 (1.00 to 7.54)     |                     |
| One-sided <i>P</i> value                  | .049                    |                     |

LS, Least squares; VRS, verbal rating score.

\*For IGA, success is defined as a score of "clear" or "almost clear."

†For IGA, responder is defined as a score of "clear" or "almost clear" or a reduction of 2 or more levels from baseline.

event. The majority of adverse events were mild or moderate in intensity. Five subjects reported severe adverse events, which included somnolence and migraine in 1 patient each in the ZPL-3893787 group and urinary tract infection, worsening AD, and pruritus in 1 patient each in the placebo group. All severe events were considered treatment-related, except for the occurrence of migraine. There were no increases in infections, including skin infections or other skin side effects. There were no relevant safety findings from clinical laboratory tests (particularly no neutropenia in the cohort treated with ZPL-3893787), physical examination findings, vital signs, or ECG findings.

A total of 17 patients withdrew during the 8-week treatment period: 10 (15%) in the ZPL-3893787 group and 7 (21%) in the placebo group (Fig 1). Two patients in the ZPL-3893787 group were discontinued because of adverse events: 1 patient with moderate headache and 1 patient with severe somnolence. All 7 patients who withdrew during treatment in the placebo group did so because of lack of efficacy.

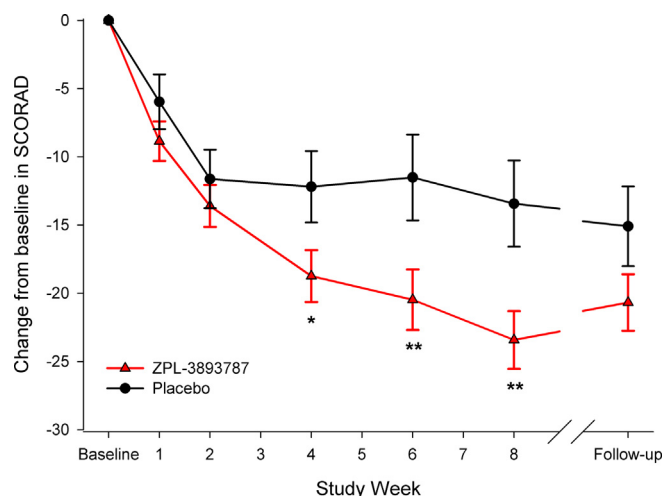


**FIG 3.** Least-squares means  $\pm$  SEs for change from baseline in SCORAD score. \* $P < .05$  versus placebo and \*\* $P < .01$  versus placebo.

## DISCUSSION

For the first time, this study shows that the oral  $H_4$  receptor inhibitor ZPL-3893787 improves inflammatory skin lesions in patients with AD, suggesting  $H_4$  receptor antagonism as a novel therapeutic option.  $H_4$  is the newest member of the histamine receptor family. It is often referred to as the “histamine receptor of the immune system” because of its predominant expression on a variety of immune cells, such as T cells, mast cells, eosinophils, and dendritic cells. There is a large body of evidence demonstrating that the  $H_4$  receptor is intimately linked to many functional inflammatory responses mediated by histamine, including chemotaxis and cell recruitment, upregulation of adhesion molecule expression, and modulation of cytokine and chemokine release.<sup>11</sup>

There is extensive scientific rationale linking activation of the  $H_4$  receptor to a range of inflammatory disorders. Of these, there is a large body of preclinical evidence and emerging clinical data supporting the utility of  $H_4$  antagonists in the treatment of pruritus and atopic skin inflammation.<sup>16</sup> For example,  $H_4$  agonists have been described to upregulate the  $T_H2$ -associated and itch-inducing cytokine IL-31,<sup>17</sup> contribute to  $T_H2$  polarization by suppressing IL-12 in antigen-presenting cells,<sup>18,19</sup> and induce proliferation and thymic stromal lymphopoietin production in human keratinocytes.<sup>20,21</sup>

Histamine has long been known as a mediator that induces itch in normal human skin, and this pruritic response was shown to be further enhanced in patients with AD.<sup>22</sup> Although  $H_1$  antagonists have demonstrated efficacy against acute itch, they have very limited value in patients with AD, suggesting the potential involvement of another histamine receptor. The  $H_4$  knockout mouse is highly protected against a variety of inflammatory and pruritic stimuli,<sup>9</sup> and selective  $H_4$  antagonists are highly effective in suppressing skin inflammation and alleviating itch in various preclinical animal models.<sup>12,23,24</sup>

