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ARTICLE

Population pharmacokinetics and exposure-response analyses for efficacy and safety of apadacitinib in patients with axial Spondyloarthritis

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Abstract

Upadacitinib is an orally administered, selective, Janus kinase inhibitor that is approved for several auto-immune conditions, such as axial spondyloarthritis, an inflammatory rheumatic disease that includes ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). The approvals of upadacitinib for the treatment of AS and nr-axSpA were based on the safety and efficacy data for upadacitinib 15 mg once-daily compared to placebo from the SELECT-AXIS 1 and SELECT-AXIS 2 studies. Population pharmacokinetic analyses based on data from 244 patients with axSpA showed that the pharmacokinetics of upadacitinib were comparable in subjects with AS and nr-axSpA. Exposure-response relationships were characterized for key efficacy and safety end points using data from 482 patients with axSpA. The exposure-response analyses for efficacy based on Assessment of SpondyloArthritis International Society (ASAS)20 and ASAS40 responses at week 14, showed a clear differentiation from placebo with no evidence of increased responses with increasing upadacitinib plasma exposures. There were no clear exposure-response trends observed for safety end points that included serious infections, herpes zoster, pneumonia, lymphopenia (grade ≥3), neutropenia (grade ≥3), or a greater than 2 g/dL decrease in hemoglobin from baseline through week 14. The exposure-response analyses for efficacy and safety presented here supported the favorable benefit–risk profile with the use of upadacitinib 15 mg once-daily for the treatment of axSpA.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Upadacitinib, an orally administered and selective Janus kinase inhibitor, is approved for the treatment of ankylosing spondylitis (AS) and non-radiographic

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axial spondyloarthritis (nr-axSpA) based on the efficacy and safety assessment from global pivotal studies SELECT-AXIS 1 and SELECT-AXIS 2.

WHAT QUESTION DID THIS STUDY ADDRESS?

The analyses presented here characterized the pharmacokinetics of upadacitinib in patients with axial spondyloarthritis (axSpA), including AS and nr-axSpA patients, as well as the exposure-response relationships for key efficacy and safety end points.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The analyses demonstrated that pharmacokinetics of upadacitinib observed in patients with axSpA were consistent with the pharmacokinetics previously observed in patients with rheumatoid arthritis. The exposure-response relationships demonstrated that plasma exposures associated with the 15 mg once-daily regimen provide a favorable benefit–risk profile for the treatment of axSpA.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Evaluation of exposure-response relationships between plasma exposures and efficacy as well as safety can support assessment of the benefit–risk profile in axSpA clinical trials.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition that mainly affects the spine and is characterized by chronic inflammatory back pain.[1] Patients with axSpA can be divided in radiographic axSpA (also known as ankylosing spondylitis [AS]) and non-radiographic axSpA (nr-axSpA)[1] based on the amount of structural damage progression in the sacroiliac joints.[2,3] Patients with AS and nr-axSpA have many epidemiological, genetic, and clinical disease characteristics in common, including disease activity, functional impairment, and responses to treatment.[4] Most patients with axSpA are HLA-B27 positive, and many patients suffer from objective signs of inflammation or extra-musculoskeletal manifestations, such as uveitis, psoriasis, and inflammatory bowel disease.[1,5,6] The overall prevalence was reported to be ~0.5% for AS and up to 1% for axSpA with some geographic variability.[7,8]

In patients with axSpA with elevated disease activity, the main initial treatment is based on nonsteroidal anti-inflammatory drugs (NSAIDs). In case of inadequate response or intolerance to NSAID therapy, the addition of biological disease-modifying antirheumatic drugs (bDMARDs), like tumor necrosis factor inhibitors and interleukin (IL)-17 inhibitors, are recommended to control inflammation.[9,10] More recently, Janus kinase (JAK) inhibitors have been included as a recommended treatment option for axSpA in treatment guidelines.[9]

Upadacitinib is an orally administered and selective JAK-inhibitor that is approved for the treatment of AS and nr-axSpA in addition to rheumatoid arthritis (RA), psoriatic arthritis (PsA), atopic dermatitis, ulcerative colitis, and Crohn's disease.[11] The approval for upadacitinib, at a regimen of 15 mg once-daily (q.d.) using extended-release tablet, in the treatment of axSpA was based on efficacy and safety data from SELECT-AXIS 1 (NCT03178487) and SELECT-AXIS 2 (NCT04169373). The study SELECT-AXIS 1 evaluated the use of upadacitinib in patients with AS who were naïve to bDMARDs and had an inadequate response or intolerance to NSAID therapy.[12] SELECT-AXIS 2 included two studies: study 1 evaluated the use of upadacitinib in patients with AS who had an inadequate response or intolerance bDMARD therapy (bDMARD-IR) and study 2 in patients with nr-axSpA.[13] SELECT-AXIS 2 was started after availability of the primary results from SELECT-AXIS 1.

