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ARTICLE

Upadacitinib pharmacokinetics and exposure-response analyses of efficacy and safety in psoriatic arthritis patients – Analyses of phase III clinical trials

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Abstract

Upadacitinib is an oral Janus kinase inhibitor approved for the treatment of rheumatoid arthritis (RA) and recently approved by the European Medicines Agency for the treatment of psoriatic arthritis (PsA). The efficacy and safety profile of upadacitinib in PsA have been established in the SELECT-PsA program in two global phase III studies, which evaluated upadacitinib 15 and 30 mg q.d. The analyses described here characterized upadacitinib pharmacokinetics and exposure-response relationships for efficacy and safety endpoints using data from the SELECT-PsA studies. Upadacitinib pharmacokinetics in patients with PsA were characterized through a Bayesian population analysis approach and were comparable to pharmacokinetics in patients with RA. Exposure-response relationships for key efficacy and safety endpoints were characterized using data from 1916 patients with PsA. The percentage of patients achieving efficacy endpoints at week 12 (American College of Rheumatology [ACR]50 and ACR70), 16 and 24 (sIGA0/1) increased with increasing upadacitinib average plasma concentration over a dosing interval, whereas no clear exposure-response trend was observed for ACR20 at week 12 or ACR20/50/70 at week 24 within the range of plasma exposures evaluated in the phase III PsA studies. No clear trends for exposure-response relationships were identified for experiencing pneumonia, herpes zoster infection, hemoglobin less than 8 g/dl, lymphopenia (grade ≥ 3), or neutropenia (grade ≥ 3) after 24 weeks of treatment. Shallow relationships with plasma exposures were observed for serious infections and hemoglobin decrease greater than 2 g/dl from baseline at week 24. Based on exposure-response analyses, the upadacitinib 15 mg q.d. regimen is predicted to achieve robust efficacy in

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patients with PsA and to be associated with limited incidences of reductions in hemoglobin or occurrence of serious infections.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Upadacitinib is a selective JAK1 inhibitor approved for the treatment of rheumatoid arthritis and approved in Europe for the treatment of psoriatic arthritis (PsA). The pharmacokinetics, efficacy, and safety of upadacitinib in patients with PsA were evaluated in two global phase III trials as monotherapy or in combination with non-biologic disease-modifying antirheumatic drugs.

WHAT QUESTION DID THIS STUDY ADDRESS?

These analyses characterized the relationships between upadacitinib plasma exposures and key efficacy and safety endpoints in patients with moderate to severe PsA.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The presented exposure-response analyses demonstrated that the plasma exposures associated with upadacitinib 15 mg q.d. regimen achieves robust efficacy in patients with PsA with limited decreases in hemoglobin or occurrence of serious infections, even under scenarios of increased exposures due to intrinsic or extrinsic factors.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Using model-based approaches, characterization of the relationships between upadacitinib plasma exposures and efficacy/safety supported optimal dose selection for upadacitinib use in patients with PsA, benefit-risk evaluation, and regulatory filings for upadacitinib.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease classified as a subtype of spondyloarthritis (SpA) and characterized by the association of arthritis and psoriasis. PsA affects men and women equally and, although it can develop at any age, onset is most common between the ages of 30 and 50 years.[1] Patients with PsA experience chronic inflammation leading to joint damage, disability, reduced quality of life, and shortened life expectancy.[2,3] Current treatment options for psoriatic arthritis include conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, biologic DMARDs (bDMARDs), and other small molecule drugs, like tofacitinib and apremilast.[4,5]

Upadacitinib is a selective and reversible inhibitor of Janus kinase 1 (JAK)[6–8] that is approved for the treatment of rheumatoid arthritis (RA) in the United States, Europe, Japan, and many other countries,[9] recently approved for the treatment of PsA by the European Medicines Agency (currently under review by other agencies), and is being developed for the treatment of several other immune-mediated inflammatory diseases.[1,10–16] JAK1 inhibition affects the signaling of a number of cytokines that are implicated in the pathogenesis of psoriatic arthritis, such as common gamma chain-containing cytokines, interferon-γ, and interleukin-12.[17]

Upadacitinib pharmacokinetics were evaluated in phase I studies in healthy subjects and in phase II and III studies across several patient populations and results have been previously described.[18–24] Upadacitinib pharmacokinetics were similar across different patient populations, such as RA, ulcerative colitis (UC), Crohn's disease (CD), and atopic dermatitis (AD).[1,25–27] Upadacitinib exposures associated with optimal clinical benefit differed from indication to indication due to the individual pathophysiological nature of each condition. In patients with RA, optimal benefit-risk exposures were achieved by the 15 mg once daily (q.d.) dose using the extended-release formulation. In subjects with dermatological inflammatory disease, such as AD, 30 mg q.d. is predicted to achieve 20% greater efficacy across different endpoints compared to 15 mg q.d..[26] Last, in patients with inflammatory bowel disease, doses exceeding 30 mg q.d. of upadacitinib are expected to provide incremental efficacy benefit during the induction period compared to 30 mg q.d. or lower doses.[25]

The population pharmacokinetic and exposure-response analyses reported in the current work were conducted using data from two global phase III studies in patients with active PsA.[10,11] These analyses were the first to characterize the pharmacokinetics of upadacitinib and the relationships between the plasma exposures of upadacitinib and its efficacy/safety in patients with moderate to severe PsA. Upadacitinib doses of 15 mg and 30 mg q.d. using the extended-release formulation were evaluated in the studies.