Importantly, the selective oral  $H_4$  antagonist JNJ-39758979 has demonstrated clinical efficacy in reducing histamine-mediated itch in healthy human subjects.<sup>25</sup> A study of JNJ-39758979 has also been conducted in Japanese patients with moderate AD. The published data showed a trend toward improvements compared with placebo in EASI scores and measures of pruritus,

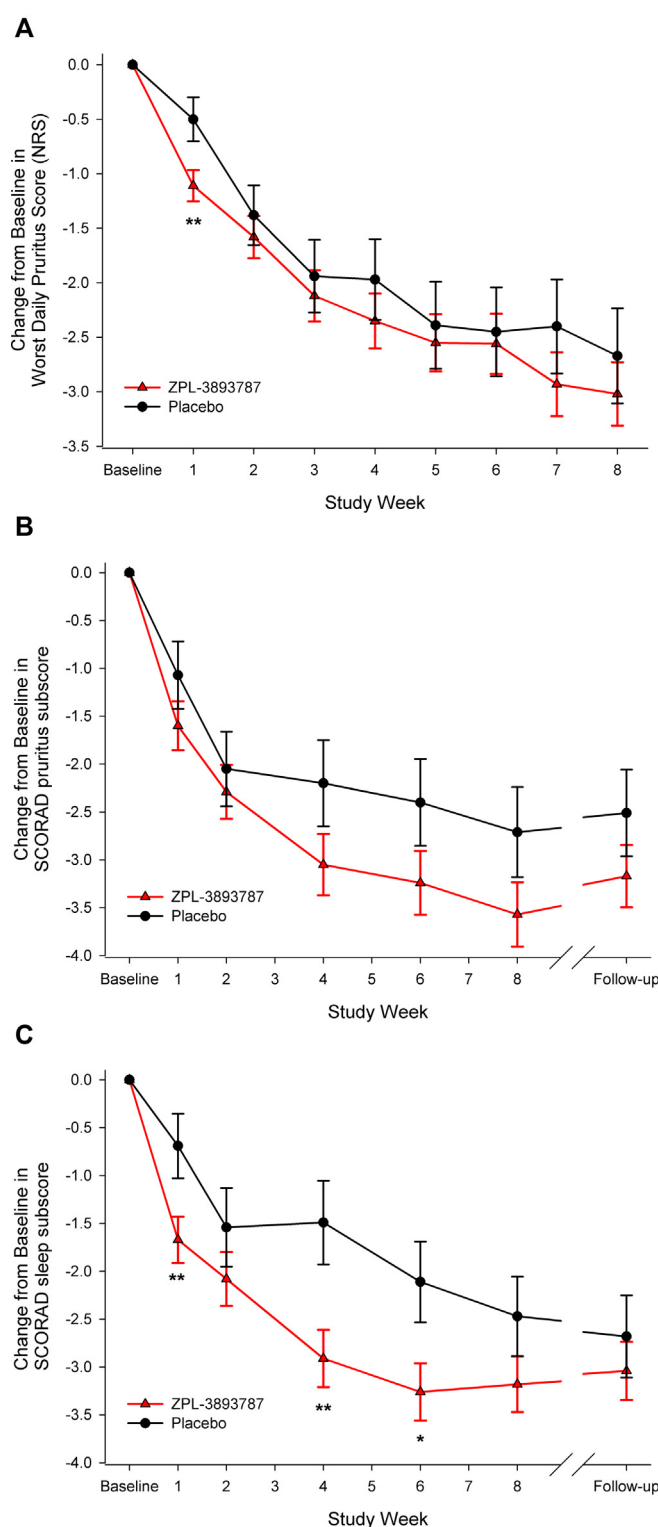


**FIG 4.** Least-squares means  $\pm$  SEs for change from baseline in worst daily pruritus NRS scores (A), SCORAD pruritus subscores (B), and SCORAD sleep subscores (C). \* $P < .05$  versus placebo and \*\* $P < .01$  versus placebo.

suggesting that the compound reduced the severity and duration of itch.<sup>10</sup> Although the development of JNJ-39758979 has been terminated because of 2 cases of agranulocytosis that the authors concluded to be compound specific and unrelated to the  $H_4$  mechanism, these data have provided the initial clinical evidence