Upadacitinib exhibits linear pharmacokinetics in the 7.5 to 45 mg q.d. dose range.[14] After administration of the extended-release tables, upadacitinib reaches a maximum plasma concentration (C_{max}) within 2 to 4 h, followed by a bi-exponential decline with an apparent terminal half-life ranging from 9 to 14 h. Upadacitinib is a substrate for cytochrome P450 (CYP) 3A, and to a minor extent for CYP2D6.[15] The population pharmacokinetics of upadacitinib in healthy volunteers and those with RA,[16,17] Crohn's disease, ulcerative colitis, and atopic dermatitis,[14] have been described previously. These analyses showed that age, sex, body weight, and race did not have a clinically meaningful effect on upadacitinib plasma exposures and that upadacitinib pharmacokinetics are consistent between these patient populations.[14] Creatinine clearance had a significant effect on upadacitinib apparent oral

clearance based on population pharmacokinetic analyses, but upadacitinib plasma exposures were estimated to be comparable between patients with mild or moderate renal impairment and those with normal renal function.[14]

The work presented here includes the population pharmacokinetics and exposure-response analyses conducted for upadacitinib in patients with axSpA. The objectives of these analyses were to characterize upadacitinib pharmacokinetics in patients with axSpA and to evaluate the relationships between upadacitinib plasma exposures and key efficacy and safety variables.

METHODS

Study design and population

The three studies (SELECT-AXIS 1 [NCT03178487] and SELECT-AXIS 2, study 1 and study 2 [NCT04169373]) were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the institutional review boards or ethics committees for each site, and each patient provided written informed consent before any study-related procedures were performed.

SELECT-AXIS 1 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 14-week phase II/III study with a 90-week open-label extension.[12] This study included patients with active AS, fulfilled modified New York criteria, were bDMARD-naïve, and had inadequate response to at least two NSAIDS or intolerance or contraindication to NSAIDS.

SELECT-AXIS 2 was conducted under a master protocol and consisted of two standalone, multicenter, phase III studies in axSpA: study 1 included patients with AS who were bDMARD-IR (defined as: an inadequate response to at least two NSAIDs or had an intolerance to or contraindication for NSAIDs; previously exposure to at least one bDMARD, and discontinuation of bDMARD therapy due to either lack of efficacy or intolerance; exposure to a second bDMARD was allowed in up to 30% of the population; patients with lack of efficacy to two bDMARDs were not eligible for the study)[18] and study 2 included patients with nr-axSpA.[13] The studies comprised of a 14-week (study 1) or 52-week (study 2) randomized, double-blind, parallel-group, placebo-controlled period followed by open-label extension. Eligibility criteria for the studies are provided in prior publications.[12,13,18] The primary end point for all three studies were assessed at week 14 based on the Assessment of SpondyloArthritis international Society (ASAS)40 response, even though study 2 of SELECT-AXIS 2 was a 52-week long placebo-controlled study which is in line with other nr-axSpA trials.[19–21] ASAS40 response was defined as at least 40% improvement and an absolute improvement of at least two units on a numerical rating scale of 0–10 from baseline in at least three of the following four domains, with no worsening in the remaining domain: patient global assessment of disease activity, patient assessment of back pain, Bath Ankylosing Spondylitis Functional Index, and inflammation defined as the mean of the Bath Ankylosing Spondylitis Disease Activity Index questions on severity and duration of morning stiffness. In all studies, patients were randomized in a 1:1 ratio to upadacitinib 15 mg q.d. or placebo.

Pharmacokinetic, efficacy, and safety assessments

Blood samples for pharmacokinetic analysis were collected in all patients in SELECT-AXIS-1 and ~30% of patients in SELECT-AXIS-2 at weeks 2, 8, 12, and 14 as prespecified in the study protocols. Plasma concentrations of upadacitinib were determined using a previously described[22] validated liquid chromatography tandem mass spectrometric method at AbbVie (North Chicago, IL) and WuXi AppTec (WaiGaoQiao Free Trade Zone, Shanghai, China). The lower limit of quantitation was 0.05 ng/mL.

The exposure-response analyses of efficacy evaluated the ASAS20 and the ASAS40 response at week 14 for all three studies, as the analyses were focused on the time of primary end point evaluations across all the studies.[23]

The adverse events and laboratory parameters evaluated for relationships with upadacitinib exposures were selected based on possible pharmacodynamic effects associated with the mode of action of JAK inhibition and included serious infections, any infection, pneumonia, herpes zoster, changes in hemoglobin (>2 g/dL decrease from baseline), lymphopenia (grade 3 or higher: $<1\times10^9$/L, grade 4: $<0.5\times10^9$/L), and neutropenia (grade 3 or higher: $<1\times10^9$/L) at or through week 14.