METHODS

Participants and design of the studies

The phase II studies (SELECT-PsA 1 and SELECT-PsA 2)[10,11] were conducted in accordance with Good Clinical Practice Guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols were approved by the institutional review board or ethics committee at each site and each patient provided written informed consent before any study-related procedures were performed.

The SELECT-PsA program included two, randomized, double-blind, phase III, multicenter studies, which enrolled patients with moderately to severely active PsA who had an inadequate response to non-bDMARDs (SELECT-PsA 1) and bDMARDs (SELECT-PsA 2). Both trials evaluated placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d.; SELECT-PsA 1 also included the active comparator adalimumab.[10,11] Patients were permitted to be on monotherapy or on up to two non-bDMARDs concomitantly. Integrated data from patients randomized to placebo, 15 mg q.d., and 30 mg q.d. from the 24-week placebo-controlled period were included in the population pharmacokinetics and exposure-response analyses.

Pharmacokinetic, efficacy, and safety assessments

Blood samples were collected at weeks 2, 4, 8, 12, 14, 16, 20, and 24 for determination of upadacitinib plasma concentrations. Validated liquid chromatography with mass spectrometric detection methods were used to determine plasma concentrations of upadacitinib at AbbVie (North Chicago, IL, USA) and WuXi AppTec (WaiGaoQiao Free Trade Zone, Shanghai, China) as previously described.[28] The lower limit of quantitation (LLOQ) of the assay of plasma samples for the determination of the concentrations of upadacitinib was 0.05 ng/ml.

The exposure-response analyses of efficacy evaluated the following endpoints: proportions of patients with PsA achieving American College of Rheumatology (ACR)20, ACR50, and ACR70 responses at weeks 12 and 24, Psoriasis Area Severity Index (PASI)75 (for patients with ≥3% body surface area [BSA] psoriasis at baseline) at weeks 16 and 24, and static Investigator Global Assessment of Psoriasis (sIGA) (0/1) and at least a 2-point improvement from baseline (for patients with baseline sIGA ≥2) at weeks 16 and 24.

The exposure-response analyses of safety included the following endpoints: proportion of patients who experienced serious infections, pneumonia, and herpes zoster infection during 24 weeks of treatment, neutropenia (grade 3 or higher: $<1 \times 10^9$/L), lymphopenia (grade 3 or higher: $<1 \times 10^9$/L, grade 4: $<0.5 \times 10^9$/L), decrease in hemoglobin by >2 g/dl decrease from baseline, hemoglobin less than 8 g/dl, and hemoglobin decrease from baseline by greater than 2 g/dl and below the lower limit for normal (women: 11.5 g/dl and men: 12.5 g/dl). All endpoints for changes in laboratory parameters (neutropenia, lymphopenia, and decreases in hemoglobin) were analyzed at week 24 using the last observation carried forward (LOCF) imputation.

Population pharmacokinetic analyses

Data from 1694 patients with PsA were included in the population pharmacokinetic analysis. Nonlinear mixed effects modeling in NONMEM 7.4.4 were used to build the population pharmacokinetic models. A Bayesian pharmacokinetic modeling approach was implemented using prior information from an upadacitinib population pharmacokinetics model, which was previously developed using data from 4170 patients (96% patients with RA and 4% healthy subjects).[29,30] The structural, statistical (inter- and intrasubject variability), and covariate components of the model were maintained. Population parameter estimates, the variance-covariance matrix of the fixed effects, and estimates for the random effects (inter- and intrasubject variability) from the RA[29] model were used as priors. All model parameters were re-estimated using the data in patients with PsA from the SELECT-PsA studies. For estimation, the PRIOR subroutine with TNPRI option and FOCE with interaction was used. Further details are presented in the Supplementary Methods.

Covariates from the prior population pharmacokinetic model for upadacitinib in healthy volunteers and patients with RA (subject population [patients vs. healthy], creatinine clearance [on clearance], and baseline bodyweight [on both clearance and volume of distribution]) were retained in the model and their effect parameters were

re-estimated using PsA data. Graphical exploration for the relationships between upadacitinib pharmacokinetic parameters and additional covariates relevant to patients with PsA were carried out. The effects of non-bDMARDs used by at least 1% of all patients on model-estimated upadacitinib exposures were evaluated. Model accuracy was evaluated based on goodness-of-fit assessments and visual predictive checks. Further details are presented in the Supplementary Methods.

Analyses of the relationships between upadacitinib plasma exposures and efficacy/safety endpoints in PsA

Data from 1916 patients with PsA were included in the exposure-response efficacy and safety analyses. Upadacitinib plasma exposures (average plasma concentration [C_{avg}]) in patients with PsA were derived using the individual predicted upadacitinib exposures based on the population pharmacokinetics model. The relationships between upadacitinib exposures and efficacy/safety endpoints were first explored through quartile plots using C_{avg} as the exposure metric. For each of the evaluated efficacy and safety variables, logistic regression models with treatment effect and exposure effect function were then evaluated to determine if there was a statistically significant effect of upadacitinib exposures on the probability of occurrence of each efficacy and safety variable. Only efficacy and safety endpoints exhibiting a statistically significant exposure effect (p value < 0.01 for the exposure effect parameter) were evaluated further using exposure-response models. Different drug effect functions such as linear, maximum response (E_{max}), and sigmoid E_{max} were evaluated to determine the best model describing the effect of upadacitinib plasma exposures on the probability of each efficacy and safety outcome.

Exposure-response model selection was based on the Akaike Information Criteria (AIC), graphical assessment of the adequacy of the models to describe the observed data, as well as model stability and precision of parameter estimates. Efficacy and safety endpoints exhibiting a statistically significant exposure effect were evaluated further using separate exposure-response models describing the logit of the probabilities to reach the endpoint.

