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Exposure-Response Analyses for Upadacitinib Efficacy in Subjects With Atopic Dermatitis—Analyses of Phase 2b Study to Support Selection of Phase 3 Doses

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Abstract

Upadacitinib is a selective Janus kinase 1 inhibitor that was recently approved for treatment of rheumatoid arthritis and is currently being evaluated for treatment of several other autoimmune diseases, including atopic dermatitis (AD). The relationships between upadacitinib plasma exposure and efficacy (assessed as Eczema Area Severity Index [EASI]-75, EASI-90, and Investigator Global Assessment [IGA] 0/1) in subjects with moderate to severe atopic dermatitis were characterized using the data from 167 subjects who were enrolled in a phase 2b dose-ranging study. Subjects were randomized to receive once daily doses of monotherapy treatment with upadacitinib extended-release 7.5, 15, or 30 mg or placebo for 16 weeks. Logistic regression models were developed and utilized to simulate efficacy for upadacitinib with an approximate phase 3 sample size. Based on exposure-response models, 15 mg once daily is predicted to achieve EASI-75, EASI-90, and IGA 0/1 responses in 48%, 26%, and 29% of subjects, respectively, compared with placebo responses of 9%, 2%, and 2%, respectively, whereas 30 mg once daily is predicted to provide an additional approximately 20% greater efficacy for these end points relative to 15 mg once daily. These analyses supported the selection of upadacitinib doses that are being evaluated in ongoing global phase 3 studies in atopic dermatitis.

Keywords

Upadacitinib, JAK inhibitor, immunology, atopic dermatitis, exposure-response, pharmacometrics

Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin disease that affects 1% to 3% of adults worldwide.[1] The most common clinical characteristics of atopic dermatitis are pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification.[2] Treatment of atopic dermatitis in adult patients depends on the extent and severity of disease. Although topical agents such as corticosteroids and emollients have been used to treat mild to moderate atopic dermatitis for decades, this treatment option is prone to poor adherence because of the inconvenience of topical applications, corticosteroid phobia, and unwanted side effects.[3] In severe cases of atopic dermatitis, topical regimens alone may not be sufficient to manage disease symptoms. Recently, dupilumab, a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling, has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of moderate to severe atopic dermatitis in adults and adolescents. Although dupilumab addresses the needs of some patients with moderate to severe atopic dermatitis, a large unmet need still exists in this population. In the dupilumab phase 3 studies, fewer than 40% of patients achieved no or almost no disease activity.[4,5]

The pathogenesis of atopic dermatitis is believed to be, in part, a consequence of increased Th2 immunity that is driven by activation of Janus kinase (JAK)-mediated signaling pathways.[6,7] The JAK family is composed of 4 family members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2), and activation of JAK pathways initiates expression of survival factors, cytokines, chemokines, and other molecules that facilitate leukocyte cellular trafficking and cell proliferation, which contribute to inflammatory and autoimmune disorders.[8] Hence, the JAK family has evoked

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considerable interest in the area of inflammatory diseases, including atopic dermatitis, leading to the development of JAK inhibitors with different selectivity profiles against JAK1, JAK2, JAK3, and Tyk2.[9] Of these pathways, inhibiting those mediated by JAK1 specifically blocks the signaling of several proinflammatory cytokines (eg, IL-31, IL-4, IL-13, and thymic stromal lymphopoietin) that are central to atopic dermatitis pathophysiology.[10,11]

Upadacitinib is an oral JAK1 inhibitor that was recently approved by the FDA, the EMA, and several other regulatory agencies for the treatment of rheumatoid arthritis (RA) with a dosing regimen of 15 mg once daily with the extended-release formulation. In addition, upadacitinib is currently under development for the treatment of several autoimmune diseases including ulcerative colitis (UC),[12] Crohn's disease (CD),[13–15] psoriatic arthritis,[16,17] giant cell arteritis,[18] axial spondyloarthritis,[19] and atopic dermatitis.[20] Upadacitinib pharmacokinetics were characterized following the administration of single and multiple doses of the immediate-release and extended-release formulations.[21–26] Upadacitinib plasma exposure was approximately dose proportional over the evaluated dose range across clinical studies and displayed no significant accumulation with repeated twice daily dosing using the immediate-release formulation or with once daily dosing using the extended-release formulation.[21,22] The extended-release tablet formulation of upadacitinib was developed to enhance patient compliance and has 76% oral bioavailability relative to the same dose of the immediate-release formulation.[23] Upadacitinib median time to the maximum observed plasma concentration (C_{max}) for the extended-release formulation is 2 to 4 hours, and the mean terminal-phase elimination half-life is 9 to 14 hours.[27]