Population pharmacokinetic analyses

Given the staggered availability of data from SELECT-AXIS 1 and 2 studies, the pharmacokinetic model was updated with data from SELECT-AXIS 1 and 2 in a sequential manner as data became available from the studies. Pharmacokinetic samples that were below the limit of quantitation (BLOQ) were included in the analysis using the M5 imputation method, where BLOQ samples were included as lower limit of quantitation/2. Pharmacokinetic data from patients with AS from SELECT-AXIS 1 were analyzed using the previously developed population

pharmacokinetic model that was based on pharmacokinetic data from 4170 patients, including healthy volunteers from phase I studies and patients with RA from phase II and phase III studies.[17] Due to the prior extensive characterization of upadacitinib pharmacokinetics, which included studies with intensive and sparse sampling, parameters from the previously built model, including covariate effects, were fixed and the model was re-run with the new AS dataset re-estimating interindividual variability (IIV) and residual error terms using the nonlinear mixed effects modeling software NONMEM. Model performance was evaluated using goodness-of-fit plots that included observed versus predicted concentration plots and conditional weighted residuals versus population predicted values as well as versus time. In addition, visual predictive checks (VPCs) of the concentration versus time profiles were generated by overlaying the observed data's percentiles with those of data simulated from the model. The same approach was repeated for SELECT-AXIS 2 (study 1: bDMARD-IR patients with AS and study 2: patients with nr-axSpA) upon availability of data from the studies.

Model-estimated upadacitinib plasma exposures (C_{avg}) were derived for each individual using their respective empirical Bayesian estimates from the population pharmacokinetic analyses. The upadacitinib C_{avg} was calculated as:

$$C_{avg}\left(\frac{ng}{mL}\right) = \frac{\text{Dose } (\mu g) * F_{rel}}{\frac{CL}{F}\left(\frac{L}{h}\right) * \text{Dosing interval (h)}} \quad (1)$$

where F_{rel} is the bioavailability of the extended-release formulation relative to immediate-release formulation (equals to 1 for immediate-release regimens) and CL/F is the apparent clearance for the IR formulation. C_{max} and C_{trough} were calculated using steady-state simulations for each subject using the post hoc empirical Bayesian estimates. C_{avg} was subsequently utilized in the exposure-response analyses.

Upadacitinib plasma exposures, estimated based on the empirical Bayesian estimates, were summarized for patients with AS and nr-axSpA with pharmacokinetic sample collection in the phase II/III clinical trials and compared to plasma exposures in subjects with RA from phase III clinical trials. Additional comparisons of plasma exposures between Asian and non-Asian subjects were performed.

Exposure-response analyses for efficacy and safety

These analyses were conducted independently for AS and nr-axSpA, as well as for the overall axSpA population.

Model-estimated upadacitinib C_{avg} for all patients in the three studies in the active arm during the double-blind placebo-controlled portion were derived using Equation 1. The values of upadacitinib C_{avg} for patients on placebo were set to zero. Graphical assessments for the efficacy and safety end points versus upadacitinib C_{avg} were generated to evaluate these exposure-response relationships. For safety end points, quartile plots were generated for end points with greater than or equal to 10 events at or through week 14 in the respective study. Logistic regression models, using glm function in R 4.2.0, were used to describe the relationships between upadacitinib C_{avg} and the different efficacy and safety endpoints (Equation 2). Treatment effect as well as nonlinear and linear logistic regression models were evaluated (Equations 3–5). Model selection was based on the Akaike Information Criterion and visual checks of the model fit and observed data.

$$\log\left(\frac{P(Y_i=1)}{1-P(Y_i=1)}\right) = \alpha + f(C_{avg,i}) + \sum_j \beta_j \cdot x_{j,i} \quad (2)$$

$$\text{Treatment Effect } f(C_{avg}) = \beta_{trt} * \begin{cases} 0_{\text{Placebo}(C=0)} \\ 1_{\text{Active Treatment}(C>0)} \end{cases} \quad (3)$$

$$\text{Linear Exposure} - \text{Response } f(C_{avg}) = \beta_{exp} * C_{avg} \quad (4)$$

$$\text{Logarithmic Exposure} - \text{Response } f(C_{avg}) = \beta_{exp} * \log(1 + C_{avg}) \quad (5)$$

where, $P(Y_i=1)$ is the probability that the observation Y from subject i is equal to 1, with 1 indicating the event of interest occurred, α is the intercept parameter, $C_{avg,i}$ is the predicted average concentration of upadacitinib in subject i. The β_j are the coefficients for potential additional covariates with respective values $x_{j,i}$ in subject i. β_{exp} is the slope for C for linear drug effect models and β_{trt} is the estimated magnitude of treatment effect.

RESULTS

A summary of the demographics and baseline characteristics of all the patients included in the population pharmacokinetic and exposure-response analyses is provided in Tables S1 and S2. Key baseline characteristics were generally consistent across all three studies and patient populations. The baseline characteristics were also consistent between patients from whom pharmacokinetic samples were collected and those without pharmacokinetic sample collection, with the main difference being that the mean CRP levels were ~40% lower in the subjects with pharmacokinetic sample collection than in