Each model includes an intercept representing the logit-transformed probability at zero concentration and the corresponding link function (i.e., linear, E_{max}, or Hill). For details, please see Supplementary Methods. The covariates investigated in the exposure-efficacy analyses on both placebo (intercept) and drug effect parameters (slope or E_{max} and one half maximal effective concentration [EC_{50}]) included: demographics (age, weight, body mass index [BMI], sex, race, and geographic region), population (bDMARD-inadequate response [IR] or non-bDMARD-IR), baseline high-sensitivity C-reactive protein (hsCRP) levels, number of prior failed biologic and non-bDMARDs, concomitant use of non-bDMARDs, and baseline disease characteristics (duration of PsA diagnosis, baseline PASI score, and baseline sIGA score). The covariates investigated in the exposure-safety analyses on both placebo (intercept) and drug effect parameters included: demographics (age, weight, BMI, sex, and race), patient population (bDMARD-IR or non-bDMARD-IR), baseline hsCRP levels, concomitant use of non-bDMARDs, baseline disease duration, and baseline hemoglobin (for analyses of changes in hemoglobin), baseline lymphocytes (for analysis of lymphopenia), and baseline neutrophils (for analysis of neutropenia).

Covariate selection was initially performed using univariate analysis. As previously described in Nader et al., a multivariate assessment was performed if more than one covariate was statistically significant. A likelihood ratio test within the stepwise forward-inclusion-backward-elimination procedure was used to test the covariates for statistical significance using p value thresholds of $p < 0.01$ and $p < 0.001$.[30]

Simulations were conducted to predict the probabilities of the efficacy and safety endpoints following treatment with placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d. regimens using the final logistic regression models. For the safety endpoints, scenarios of 25%, 50%, and 75% increase from target 15 mg q.d. exposures were also evaluated.

Further details on the analyses, including the structure, selection, and evaluation of the models, as well as covariate testing can be found in the Supplementary Methods.

RESULTS

A summary of the demographics and baseline characteristics included in the population pharmacokinetics and exposure-response analyses are provided in Tables S1 and S2. Mean baseline hsCRP was 11.9 mg/ml, mean baseline PASI was 7.6, mean age was 52 years, and mean body weight was 87 kg. Approximately 46% of patients included in the analyses were men. Overall, the characteristics of the baseline demographic were consistent with a conventional PsA population.[1,31]

Population pharmacokinetic analysis

Upadacitinib plasma concentration-time profiles were adequately described by a two-compartment model with

mixed zero- and first-order absorption with lag time for the extended-release formulation and linear elimination. Estimates of upadacitinib population pharmacokinetic parameters from the model updated with PsA data are consistent with prior estimates based on analyses of data from healthy subjects and patients with RA. The model parameter estimates are presented in the (Table S3). The model goodness-of-fit plots and visual predictive checks (VPCs), presented in Figure 1, demonstrated that the model adequately characterized upadacitinib pharmacokinetics in patients with RA. Median (5th and the 95th percentiles) population pharmacokinetic model-predicted C_{avg} values in patients with PsA were 15.2 (9.59, 28.7) ng/ml for the 15 mg q.d. and 28.9 (19.1, 54.9) ng/ml for the 30 mg q.d. dosing regimens (Table 1) and were similar to upadacitinib plasma exposures compared to patients with RA[30] (Table 1). The exponents for the effect of body weight on apparent oral clearance (CL/F) and central volume of distribution (Vc/F) were estimated to be 0.12 and 0.86, respectively. Upadacitinib plasma exposures were similar between patients who were co-administered DMARDs (apremilast, hydroxychloroquine, sulfasalazine, and leflunomide), and patients who did not receive these DMARDs. The estimated exponents for the effect of body weight on upadacitinib Vc/F and clearance as well as the effect of creatinine clearance on upadacitinib oral