**TABLE III.** Incidence of treatment-emergent adverse events

|                                        | No. of patients (%)     |                     |                   |
|----------------------------------------|-------------------------|---------------------|-------------------|
|                                        | ZPL-3893787<br>(n = 65) | Placebo<br>(n = 33) | Total<br>(n = 98) |
| Patients with any AE                   | 43 (66)                 | 21 (64)             | 64 (65)           |
| Patients with any serious AE           | 0                       | 1 (3)               | 1 (1)             |
| Patients with any severe AE            | 2 (3)                   | 3 (9)               | 5 (5)             |
| Patients with any treatment-related AE | 15 (23)                 | 10 (30)             | 25 (26)           |
| AEs in $\geq 5\%$ of total patients    |                         |                     |                   |
| Nasopharyngitis                        | 12 (18)                 | 8 (24)              | 20 (20)           |
| Headache                               | 7 (11)                  | 4 (12)              | 11 (11)           |
| Eczema                                 | 4 (6)                   | 1 (3)               | 5 (5)             |
| Dermatitis, atopic                     | 0                       | 5 (15)              | 5 (5)             |

*Eczema* is the overall term for lesional skin; *Dermatitis, atopic* was meant to address a more specific worsening of AD in the protocol.

that H<sub>4</sub> receptor antagonism might have therapeutic utility in patients with AD.

In the current study using the selective H<sub>4</sub> receptor antagonist ZPL-3893787, demographics and baseline characteristics were similar across the 2 treatment groups and were considered consistent with the moderate-to-severe AD population investigated in other clinical studies.<sup>5</sup> The primary efficacy end point was change from baseline to week 8 of the mean worst daily pruritus score over 7 days by using NRS for the FAS. Although a reduction in NRS score was observed with ZPL-3893787, a similar reduction was also observed with placebo; consequently, the difference between the treatment groups was not statistically significant (1-sided  $P = .249$ ). Of note, indicators of itch reduction (ie, patient-reported pruritus and sleep subscores from SCORAD) indicated an effect of ZPL-3893787 on itch. Although in general the results of the sensitivity analyses were consistent with the primary analysis, it should be noted that the worst-case imputation for the FAS showed a statistically significant difference between the treatment groups (1-sided  $P = .009$ ). This is due to the fact that the worst-case imputation was used for the 7 patients who withdrew because of lack of efficacy, all of whom were in the placebo group.

We cannot exclude that the placebo effect was partly a result of application of topical corticosteroids, which were allowed as rescue medication and are known to reduce pruritus in patients with AD.<sup>26</sup> Indeed, we observed a trend toward greater use of topical corticosteroids in the placebo group.

Statistically significant differences between the treatment groups were seen in assessments of the severity of eczematous/inflammatory skin lesions, including treatment success from IGA, EASI, and SCORAD. Differences between the ZPL-3893787 study group and the placebo group started to diverge from week 1 or 2 and reached statistical significance by 4 (SCORAD) to 6 (EASI) weeks, indicating a quick onset of clinical efficacy on skin inflammation. EASI and SCORAD scores might not have reached a plateau in the ZPL-3893787 group at 8 weeks. We could expect greater long-term efficacy of ZPL-3893787 from time courses shown for EASI and SCORAD because the reduction of these scores still had not reached a plateau in the treatment group after the defined clinical end point of 8 weeks. Therefore more studies on objective findings should be pursued before the drug is promoted for clinical use.

The incidence of treatment-emergent adverse events was similar in both treatment groups. The majority of adverse events

were mild or moderate in intensity, and no increases in infections, including skin infections or other skin side effects, were observed. There were no relevant safety findings from clinical laboratory tests (particularly no neutropenia in the cohort treated with ZPL-3893787), physical examination findings, vital signs, or ECG findings.

In summary, ZPL-3893787 showed clinically meaningful anti-inflammatory effects over placebo on the key efficacy assessments EASI, IGA, and SCORAD, whereas the effect on itch reduction was possibly partially confounded by use of rescue medication in the placebo group. Importantly, ZPL-3893787 appeared safe and well tolerated after once-daily oral dosing for 8 weeks. Therefore ZPL-3893787 warrants further investigation in larger studies in patients with AD.

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**Clinical implications: ZPL-3893787 is a novel, orally available, selective H<sub>4</sub> receptor antagonist that has shown clinically significant anti-inflammatory effects in patients with AD and hence represents a potential new treatment option.**

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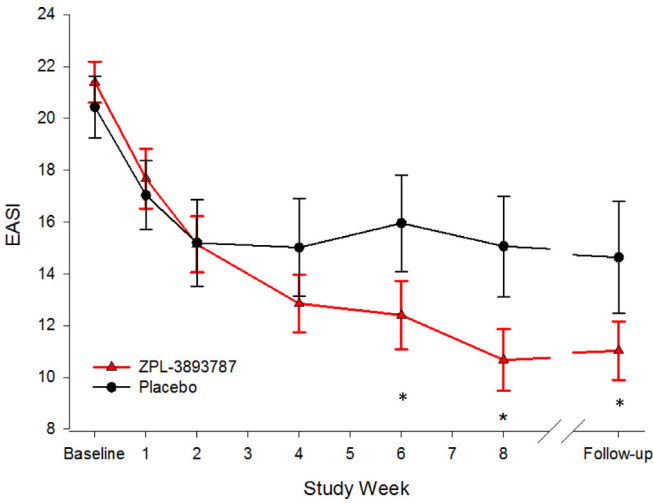