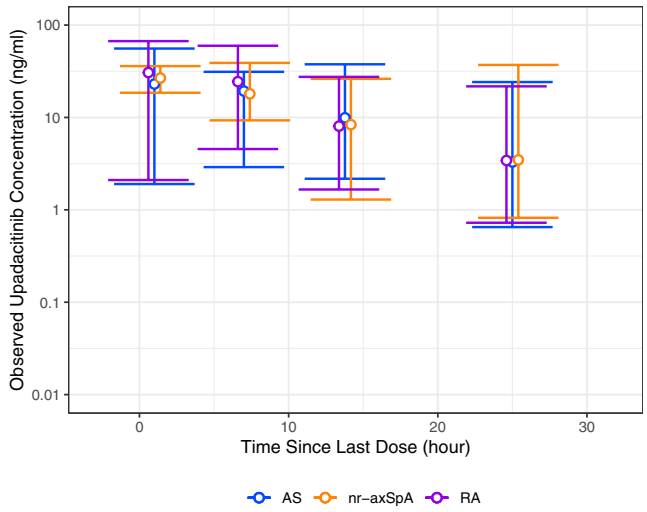

FIGURE 1 Observed upadacitinib concentrations versus binned time since last dose in AS and nr-axSpA populations compared to patients with RA in phase III studies. Circles shows median observed concentrations per indication, and error bars show the 5th/95th percentiles of the observed data per time bin. AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; RA, rheumatoid arthritis.

the subjects without pharmacokinetic sample collection. However, previous analyses have shown that CRP levels do not impact the pharmacokinetics of upadacitinib in subjects with other rheumatological diseases (e.g., RA and PsA) which included a wide range of CRP levels.[17] These baseline characteristics were also generally similar to the patients with RA that were included in the initial model development, with the key difference being that the RA patient population was primarily female (76%) whereas the axSpA population was more evenly balanced with 40% female subjects.

The population pharmacokinetic analyses datasets were based on pharmacokinetic data from 173 patients with AS and 71 patients with nr-axSpA. Exposure-response analyses were based on efficacy and safety data from 339 patients with AS and 143 patients with nr-axSpA, which included patients on upadacitinib as well as patients on placebo.

Observed upadacitinib plasma concentrations from the patients with AS and nr-axSpA were comparable to plasma concentrations observed in patients with RA who received 15 mg q.d. extended-release in previous phase III clinical trials (Figure 1).

Population pharmacokinetic analysis

The population pharmacokinetic model consisted of a two-compartment model with mixed zero-and first-order absorption with lag time for the extended-release formulation and linear elimination. Patient population (patients vs. healthy volunteers), creatinine clearance, and body weight on apparent oral clearance and body weight on volume of distribution of the central compartment were included as covariates in the model. The clearance of upadacitinib was estimated to be ~25% lower in patients compared to healthy volunteers. Increasing creatinine clearance was associated with increased clearance and increasing body weight was estimated to result in increasing clearance and the apparent volume of distribution of the central compartment.

The pharmacokinetics of upadacitinib in patients with AS from SELECT-AXIS 1 were adequately described with the population pharmacokinetic model with fixed parameters, however, re-estimation of the volume of distribution of the central compartment improved the stability of the model in terms of successful estimation and covariance steps. The population estimate for the apparent volume of distribution of the central compartment of 171 L was similar to estimate of 156 L obtained from the previously developed RA model.[17] The IIV and residual error were also re-estimated to describe the variability in the pharmacokinetics of upadacitinib in this patient population. This model was considered the final population pharmacokinetic model of the axSpA population and was subsequently used to evaluate upadacitinib pharmacokinetics in patients with AS and nr-axSpA from SELECT-AXIS 2, without re-estimation of any parameters. The model parameters for the final population pharmacokinetic model are shown in Table S3.

The goodness-of-fit plots and VPCs (Figure 2a [linear scale], Figure 2b [logarithmic scale], and Figure 3, respectively), indicate that the model adequately characterizes the pharmacokinetics of upadacitinib in patients with AS and nr-axSpA, within the range of the upadacitinib exposures evaluated in SELECT-AXIS 1 and SELECT-AXIS 2. The lack of a trend in the conditional weighted residuals versus time or population predicted concentration confirms the lack of bias in the model. The VPCs, stratified by patient population, demonstrate that the population pharmacokinetic model can describe the median trend and variability in the pharmacokinetics of upadacitinib in patients with AS and nr-axSpA. The absorption phase in the VPC for nr-axSpA is not entirely captured by the model, likely due to the limited data soon after administration of upadacitinib.

The model-estimated upadacitinib steady-state plasma exposures in the patients with AS, nr-axSpA, and RA are shown in Table 1, highlighting the similarity in the pharmacokinetics of upadacitinib across these populations. In addition, Figure 4 shows the model-estimated average plasma exposures in Asian and non-Asian patients with AS, nr-axSpA, and RA are comparable.