A Phase 2b dose-ranging study (NCT02925117) that evaluated 7.5, 15, and 30 mg doses of the extended-release formulation of upadacitinib or placebo given once daily in subjects with moderate to severe atopic dermatitis demonstrated favorable efficacy after 16 weeks of treatment.[20] The primary end point in the study was percentage improvement in Eczema Area and Severity Index (EASI) from baseline in week 16, and main secondary end points were proportions of patients achieving improvement of ≥50%/≥75%/≥90% from baseline in EASI (EASI 50/75/90) in weeks 8 and 16; proportions of patients achieving Investigator Global Assessment (IGA) 0/1 in week 16. Subjects randomized to upadacitinib 7.5, 15, and 30 mg groups showed 39%, 62%, and 74% mean improvement, respectively, in EASI from baseline in week 16, compared with 23% with placebo. This phase 2b study was the first study to investigate a selective JAK1 inhibitor monotherapy for the treatment of atopic dermatitis and was the basis for granting breakthrough therapy designation by the FDA to upadacitinib development in atopic dermatitis. The analyses reported here were conducted to characterize upadacitinib exposure-response relationships for efficacy in atopic dermatitis using data from the phase 2b dose-ranging study, and the exposure-response models were utilized to predict upadacitinib efficacy using an approximate phase 3 sample size and support dose selection for phase 3 atopic dermatitis trials. These analyses supported initiation of 4 ongoing upadacitinib phase 3 trials in subjects with moderate to severe atopic dermatitis.[28–31]

Methods

Study Design and Participants

The study was conducted in accordance with Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the institutional review board or ethics committee for each site, and each patient provided written informed consent before any study-related procedures were performed.

The study was a phase 2b double-blind, randomized, parallel-group, multicenter dose-ranging trial conducted to evaluate the safety and efficacy of multiple doses of upadacitinib versus placebo in subjects with moderate to severe atopic dermatitis. The details of the study design were previously reported.[20] Briefly, 167 subjects were enrolled in this study and randomized in equal ratios to receive oral placebo or extended-release upadacitinib (AbbVie, North Chicago, Illinois) 7.5, 15, or 30 mg once daily. Eligible patients were 18 to 75 years old at screening, with a dermatologist confirmed diagnosis of atopic dermatitis according to Hanifin and Rajka criteria,[32] with symptoms for 1 year or more before baseline. The patients had moderate to severe atopic dermatitis, defined as EASI value of 16 or more, affected body surface area ≥ 10%, and IGA 3 or more at baseline. They had an inadequate response to topical corticosteroids or topical calcineurin inhibitors within 1 year before screening or were patients for whom topical treatments were otherwise medically inadvisable. Subjects were excluded from the phase 2 study if they had any prior exposure to dupilumab or exposure to systemic therapies for atopic dermatitis including corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 inhibitors, and mycophenolate mofetil within 4 weeks prior to baseline. All patients were to use an additive-free bland emollient twice daily for 7 days or more before baseline and during the study.[20] Pharmacokinetics and efficacy data from the 16-week double-blind, randomized treatment period were used for the exposure-response analyses.

Pharmacokinetic and Efficacy Assessments

During the 16-week period, sparse blood samples for determination of upadacitinib plasma concentrations

were collected in weeks 2 and 4 prior to dosing and in weeks 8, 12, and 16 at any time during the visit. Plasma concentrations of upadacitinib were measured using a validated liquid chromatography method with mass spectrometric detection, as previously described.[22,26,33] Upadacitinib pharmacokinetics were characterized using population pharmacokinetics analyses using data from the phase 2b atopic dermatitis study, and data from phase 1 and phase 2 studies in healthy subjects and subjects with RA, Crohn's disease, and ulcerative colitis. Details of the population pharmacokinetic analyses were previously reported.[22] Efficacy assessments (EASI and IGA) were recorded at baseline and during clinic visits in weeks 2, 4, 8, 12, and 16. Exposure-response analyses were conducted for efficacy in week 16, which is the point for the primary end-point assessment.