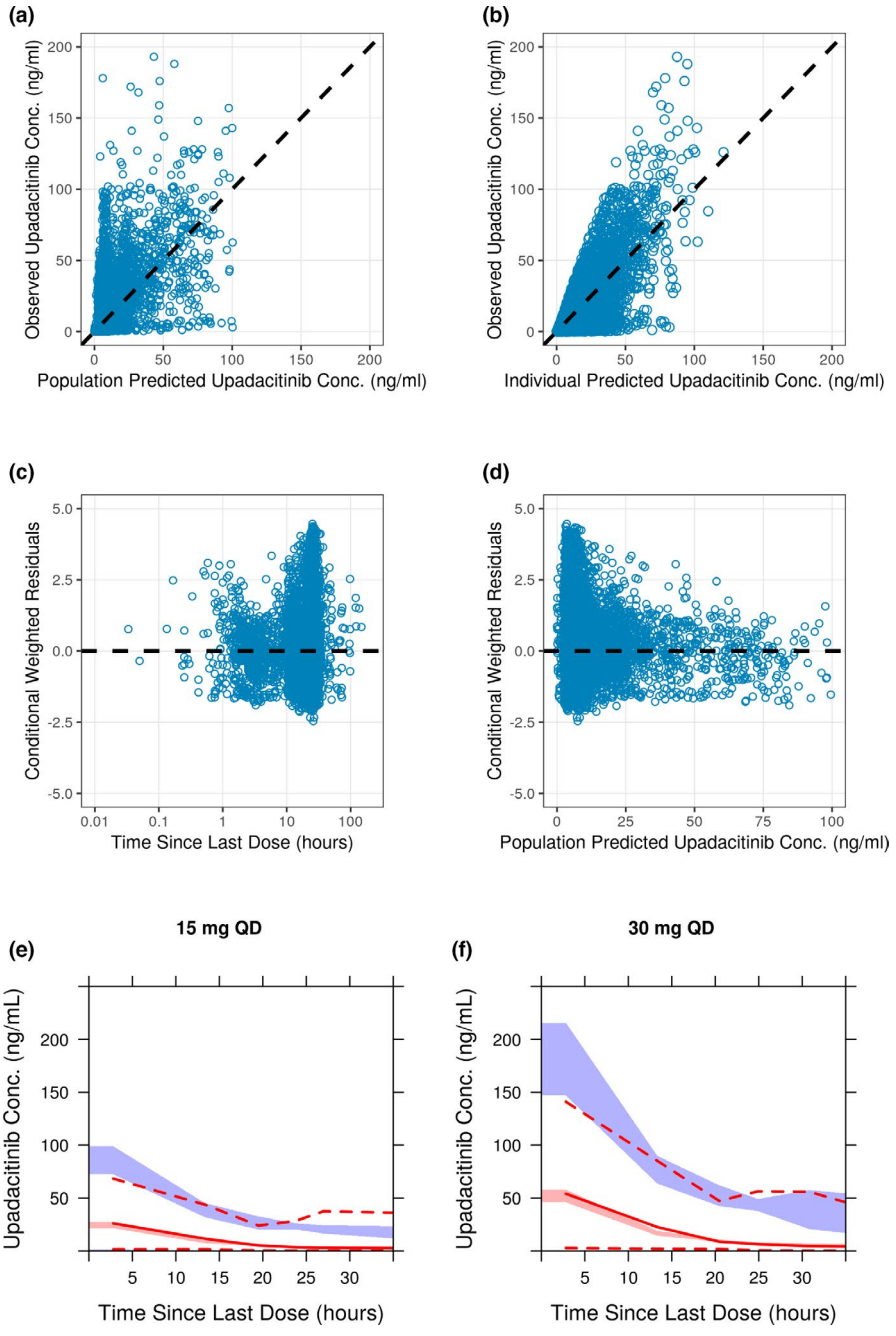

FIGURE 1 Goodness-of-fit plots of upadacitinib pharmacokinetic model and visual predictive checks (VPCs) of upadacitinib concentration versus time since last dose for patients with PsA stratified by dose (data from phase III PsA studies). (a) Observed versus population predicted concentrations. (b) Observed versus individual predicted concentrations. (c) Conditional weighted residuals versus time since last dose. (d) Conditional weighted residuals versus population predicted concentrations. (e) VPCs 15 mg upadacitinib. (f) VPCs 15 mg upadacitinib. VPCs: The shaded blue areas represent the 95% prediction interval of the 2.5th and 97.5th percentiles of simulated concentrations, the red shaded areas represent the 95% prediction interval of the 50th percentile of simulated concentrations, the solid red line represents median of the observed concentrations and dashed red lines represent the 2.5th and 97.5th percentile of the observed concentrations. PsA, psoriatic arthritis

Model	Dose group	C_{avg} (ng/ml) median (5th–95th percentile)	C_{max} (ng/ml) median (5th–95th percentile)	C_{min} (ng/ml) median (5th–95th percentile)
PsA	15 mg q.d.	15.2 (9.59–28.7)	37.6 (27.1–49.3)	4.24 (1.50–19.3)
	30 mg q.d.	28.9 (19.1–54.9)	74.0 (55.6–97.8)	8.06 (2.97–34.5)
RA	15 mg q.d.	14.9 (9.75–29.2)	41.1 (29.8–53.0)	3.73 (1.51–18.1)
	30 mg q.d.	29.5 (19.4–55.5)	81.9 (61.4–109)	7.52 (2.92–31.6)

TABLE 1 Summary of model-estimated upadacitinib plasma exposures (C_{avg}, C_{max}, and C_{min}) for 15 mg and 30 mg q.d. dosing regimens at steady-state in patients with PsA and comparison to patients with RA