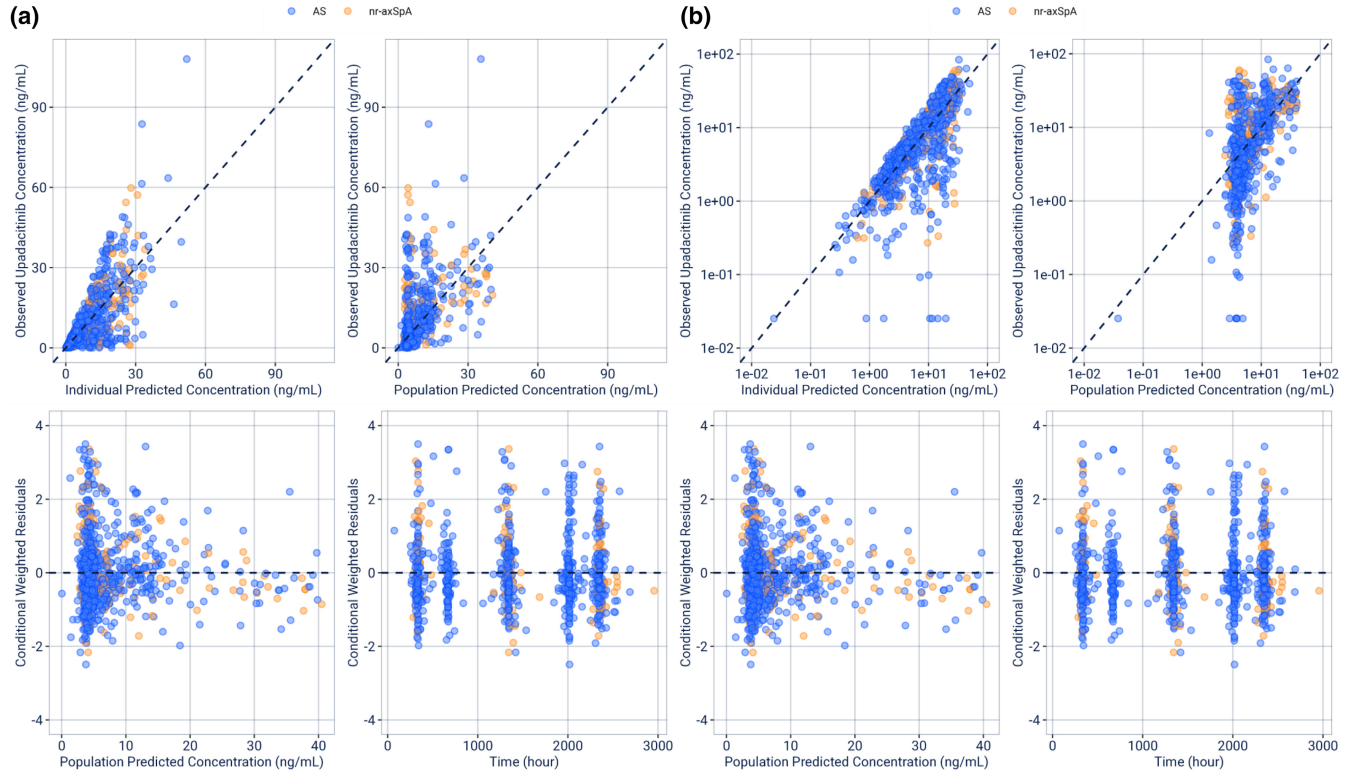

FIGURE 2 Goodness-of-fit plot for upadacitinib final population pharmacokinetic model by indication. Circles show individual observed pharmacokinetic data on an (a) linear and (b) logarithmic scale. Black dashed line shows line of unity in the individual predicted and population predicted plots. For the conditional weighted residual (CWRES) plots, the black dashed line shows the CWRES of 0. AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis.

Evaluation of upadacitinib exposure-response relationships for efficacy in axSpA

Graphical assessment of exposure-response trends for the percentage of patients who achieved ASAS20 or ASAS40 at week 14 versus upadacitinib C_{avg} show that upadacitinib C_{avg} associated with the 15 mg q.d. dosing regimen (Table 1) resulted in higher ASAS20 and ASAS40 response rates compared to placebo (Figure 5). There were no clear trends for exposure-response relationships for either end point within the range of upadacitinib plasma exposures evaluated in SELECT-AXIS 1 and SELECT-AXIS 2.

Logistic regression models were developed for the ASAS20 and ASAS40 end points at week 14 for AS, nr-axSpA, as well as all patients with axSpA, and a treatment effect model best described the exposure-response relationships for both the end points across all populations (Figure S1). These results further supported the significant effect of the upadacitinib 15 mg q.d. on ASAS20 and ASAS40 response versus placebo, with no evidence of increased efficacy response rates with increasing upadacitinib exposures, within the range of plasma exposures evaluated in the SELECT-AXIS 1 and SELECT-AXIS 2.

Evaluation of upadacitinib exposure-response relationships for safety in axSpA

There were an insufficient number of events (<10) for serious infections, herpes zoster, pneumonia, lymphopenia (grade ≥3), neutropenia (grade ≥3), or a greater than 2 g/dL decrease in hemoglobin from baseline to evaluate exposure-response relationships. Therefore, the occurrence of any infection through week 14 was the only safety variable that was evaluated via quartile plots and logistic regression.

There were no clear exposure-response trends evident across all the patient populations experiencing any infection through week 14 in SELECT-AXIS 1 and SELECT-AXIS 2 (Figure 6), as supported by a treatment effect model that best described the relationship (Figure S2). The percentage of patients experiencing any infection within each exposure quartile was similar to placebo.