Exposure-Response Analyses of Upadacitinib Efficacy

Upadacitinib exposure-response relationships for efficacy were evaluated using logistic regression analyses for EASI-75, EASI-90, and IGA 0/1 end points in week 16. Upadacitinib individual average plasma concentrations over a dosing interval at steady state based on the empirical Bayesian individual pharmacokinetic parameters in subjects with atopic dermatitis from the population pharmacokinetic model[22] were used as the exposure metric for the analyses.

Different functions describing the correlation between upadacitinib C_{avg} and the different binary response variables were performed. A separate analysis was conducted for each efficacy end point. Mathematically, the logit of the probabilities to reach the end point was described as:

$$\ln \frac{P(Y=1)}{1-P(Y=1)} = f\left(C_{avg}\right)$$

where Y denotes the binary variable of response, with $P(Y=1)$ representing the probability of the response being reached. Different link functions for correlation with C_{avg} were explored to obtain optimal fits to the observed data.

$$f\left(C_{avg}\right) = \text{Int} + \text{slope}.C_{avg} \text{ (linear model)}$$

$$f\left(C_{avg}\right) = \text{Int} + \frac{E_{max}.C_{avg}}{C_{avg} + EC_{50}} \text{ (E_{max} model)}$$

$$f\left(C_{avg}\right) = \text{Int} + \frac{E_{max}.C_{avg}{}^{h}}{C_{avg}{}^{h} + EC_{50}{}^{h}} \text{ (sigmoid E_{max} model)}.$$

The parameter Int refers to the intercept (the logit-transformed probability of placebo response). The parameter slope denotes the slope (in a logit scale) of the exposure-response relationship in the linear model, whereas the parameters E_{max}, EC_{50}, and h denote the maximal effect of upadacitinib, the upadacitinib average plasma concentration that achieves half-maximal effect and the Hill coefficient, respectively. It is to be noted that all these parameters are to be interpreted as being in the logit scale. Statistical significance of the drug effect was declared at $P < .01$ using a likelihood ratio test (relative to a null model of no drug effect as reference).

Logistic regression models were built using the *glm* (for logistic regression models with linear link) and *gnm* (for logistic regression models with E_{max} link) functions in R (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria).

The effect of relevant covariates were tested on intercept and slope (if linear-link function was used) or intercept, maximum upadacitinib effect (E_{max}), and upadacitinib average plasma concentration that achieves half-maximal effect (EC_{50}), if an E_{max}-link function was used. The covariates evaluated included baseline age, sex, baseline body weight, race (Asian vs non-Asian), baseline body surface area affected by atopic dermatitis, baseline disease duration, and baseline EASI for all efficacy end points.

Continuous covariates were centered at their median and included in the model as follows:

$$P_i = P + (\text{COV}_i - \text{COV}_{med}) \cdot eff$$

where P_i is the parameter value for individual i with covariate value COV_i, COV_{med} is the median value of the covariate, P is the typical value of the parameter (when $\text{COV}_i = \text{COV}_{med}$), and eff is the estimated slope of the covariate relationship.

Binary covariates were included in the model as follows:

$$P_i = P + \text{COV}_i \cdot eff$$

where COV_i denotes the binary covariate value of 0 or 1 for individual i and P is the typical value (reference subject with covariate value of zero) of the parameter.

The selection of logistic regression models was based on Akaike information criteria, goodness of fit, and adequate precision of parameter estimates. The models selected based on these criteria for the different end points were utilized as the starting models for further testing of covariates.

For covariate selection, univariate analysis (evaluating 1 covariate at a time) was first performed. If more than 1 covariate was statistically significant, a multivariate assessment was performed. Covariates were tested for statistical significance using the likelihood ratio test by the stepwise forward-inclusion/backward-elimination procedure, with P-value thresholds of $P < .01$ and $P < .001$, respectively.

The developed models were evaluated both during development and after the model development was completed, using observed versus predicted proportions for logistic regression models. Model evaluations determined the predictive performance of the developed models and examined the usefulness of the models for describing observations.