Abbreviations: C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

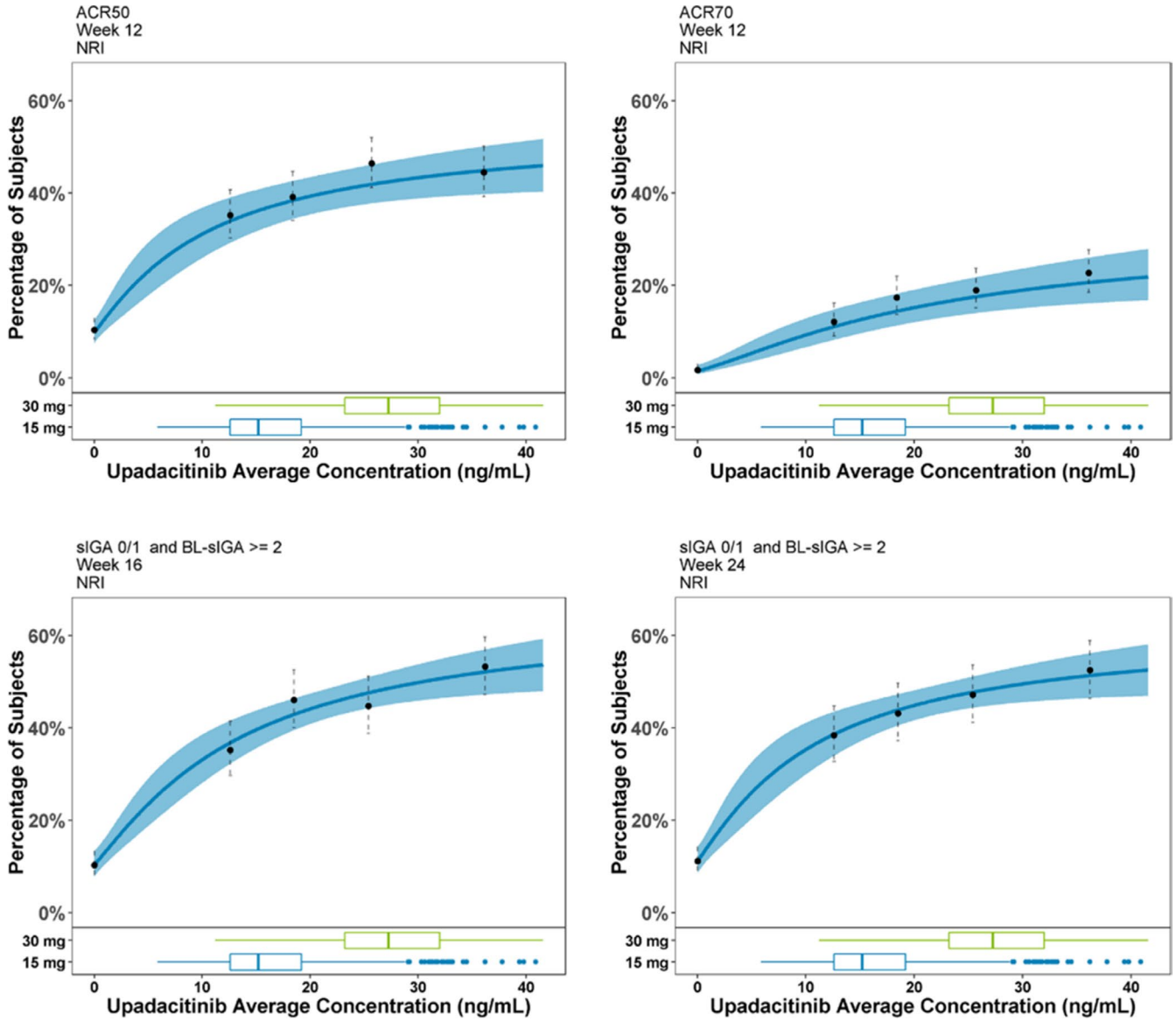

FIGURE 2 Observed and model-predicted ACR50 and ACR70 responses (NRI) at week 12 and sIGA 0/1 responses at week 16 and week 24 versus upadacitinib C_{avg} (final models). The blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial confidence intervals of binned observed rates. ACR, American College of Rheumatology; C_{avg}, average plasma concentration

clearance was consistent between this analysis (updated with data from PsA studies) and prior analysis in patients with RA and healthy subjects.[30]

Evaluation of upadacitinib exposure-response relationships for efficacy in PsA

The relationships between upadacitinib exposures and efficacy and safety endpoints were first explored through quartile plots using upadacitinib C_{avg} as the exposure metric. Additionally, stepwise logistic regression analyses were constructed to test for the relationship between each endpoint and upadacitinib plasma exposures (C_{avg}) in PsA patients.

For ACR20, a statistically significant treatment effect but no statistically significant exposure-response relationship was present at either week 12 or week 24, suggesting that upadacitinib 15 mg q.d. exposures achieve the plateau for ACR20 in PsA. For ACR50 and ACR70, there was a statistically significant treatment effect for each endpoint at both week 12 and week 24, with significant exposure-response relationships only present at week 12. An E_{max} with intercept model best described upadacitinib exposure-response relationships for week 12 ACR50 and ACR70 endpoints based on AIC and assessment of the observed and predicted responses (Figure 2). Significant covariates in the final ACR50 exposure-response model included effects of age, BMI, and bDMARD-IR versus DMARD-IR population on intercept and hsCRP on E_{max}. The final ACR70 model included age, sex, and population on intercept, and hsCRP as covariates on E_{max}. Final model parameter estimates are shown in Table S4.

Model-estimated ACR50 and ACR70 responses for upadacitinib 15 mg q.d., 30 mg q.d. regimens, and placebo at week 12 stratified by the significant covariates in the final ACR model are shown in Figure 3.

For PASI75 responses at week 16 and week 24, there was a statistically significant treatment effect, but no significant exposure-response relationship, suggesting upadacitinib 15 mg q.d. exposures maximize efficacy for PASI75 in PsA. For sIGA 0/1 at week 16 and week 24, there was a statistically significant treatment effect and exposure-response relationship at week 16 and week 24. The relationship between upadacitinib C_{avg} and the percentage of patients achieving sIGA 0/1 at week 16 and week 24 was best described by E_{max} with intercept model (Figure 2). None of the evaluated covariates had statistically significant effects on intercept, EC_{50} or E_{max} for the sIGA.

The model-estimated clinical efficacy responses of ACR50, ACR70, and sIGA0/1 following placebo and upadacitinib 15 mg and 30 mg q.d. dosing regimens are presented in Table 2.