**FIG E1.** Mean  $\pm$  SE EASI scores. \* $P < .05$  versus placebo.

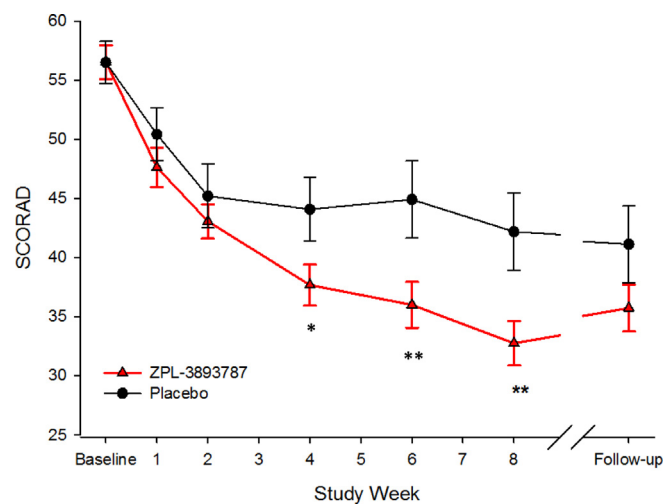


**FIG E2.** Mean  $\pm$  SE SCORAD scores. \* $P < .05$  and \*\* $P < .01$  versus placebo.

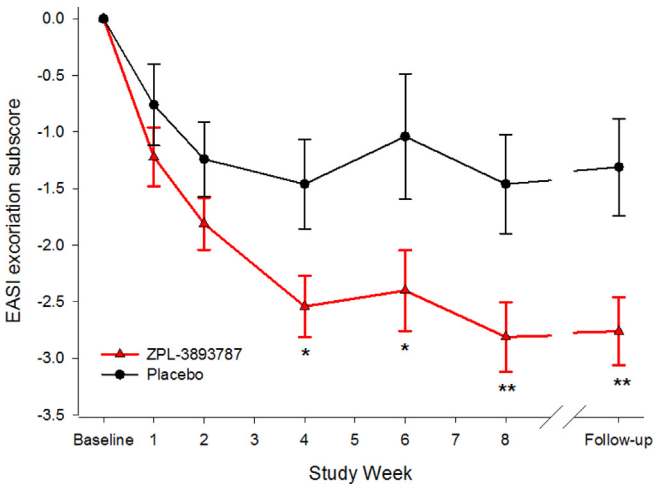


**FIG E3.** Least-squares means  $\pm$  SEs for change from baseline in EASI excoriation subscores. \* $P < .05$  versus placebo and \*\* $P < .01$  versus placebo.

**TABLE E1.** Change from baseline in NRS worst pruritus score: Sensitivity analysis

| Method*            | ZPL-3893787 |               | Placebo |               | LS difference: ZPL-3893787 – placebo (90% CI) | P value (1-sided) |
|--------------------|-------------|---------------|---------|---------------|-----------------------------------------------|-------------------|
|                    | No.         | LS means (SE) | No.     | LS means (SE) |                                               |                   |
| MI† FAS            | 65          | −3.02 (0.291) | 33      | −2.67 (0.437) | −0.35 (−1.21 to 0.41)                         | .249              |
| MI† PP             | 58          | −3.15 (0.300) | 29      | −2.81 (0.435) | −0.35 (−1.22 to 0.52)                         | .251              |
| Observed case      | 53          | −3.16 (0.308) | 26      | −2.86 (0.441) | −0.30 (−1.19 to 0.60)                         | .291              |
| LOCF               | 63          | −2.80 (0.283) | 33      | −2.36 (0.397) | −0.44 (−1.25 to 0.37)                         | .185              |
| Worst-case MI FAS‡ | 65          | −3.02 (0.324) | 33      | −1.75 (0.435) | −1.27 (−2.16 to −0.38)                        | .009              |

LOCF, Last observation carried forward; LS, least squares; MI, missing imputed; PP, per protocol.

\*ANCOVA model included baseline score as a covariate and treatment.

†Missing data were imputed with Markov chain Monte Carlo imputation methods.

‡Missing data were imputed with Markov chain Monte Carlo imputation methods, and information missing week 8 scores were set to a score of 10.