The developed logistic regression models were used to conduct simulations to predict the probabilities of the end points in week 16 for different upadacitinib doses (placebo and 7.5, 15, and 30 mg once daily) per dose group. The simulations incorporated interindividual variability in upadacitinib pharmacokinetics and covariate distributions by resampling exposures and covariates from the subjects in the study. The variability associated with the precision of the parameter estimates in the logistic regression models was also included in the simulations by sampling the parameters from a multivariate random normal distribution with means and covariance terms that were estimated in the logistic regression models. All simulations were conducted with 200 replicates for 270 subjects (representative of a phase 3 sample size) at each dose level.

Results

Subject Demographics and Baseline Characteristics

Available plasma exposure and efficacy data from a total of 167 subjects with moderate to severe atopic dermatitis who were enrolled in the phase 2b study were included in the exposure-response analyses. A summary of demographics and baseline characteristics for subjects included in the exposure-response analyses is shown in Table 1. At baseline, the mean ± SD age of subjects included in the analyses was 39.9 ± 15.8 years, EASI score was 30.9 ± 13.6, and the percentage of body surface area affected by atopic dermatitis was 46.3% ± 22.5%.

Table 1. Summary of Demographic and Other Intrinsic Factors for Subjects Included in the Analyses Data Sets

Characteristic		All Subjects (n = 167)
Age (years)	n	167
	Mean (SD)	39.9 (15.8)
	Median	37.0
	Min-Max	18.0-75.0
Body weight (kg)	n	167
	Mean (SD)	79.2 (19.5)
	Median	76.5
	Min-Max	45.0-150
Sex	Male	104 (62%)
	Female	63 (38%)
Asian race	No	129 (77%)
	Yes	38 (23%)
Percentage of body surface area affected by atopic dermatitis	n	167
	Mean (SD)	46.3 (22.5)
	Median	42.0
	Min-Max	12.0-99.0
EASI Score at baseline	n	167
	Mean (SD)	30.9 (13.6)
	Median	26.4
	Min-Max	16.0-69.6
Disease duration at baseline (years)[a]	n	166[b]
	Mean (SD)	25.9 (16.8)
	Median	23.5
	Min-Max	0.0-72.0

SD, standard deviation.
[a]Disease duration was rounded to whole years. Minimum disease duration was 8 days.
[b]Baseline disease duration was missing for 1 subject, and baseline for NK cells was missing for 6 subjects.

Upadacitinib Pharmacokinetics in Subjects With Atopic Dermatitis

A population pharmacokinetic model was developed for upadacitinib using data from the phase 2b dose-ranging study in atopic dermatitis as well as data across phase 1 and phase 2 studies in healthy subjects and subjects with RA, Crohn's disease, or ulcerative colitis.[22] As previously reported, upadacitinib pharmacokinetics were adequately described by a 2-compartment model with mixed zero- and first-order absorption with lag time for the extended-release formulation. The model was parameterized in terms of clearance and volume (eg, clearance, intercompartmental clearance, volume of distribution of the central compartment, volume of distribution of peripheral compartment), as well as a bioavailability term for the extended-release (used in phase 1, phase 2 ulcerative colitis, and atopic dermatitis studies) relative to the immediate-release (used in phase 1, RA phase 2, and Crohn's disease phase 2 studies) formulations. Covariates included in the final model were creatinine clearance, subject population (healthy subjects vs subjects with atopic dermatitis, ulcerative colitis, or Crohn's disease vs subjects with rheumatoid arthritis) and sex on apparent oral clearance and sex and body weight on apparent volume of distribution of the central compartment. Summary of upadacitinib model-estimated exposures for the ER regimens evaluated in the atopic dermatitis phase 2b study is presented in Table 2.

Table 2. Upadacitinib Model-Predicted (Median [5th to 95th Percentiles]) Plasma Exposures During a Dosing Interval at Steady State for the Extended-Release Regimens Evaluated in the atopic dermatitis Phase 2 Study

	7.5 mg Once Daily	15 mg Once Daily	30 mg Once Daily
C_{avg}, ng/mL	7.8 (4.7-15.7)	13.7 (9.5-25.5)	29.7 (19.2-58.6)
C_{max}, ng/mL	22.6 (15.7-39.1)	41.2 (27.7-65.8)	84.8 (59.7-135)
C_{min}, ng/mL	2.0 (0.56-6.2)	2.7 (1.2-11.3)	6.6 (2.1-22.1)