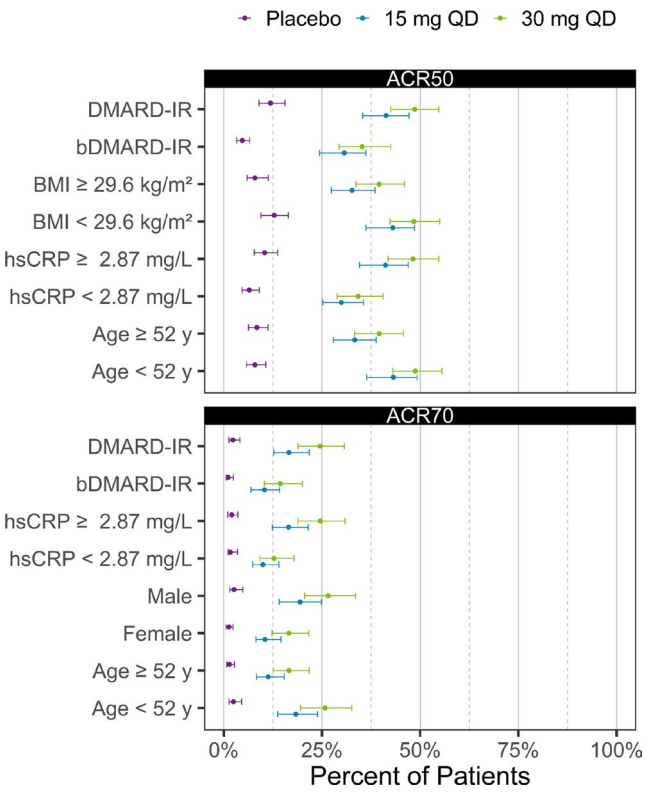

FIGURE 3 Model-predicted ACR50 and ACR70 response for 15 mg q.d., 30 mg q.d. regimens and placebo at week 12 stratified by covariate subgroups. ACR, American College of Rheumatology; bDMARD, disease-modifying antirheumatic drugs; BMI, body mass index; DMARD, modifying antirheumatic drugs

Exposure-response relationships for upadacitinib safety and effects on laboratory parameters in PsA

Exploratory exposure-response quartile plots and logistic regression were performed for the safety endpoints. For the following endpoints, a logistic regression model could not be fitted due to lack of observations: hemoglobin less than 8 g/dl at week 24, lymphopenia grade 4, and neutropenia grade 3 or higher. There were no statistically significant exposure-response relationships with herpes zoster infection, pneumonia, hemoglobin less than 8 g/dl, lymphopenia grade 3 or higher, and neutropenia grade 3 or higher at week 24. There were statistically significant exposure-response relationships for the occurrence of serious infections, decrease in hemoglobin from baseline by greater than 2 g/dl, and decrease in hemoglobin from baseline by greater than 2 g/dl with hemoglobin less than the lower limit for normal at week 24. The results of the dose-response analyses for the safety of upadacitinib in the SELECT-PsA 1 and SELECT-PsA 2 trials has been previously reported.[10,11] The percentage of patients experiencing serious infections through week 24 were 0.9%, 1.2%, and 2.6% in SELECT-PsA 1, and 0.5%, 0.5% and 2.8% in

TABLE 2 Model-simulated clinical efficacy responses (% responders) at weeks 12, 16, and 24 following placebo and upadacitinib 15 mg and 30 mg q.d. regimens

Clinical efficacy response variable[a]	Placebo	Upadacitinib 15 mg q.d.	Upadacitinib 30 mg q.d.
ACR50 at week 12	11% (7%–15%)	37% (32%–43%)	45% (39%–50%)
ACR70 at week 12	2% (1%–3%)	14% (10%–19%)	21% (16%–26%)
sIGA 0/1 at week 16	10% (7%–14%)	40% (34%–45%)	49% (43%–55%)
sIGA 0/1 at week 24	11% (8%–16%)	40% (36%–47%)	49% (42%–55%)

Abbreviations: ACR50, American College of Rheumatology 50% improvement criteria; ACR70, American College of Rheumatology 70% improvement criteria; sIGA, static Investigator Global Assessment of Psoriasis.

[a]Median and 90% prediction interval.

SELECT-PsA 2 for placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d., respectively.

The relationship between upadacitinib C_{avg} and probability of experiencing serious infections was best described by a linear drug effect model with intercept (Figure 4). Baseline patient age was identified as a significant covariate on intercept. The incidence of experiencing greater than 2 g/dl decrease in hemoglobin from baseline at week 24 was best described by an E_{max} with intercept model (Figure 4). Statistically significant covariates included in the logistic regression model for greater than 2 g/dl decrease in hemoglobin were baseline hemoglobin on intercept and patient's age on EC_{50}. The relationship between upadacitinib C_{avg} and the probability of experiencing a decrease in hemoglobin from baseline by greater than 2 g/dl with hemoglobin less than the lower limit for normal was best described by a logistic regression model with an E_{max} drug effect model with intercept including patient's age as a covariate on EC_{50} (Figure 4).

Final model parameter estimates and safety responses for upadacitinib 15 mg q.d., upadacitinib 30 mg q.d., and placebo at week 24 (LOCF) stratified by statistically significant covariates are presented in Table S5.

The model-simulated clinical safety responses following placebo and upadacitinib 15 mg and 30 mg q.d. dosing regimens are provided in Table 3. The simulations of increased upadacitinib C_{avg} on safety responses relative upadacitinib 15 mg q.d. at week 24 are shown in Table S6.