DISCUSSION AND CONCLUSIONS

The pivotal studies for the treatment of axSpA including AS and nr-axSpA evaluated the efficacy and safety

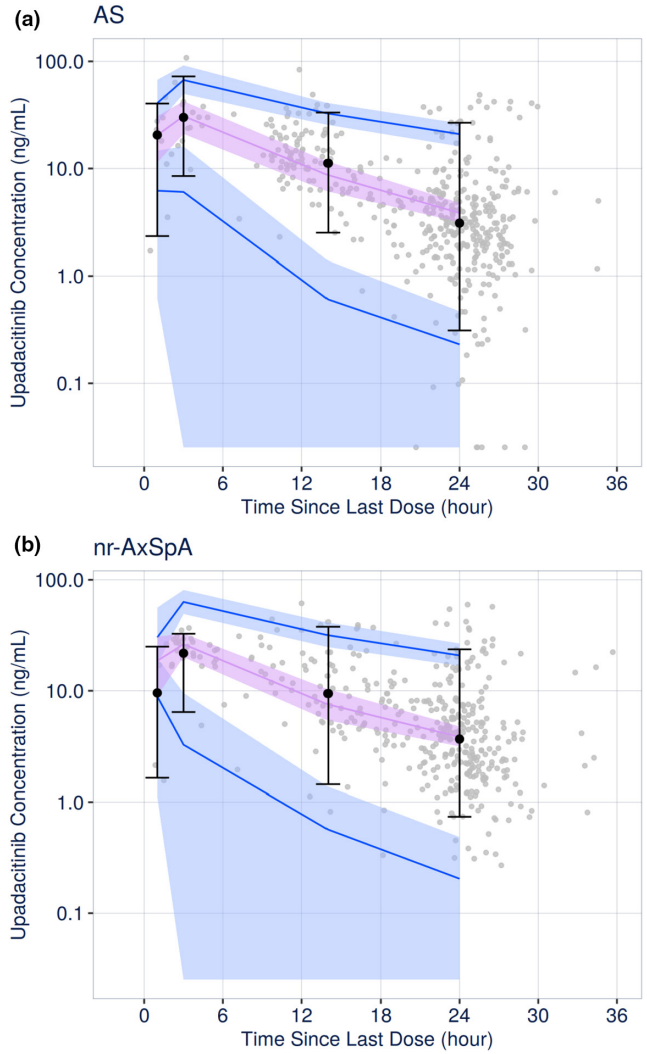

FIGURE 3 Visual predictive checks for upadacitinib final population pharmacokinetic model by indication. The blue lines represent the 90% prediction interval of the model, the shaded blue areas are the associated 90% confidence intervals of the 5th and 95th percentiles of simulated concentrations. The purple line represents the predicted median and the purple shaded area is its 90% confidence interval. The solid black line and dashed black lines represent the median and 90% inter-percentile range (5th to 95th percentile) of the observed data, respectively. Circles denote individual observed concentrations. AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis.

of upadacitinib 15 mg q.d. in a placebo-controlled manner with a primary end point assessment after 14 weeks of treatment. The dose selection for SELECT-AXIS 1 was based on available data from use of upadacitinib in the treatment of RA, results for another JAK-inhibitor AS study,[24] and overlap of inflammatory pathways between RA and axSpA.[25,26] Based on exposure-response analyses for upadacitinib efficacy in RA and PsA, upadacitinib plasma exposures associated with 15 mg q.d. approached a plateau for efficacy, with no clinically meaningful increase in efficacy with doubling exposures.[25,27] Dose selection for SELECT-AXIS 2 was then guided by the available efficacy and safety data from SELECT-AXIS 1. Therapies that are approved for RA and AS or nr-axSpA generally recommend the same dosing regimen for both indications.[11] These therapies include TNF-inhibitors (adalimumab, certolizumab pegol, etanercept, and golimumab), and another JAK-inhibitor (tofacitinib).[28–32]

The analyses described herein assessed upadacitinib pharmacokinetics and exposure-response relationships in patients with axSpA and supported the favorable benefit–risk profile of upadacitinib 15 mg q.d., within the range of the plasma exposures evaluated in the phase II/III clinical trials, for the treatment of axSpA.

Upadacitinib pharmacokinetics were similar in patients with axSpA and RA, as demonstrated in the observed plasma concentration-profiles in the two populations. This supported the use of the previously established pharmacokinetic model for the RA population to describe upadacitinib pharmacokinetics in patients with axSpA.[17] The population pharmacokinetic model adequately characterized upadacitinib pharmacokinetics in patients with axSpA. The model-estimated upadacitinib plasma exposures were comparable among patients with AS, nr-axSpA, and RA. In addition, Asian and non-Asian patients with AS and nr-axSpA, consistent with previous findings in other patient populations (RA, atopic dermatitis, and psoriatic arthritis) and healthy volunteer pharmacokinetic studies, indicated that race does not have a clinically meaningful impact on the pharmacokinetics of upadacitinib.[14,15]

TABLE 1 Summary of upadacitinib model-estimated plasma exposure parameters for the 15 mg once daily regimen in patients with axSpA (AS and nr-axSpA) and RA in phase III clinical trials.