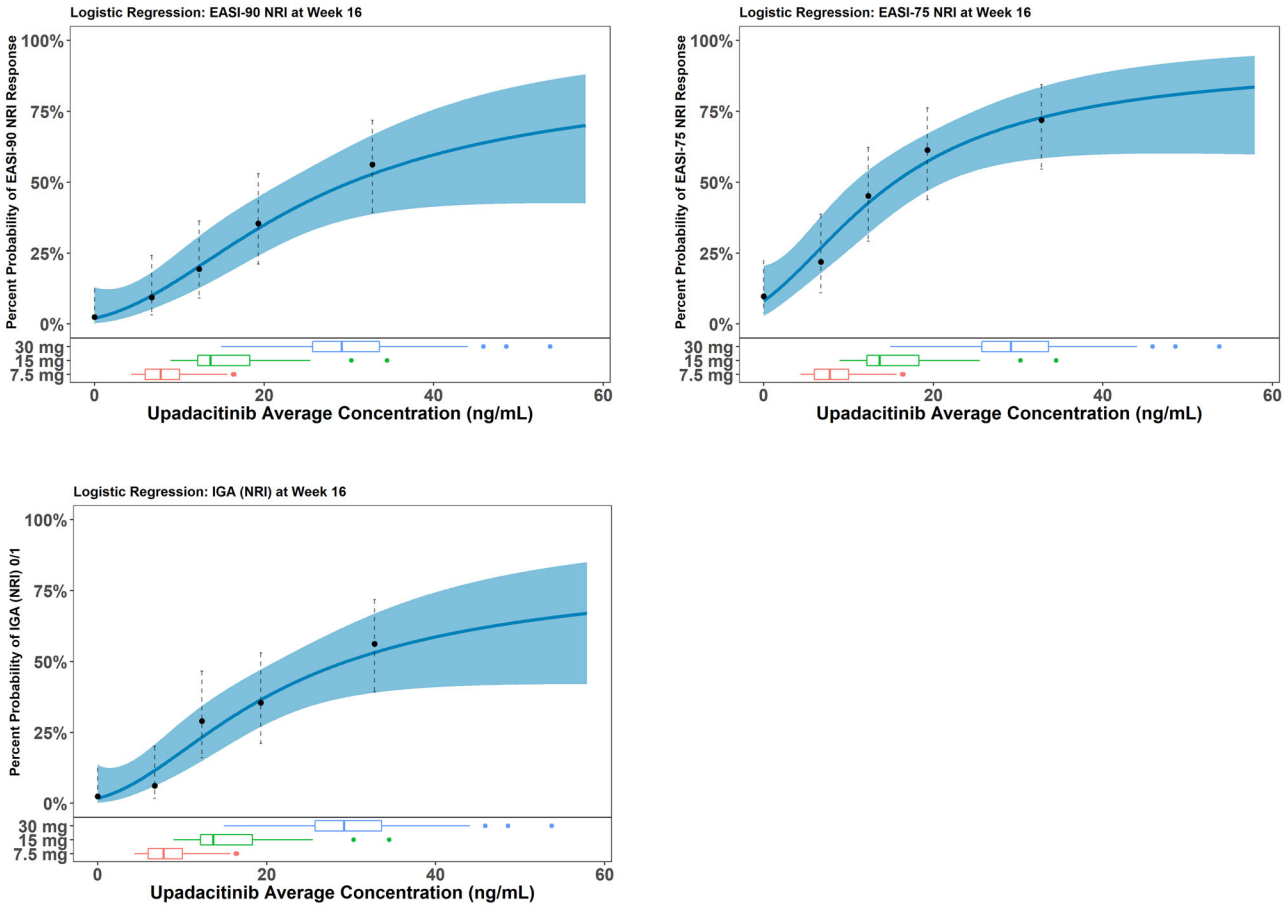

Figure 1. Observed and predicted EASI and IGA responses (NRIs) for atopic dermatitis subjects in week 16 versus upadacitinib average concentration. The solid blue line denotes median predicted probability, whereas the band indicates the 95% confidence interval (CI) of predictions. The observed data are binned into placebo and upadacitinib C_{avg} quartiles (black dots denoting median and error bars the binomial CIs). The red, green, and blue vertical lines at the bottom represent model-predicted median C_{avg} over a dosing interval at steady state for 7.5, 15, and 30 mg doses, whereas the hinges in the box plot represent the 25th and 75th percentiles, and the horizontal lines denote the lowest or highest value within 1.5 times the interquartile range from the lower or upper hinge, respectively. Observations above and below 1.5 times the interquartile range are denoted as individual dots.