DISCUSSION

These analyses represent the first assessment of upadacitinib pharmacokinetics and exposure-response relationships in patients with moderate to severe PsA. Upadacitinib pharmacokinetics were extensively characterized in prior analyses using data from healthy subjects and patients with moderate to severe RA.[20] Therefore, for the analyses of data from the phase III PsA studies, a Bayesian modeling approach was implemented for pharmacokinetic analyses leveraging the prior pharmacokinetic model developed using data from healthy subjects and patients with RA.[20] The present analyses demonstrated similarity in upadacitinib pharmacokinetics as well as exposure-response relationships for both efficacy and safety between the PsA and RA patient populations, with exposures associated with the 15 mg q.d. regimen exhibiting an optimal benefit-risk profile.[19,30] The similarity of observed upadacitinib exposure-response relationships between PsA and RA might be attributed to similarity of inflammatory burden and inflammatory joint manifestations between these two diseases.[32]

The effects of covariates on upadacitinib pharmacokinetic parameters were consistent in this analysis (updated with PsA patient data) with prior analyses in healthy subjects and patients with RA.[20] These results support that body weight and mild/moderate renal impairment are statistically significant, but nonclinically relevant, covariates on upadacitinib oral clearance. Additionally, model-estimated upadacitinib exposures were comparable in patients with PsA who received different non-bDMARDs concomitantly with upadacitinib, supporting that non-bDMARDs commonly used in PsA (e.g., methotrexate, sulfasalazine, and leflunomide) have no effect on upadacitinib pharmacokinetics.

Statistically significant exposure-dependent increases in upadacitinib efficacy were observed for ACR50 and ACR70 at week 12 and for sIGA 0/1 at week 16 and week 24, but not for ACR20 at week 24 or for any other evaluated endpoints at week 12 or week 24 within the range of exposures evaluated in the phase III trials for 15 mg and 30 mg q.d. doses. This suggests that 15 mg exposures are at the plateau of response for ACR20 and PASI75 at week 12 and for all evaluated efficacy endpoints at week 24 except of sIGA 0/1. Based on exposure-response models, a dose of 30 mg q.d. is predicted to provide limited additional efficacy benefit over 15 mg q.d. for some, but not all, of the evaluated endpoints (8% and 7% higher percentage of patients achieving ACR50 and ACR70, respectively, at week 12, but not at week 24, and 9% higher percentage of patients achieving sIGA0/1 at week 16 or week 24), with

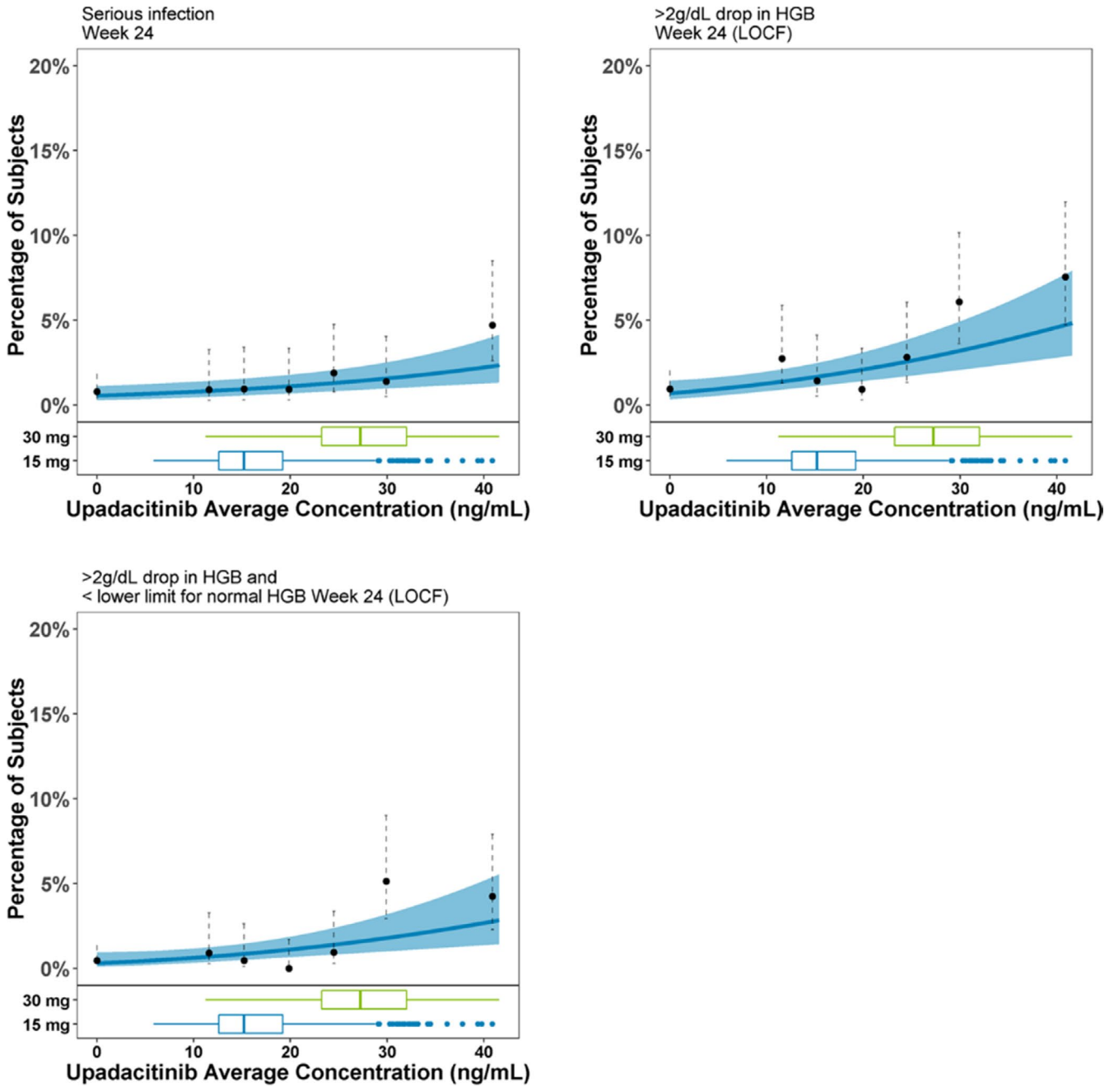

FIGURE 4 Observed and model-predicted percentage of patients with PsA with serious infections, greater than 2 g/dl decrease in hemoglobin, or greater than 2 g/dl with hemoglobin less than the lower limit for normal up to week 24 (final model). The blue solid line represents median predicted response and the blue shaded area represent 95% confidence intervals of the predicted response. The dots and error bars represent median and 95% binomial confidence intervals of binned observed rates. LOCF, last observation carried forward; PsA, psoriatic arthritis