Population (*N*)	C_{avg} (ng/mL)	$AUC_{ss,24}$ (ng/mL day)	C_{trough} (ng/mL)	C_{max} (ng/mL)
AS ($N=173$)	14.5 (9.78, 25.9)	348 (235, 621)	3.71 (1.20, 19.2)	38.8 (27.7, 51.4)
nr-axSpA ($N=71$)	14.8 (10.5, 25.5)	355 (252, 612)	4.58 (1.51, 18.8)	37.3 (26.6, 51.0)
RA ($N=1592$)	14.9 (9.74, 29.2)	357 (234, 701)	3.72 (1.51, 17.9)	41.1 (29.9, 53.0)

Note: All data are presented as median (5th to 95th percentile).

Abbreviations: AS, ankylosing spondylitis; AUC_{ss}, area under the curve at steady-state; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis; C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; RA, rheumatoid arthritis.

The exposure-response analyses for upadacitinib utilized model-estimated C_{avg}, as the exposure metric, which is consistent with exposure-response analyses conducted in other patient populations.[27,33,34] The exposure-response analyses for efficacy in axSpA demonstrated a higher response for the upadacitinib 15 mg q.d. arm compared to placebo with no trend toward higher response rates with increasing upadacitinib plasma exposures within the 15 mg q.d. arm. These findings are consistent when the data for the two subpopulations (AS and nr-axSpA) are analyzed individually or when the data are pooled together (Figure 4). This indicates that 15 mg q.d. is an appropriate dosing regimen for the treatment of axSpA.

There were no clear exposure-response relationships for any of the safety variables that were evaluated, likely due to the low number of events. The rate of infections, including serious infections, is typically lower in patients with axSpA compared to patients with RA given that patients with axSpA are younger, use less immunosuppressive therapies, and have less comorbidities.[35,36] Patients that experienced any infection through week 14, had a sufficient number of events for exposure-response analyses, however, the selection of a treatment effect model with a nominal $p > 0.05$ indicated that the model could not differentiate the effect of upadacitinib or placebo on this variable.

One of the limitations of these exposure-response analyses is that they were conducted with a relatively limited range of plasma exposures from only one dose level and at a single point in time. This could have limited the ability to fully characterize the exposure-relationship for upadacitinib in axSpA over a wide range of exposures. However, even with a one dose level, these analyses were valuable in confirming the lack of increase in efficacy with increasing exposures and in demonstrating consistency in efficacy across the range of plasma exposures associated with the 15 mg q.d. dosing regimen within the axSpA patient population (AS and nr-axSpA). It is acknowledged that assessment of longitudinal data can potentially provide a more robust assessment of exposure-response

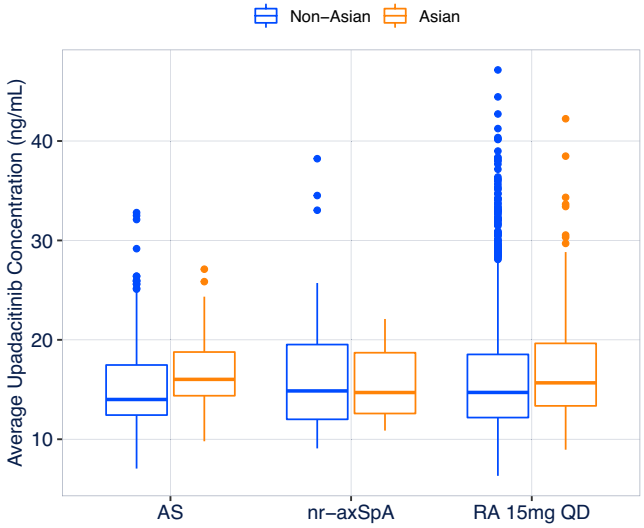

FIGURE 4 Upadacitinib average plasma concentration for the 15 mg once-daily regimen in patients with AS, nr-axSpA, and RA stratified by race. Boxplots show the median and inter-quartile range (IQR). The error bars show 1.5 times the IQR and circles denote the outliers. AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; RA, rheumatoid arthritis.