Exposure-Response Relationships for Upadacitinib Efficacy in Subjects With Atopic Dermatitis

There were statistically significant relationships between increasing upadacitinib C_{avg} and the percentage of subjects achieving EASI-75, EASI-90, and IGA 0/1 response in week 16. Logistic regression models with E_{max} drug effect function adequately described the exposure-response relationships between upadacitinib C_{avg} and each of the efficacy end points. The predicted percentage of subjects achieving each of the different efficacy end points compared with observed data for different upadacitinib plasma exposure quartiles as well as placebo are shown in Figure 1. The parameter estimates of the final models for the different end points are shown in Table 3. None of the covariates investigated remained statistically significant at the end of the step-wise forward-inclusion/backward-elimination procedure.

Table 3. Parameter Estimates of the Logistic Regression Models for the Relationships Between Upadacitinib Plasma C_{avg} and the Probability of Achieving Different Efficacy End Points (NRI) in Week 16

End Point	Parameter	Estimate (%RSE)	95%CI
EASI-75	Intercept	−2.43 (23%)	−3.5 to −1.35
	E_{max}	5.35 (17%[a])	3.06 to 9.36
	EC_{50} (ng/mL)	18.6 (26%[a])	4.28 to 81.1
EASI-90	Intercept	−3.87 (26%)	−5.85 to −1.9
	E_{max}	6.2 (13%[a])	3.86 to 9.95
	EC_{50} (ng/mL)	18.1 (29%[a])	3.5 to 93.7
IGA 0/1	Intercept	−4.03 (28%)	−6.21 to −1.84
	E_{max}	5.78 (12%[a])	3.78 to 8.83
	EC_{50} (ng/mL)	12.8 (31%[a])	2.77 to 59.3

[a] The parameter was estimated on a transformed exponential scale and the %RSE is given on this scale.

The simulated percentage of subjects achieving each of the different efficacy end points in a phase 3-like sample size based on simulations using the established

Table 4. Simulated Percentage of Subjects Assuming Phase 3 Sample Size Who Achieve Different Efficacy End Points (NRI) in Week 16

Dose Group	Placebo	7.5 mg Once Daily	15 mg Once Daily	30 mg Once Daily
EASI-75	9 (3-17) [10]	32 (22-40) [29]	48 (36-60) [52]	68 (54-81) [69]
EASI-90	2 (0-10) [2]	14 (10-23) [14]	26 (17-36) [26]	48 (31-62) [50]
IGA 0/1	2 (0-11) [2]	17 (10-27) [14]	29 (19-40) [31]	49 (31-63) [50]

Note: Results represent median percentage of subjects (5th and 95th percentiles) from 200 replicates with 270 subjects/dose group in each replicate [observed percentage of subjects].

exposure-response models for different upadacitinib doses is shown in Table 4.

Discussion

These analyses represent, to our knowledge, the first characterization of exposure-response relationships for JAK1 inhibitor efficacy in subjects with moderate to severe atopic dermatitis. The percentage of subjects achieving EASI-75, EASI-90, and IGA 0/1 after 16 weeks of treatment with upadacitinib monotherapy increased with increasing upadacitinib plasma exposure. The effect of upadacitinib on increasing the percentage of subjects achieving each of the efficacy end points was adequately described by logistic regression models with E_{max} drug effect function. Using a phase 3-like sample size, upadacitinib plasma exposures associated with a 15 mg once daily dose using the extended-release formulation are predicted to achieve EASI-75, EASI-90, and IGA 0/1 responses in 48%, 26%, and 29%, respectively, of subjects with moderate to severe atopic dermatitis compared with 9%, 2%, and 2%, respectively, for placebo. The upadacitinib 30 mg once daily dose using the extended-release formulation is predicted to result in approximately 20% greater percentage of subjects achieving EASI-75, EASI-90, and IGA 0/1 responses compared with the 15 mg once daily dose. These data indicate the potential for upadacitinib to provide meaningful improvement in efficacy relative to currently approved therapies.[34] This estimated efficacy and the clear illustration of the relationship between upadacitinib exposure and response supported the advancement of upadacitinib to phase 3 clinical trials in atopic dermatitis. Results from the presented exposure-response analyses supported the selection of upadacitinib 15 and 30 mg once daily doses to evaluate in 4 phase 3 trials in subjects with moderate to severe atopic dermatitis.