overlapping 90% prediction intervals for all endpoints (Table 2). Therefore, the additional potential efficacy benefit of increasing upadacitinib plasma exposures beyond 15 mg q.d. exposures was not consistent across the different efficacy endpoints and was mostly observed in early assessments (e.g., week 12) than in later timepoints. In the exposure-response analyses, C_{avg} was used as the exposure metric in the models rather than trough concentration given the relatively short half-life of upadacitinib (~8 to 14 h), thus yielding minimum concentration (C_{min}) more variable and possibly less robust measure of clinically relevant exposure than C_{avg} or area under the curve ($AUC_{0\text{-}tau}$). Exposure-response relationships with C_{avg} are also reflective of the relationship with $AUC_{0\text{-}tau}$ given that both parameters are directly derived from dose and clearance.

Safety variable[a]	Placebo	Upadacitinib 15 mg q.d.	Upadacitinib 30 mg q.d.
Percentage of patients with serious infections	1% (0%–2%)	2% (0%–3%)	2% (1%–4%)
Percentage of patients with Hgb >2 g/dl decrease from baseline	1% (0%–2%)	3% (1%–4%)	4% (2%–7%)
Percentage of patients with Hgb >2 g/dl decrease from baseline and less than normal Hgb levels	0% (0%–2%)	1% (0%–3%)	3% (1%–6%)

TABLE 3 Model-simulated percentage of patients with serious infections or changes in laboratory parameters at week 24 in scenarios of increased upadacitinib C_{avg} relative to placebo and upadacitinib 15 mg and 30 mg q.d. regimens

Abbreviations: C_{avg}, average plasma concentration; Hgb, haemoglobin.

[a]Median and 90% prediction interval.

Baseline hsCRP was the only statistically significant covariate affecting upadacitinib E_{max} in the logistic regression models for ACR50 and ACR70, indicating increased upadacitinib efficacy in patients with PsA with high baseline hsCRP compared with patients with PsA with lower hsCRP. This is in agreement with other studies, which demonstrated that higher hsCRP levels at baseline are associated with better outcomes and sustained treatment response.[33] All other covariates identified as statistically significant in the model (e.g., bDMARD-IR population, BMI, and age) only affected the intercept (placebo response), suggesting that these covariates have no effect on upadacitinib efficacy in PsA. Simulations using the exposure-response models demonstrated that the difference in model-estimated ACR50 and ACR70 responses between 15 mg and 30 mg were consistent regardless of baseline hsCRP (Figure 3). Taken together, these assessments support the selection of 15 mg q.d. as the optimal dose across patients with PsA with different baseline characteristics.

Exposure-dependent changes for standard safety endpoints were observed for the probability of occurrence of serious infections, hemoglobin decrease greater than 2 g/dl from baseline, and hemoglobin decrease greater than 2 g/dl with hemoglobin less than the lower limit for normal. The percentage of patients estimated to experience serious infections, hemoglobin decreases greater than 2 g/dl from baseline and hemoglobin decrease greater than 2 g/dl with hemoglobin less than the lower limit for normal with 15 mg q.d. were estimated to be 2%, 3%, and 1% compared to 1%, 1%, and 0%, for placebo, respectively (Table 3). Increases in upadacitinib average and C_{max} up to 75% from the target 15 mg q.d. exposures are predicted to result in up to 1% to 2% increase in the percentage of patients experiencing serious infections, decrease in hemoglobin of greater than 2 g/dl, and decrease in hemoglobin of greter than 2 g/dl with hemoglobin less than the lower limit for normal compared to 15 mg q.d. target exposures. This supports that relatively limited increases in upadacitinib plasma exposures (e.g., due to mild, moderate, and severe renal or due to mild and moderate hepatic impairment) are not expected to be associated with clinically significant increases in upadacitinib plasma exposures in patients with PsA.[22,23]

In summary, along with efficacy and safety results from dose-response analyses of the phase III trials,[10,11] upadacitinib exposure-response analyses of data up to week 24 demonstrated that upadacitinib plasma exposures associated with the 15 mg q.d. regimen are predicted to achieve robust efficacy in patients with PsA with limited decreases in hemoglobin or occurrence of serious infections, even under scenarios of increased exposures due to intrinsic or extrinsic factors. These analyses represent a case for application of model-informed drug development in assessing benefit-risk, dose selection, and regulatory submissions using data from phase III clinical trials.

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CONFLICT OF INTEREST

B.E., J.K.A., and M.F.M. are employees of AbbVie and may hold AbbVie stock or stock options. E.M. and S.G. are former employees of AbbVie and may hold stock or stock options.

AUTHOR CONTRIBUTIONS

E.M., B.E., S.G., J.K.A., and M.F.M. wrote the manuscript. E.M., B.E., S.G., J.K.A., and M.F.M. designed the research. E.M., B.E., S.G., and M.F.M. performed the research. E.M., B.E., S.G., J.K.A., and M.F.M. analyzed the data.

TRIAL REGISTRATION

ClinicalTrials.gov identifiers: NCT03104374 and NCT03104400.

DATA SHARING 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 (e.g., 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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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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