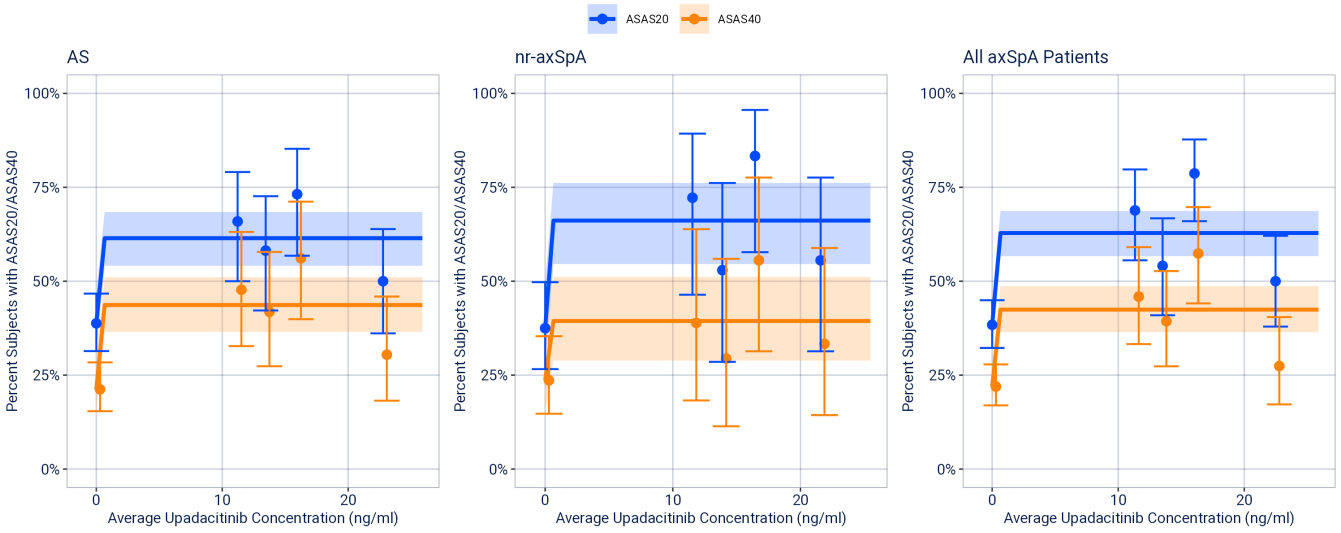

FIGURE 5 Logistic regression model fits for ASAS20 and ASAS40 at week 14 in patients with axSpA stratified by patient population. AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis.

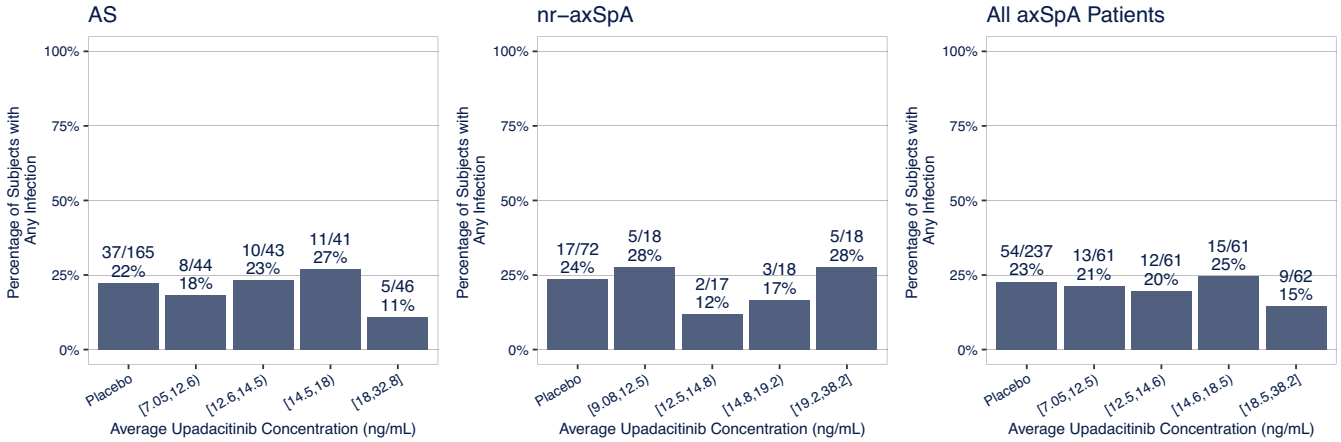

FIGURE 6 Exposure-response quartile plots for patients with axSpA experiencing any infection through week 14 stratified by patient population. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis.

relationships and the identification of covariates that might impact the exposure-response relationships, however, exposure-response analyses of clinical assessments at a single timepoint (typically at the primary efficacy end point time), similar to the presented analyses, are nevertheless valuable in demonstrating the consistency of the clinical benefit across the range of plasma exposures achieved with the recommended dosing regimen, thereby supporting dose justification for regulatory filings.

Overall, the results of these analyses support the use of upadacitinib 15 mg q.d. dose for the treatment of patients with axSpA including AS and nr-axSpA, with no evidence of increased efficacy response rates with increasing upadacitinib exposures. These analyses supported the favorable benefit–risk profile established for the use of 15 mg q.d. upadacitinib in the treatment of AS and nr-axSpA.

AUTHOR CONTRIBUTIONS

S.B., D.E., S.S., I.-H.S., P.W., W.L., and M.-E.F.M. wrote the manuscript. S.B., D.E., S.S., I.-H.S., P.W., W.L., and M.-E.F.M. designed the research. S.B., D.E., S.S., I.-H.S., P.W., W.L., and M.-E.F.M. performed the research. S.B., D.E., S.S., I.-H.S., P.W., W.L., and M.-E.F.M. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

All authors are current employees of AbbVie and may hold AbbVie stock or stock options.

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 (e.g., protocols, clinical study reports, or analysis plans), 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. These 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, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. 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://vivli.org/ourmember/abbvie/ then select "Home."

CLINICAL TRIAL REGISTRATION

SELECT-AXIS 1 (NCT03178487), and SELECT-AXIS 2 (NCT04169373).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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