Differences have been observed in the maximally efficacious upadacitinib plasma concentrations across different autoimmune diseases. In subjects with moderate to severe RA, upadacitinib plasma exposures associated with 15 mg once daily achieved the plateau for efficacy[35,36]; upadacitinib exposures associated with 30 mg once daily were estimated to result in a <5% increase in the percentage of subjects achieving the efficacy end-points ACR 20/50/70 responses or DAS-28 low disease activity and clinical remission, compared with 15 mg once daily exposures.[36] Therefore, the 15 mg once daily dose of upadacitinib was selected as the clinical dose, and this dose received regulatory approval for treatment of RA. Results from the present exposure-response analyses for upadacitinib efficacy in atopic dermatitis indicate that 30 mg once daily has the potential to provide meaningfully differentiated efficacy from 15 mg once daily, unlike in RA. Consistent with these findings in atopic dermatitis, upadacitinib plasma exposures associated with doses higher than 15 mg once daily were predicted to provide greater efficacy for induction of remission in Crohn's disease and ulcerative colitis based on exposure-response analyses of phase 2 trials.[37,38] These differences in the maximally efficacious exposures between autoimmune diseases can be attributed to differences in the cytokines involved in the pathogenesis of the diseases. Levels of IL-6, IL-1β, tumor necrosis factor-α, and interferon-γ, for example, have been reported to be elevated in RA,[39–42] whereas IL-4, IL-5, IL-13, IL-22, IL-31, and IL-33 are more prominently impacted in atopic dermatitis[43,44]; these cytokine differences along with the different accessibility of inflammation sites to drugs in different diseases may contribute to different exposure-response relationships between inflammatory diseases.

The effects of demographics and baseline disease characteristics on upadacitinib efficacy in atopic dermatitis have been evaluated within the exposure-response analyses. None of the evaluated covariates (eg, age, body weight, baseline body surface area affected by atopic dermatitis, and baseline EASI) had a statistically significant effect on upadacitinib exposure-response model parameters. However, it is expected that the ongoing 4 phase 3 studies in atopic dermatitis with much larger sample sizes would provide greater power to evaluate covariate effects compared with this phase 2b study.

Safety results from the phase 2b study in atopic dermatitis have been previously reported.[20] No dose-limiting safety events were observed in the study in atopic dermatitis, and no dose relationship was observed for serious infections or for overall incidence of adverse events. Advancing the 15 and 30 mg doses to phase 3 will enable robust characterization of the benefit/risk profile of each dose level. Exposure-response assessment of upadacitinib safety in subjects with atopic dermatitis is warranted using the larger sample size from the ongoing phase 3 studies.

In conclusion, upadacitinib demonstrated clear and significant exposure-response relationships for efficacy end points in subjects with atopic dermatitis. Based on exposure-response analyses of the phase 2b study, upadacitinib plasma exposures associated with 30 mg once daily are predicted to be associated with clinically meaningful greater efficacy compared with 15 mg once daily, unlike previous observations in RA. This work supported the dose selection for phase 3 studies for upadacitinib in subjects with moderate to severe atopic dermatitis.

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Conflicts of Interest

M.F.M., S.G., and H.D.T. are employees of AbbVie and may hold stock. A.A.O. was employed at AbbVie when this work was conducted and may hold AbbVie stock.

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AbbVie provided financial support for the study and participated in the design, study conduct, analysis and interpretation of data, as well as the writing, review, and approval of the article.

Author Contributions

Mohamed-Eslam F. Mohamed, Sathej Gopalakrishnan, Henrique D. Teixeira, and Ahmed A. Othman wrote the manuscript. Mohamed-Eslam F. Mohamed, Sathej Gopalakrishnan, Henrique D. Teixeira, and Ahmed A. Othman designed the research. Mohamed-Eslam F. Mohamed, Sathej Gopalakrishnan, Henrique D. Teixeira, and Ahmed A. Othman performed the research. Mohamed-Eslam F. Mohamed, Sathej Gopalakrishnan, Henrique D. Teixeira, and Ahmed A. Othman analyzed the data.

Data Availability Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and statistical analysis plan (SAP) and execution of a data-sharing agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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