Exposure–Response Analyses of Upadacitinib Efficacy and Safety in Phase II and III Studies to Support Benefit–Risk Assessment in Rheumatoid Arthritis

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Exposure–response analyses of upadacitinib (UPA) key efficacy and safety end points (3,685 and 4,577 subjects for efficacy and safety, respectively) using data from phase II and phase III rheumatoid arthritis (RA) studies were conducted to support benefit–risk assessment. Percentage of subjects achieving American College of Rheumatology (ACR)20/50/70, disease activity score 28 (C-reactive protein) (DAS28-CRP) ≤ 3.2, and DAS28-CRP < 2.6 increased with increasing UPA plasma exposures. With the small number of observed safety events, no clear trends for exposure–response relationships were identified for pneumonia, herpes zoster infection, changes in platelet count, lymphopenia (Grade ≥ 4), or neutropenia (Grade ≥ 3) up to Week 26. Shallow exposure–response relationships were observed for > 2 g/dL decrease in hemoglobin, lymphopenia Grade ≥ 3 at Week 12/14, and serious infections at Week 24/26. Exposure–efficacy analyses demonstrate that UPA 15 mg q.d. (once daily) dose provided the optimal benefit–risk in RA through maximizing efficacy with only small incremental benefit with 30 mg q.d.; and with consistency across RA subpopulations and with UPA monotherapy or combination with conventional synthetic disease-modifying antirheumatic drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Upadacitinib is a selective JAK1 inhibitor evaluated in several phase III trials as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in different patient populations with rheumatoid arthritis (RA).

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The study evaluated upadacitinib exposure–efficacy and exposure–safety relationships using data from two phase IIb and five phase III trials in order to support the benefit–risk assessment of upadacitinib treatment in patients with RA.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The presented analyses characterize the exposure–efficacy and exposure–safety profiles associated with upadacitinib treatment in RA, including the effects of patient and disease covariates and the effects of altered upadacitinib exposures due to intrinsic or extrinsic factors using data from more than 3,500 patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Utilizing model-based approaches and a large data set from more than 3,500 RA patients, these analyses add key dimensions to the benefit–risk assessments of upadacitinib in RA and were key in supporting the proposed dosing recommendations in this patient population.

Upadacitinib (ABT-494) is a selective Janus kinase (JAK)1 inhibitor being developed for the treatment of several inflammatory disorders, including rheumatoid arthritis (RA), ulcerative colitis, atopic dermatitis, Crohn's disease, psoriatic arthritis, axial spondyloarthritis, and giant cell arteritis.[1–13] The JAKs are a family of tyrosine kinases (JAK1, 2, and 3 and tyrosine kinase 2) that mediate

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receptor signaling for several cytokines involved in inflammatory diseases as well as normal immune function.[14] Upadacitinib potently inhibits JAK1, but is less potent against the other isoforms, such as JAK2, JAK3, and tyrosine kinase 2 (Tyk2).[15,16] The enhanced selectivity of upadacitinib against JAK1 may offer an improved benefit–risk profile compared with less selective JAK inhibitors.[17,18] Upadacitinib demonstrated robust efficacy and acceptable safety in two phase II and in five phase III studies in subjects with moderate to severe RA.[2–6,19]

Upadacitinib pharmacokinetics were thoroughly characterized following the administration of the immediate-release and extended-release formulations through noncompartmental analyses in phase I studies[20,21] as well as through population pharmacokinetic analyses across phase I to III studies.[21,22] Upadacitinib is a nonsensitive substrate for metabolism by cytochrome P450 3A4 isozyme (CYP3A); ~30% of upadacitinib dose is recovered in urine and feces as metabolites.[23] Strong CYP3A inhibition by ketoconazole increased upadacitinib plasma exposures by ~75% compared with administration of upadacitinib alone.[24] In subjects with mild, moderate, and severe renal impairment, upadacitinib area under the curve (AUC) was 18%, 33%, and 44% higher than matched controls.[25] In subjects with mild or moderate hepatic impairment, upadacitinib AUC was < 30% higher than matched controls.[23] Upadacitinib was administered in early phase I studies and in phase II studies in the form of immediate-release formulation and in phase III studies as extended-release formulation.

Phase IIb studies evaluated a range of upadacitinib doses (3–18 mg twice daily (b.i.d.) and 24 mg once daily (q.d.) using the immediate-release tablet formulation) in patients with RA who were inadequate responders to anti-tumor necrosis factor (anti-TNF) in BALANCE-I or to methotrexate (MTX) in BALANCE-II.[5,6] Exposure–response analyses of the key efficacy end points in the phase IIb studies demonstrated that upadacitinib exposures associated with 6 mg b.i.d. to 12 mg b.i.d. doses using the immediate-release formulation, or 15 mg q.d. to 30 mg q.d., respectively, using the extended-release formulation, were predicted to maximize efficacy assessed as the percentage of subjects achieving American College of Rheumatology (ACR)20/50/70 responses.[6] Therefore, upadacitinib doses of 15 mg and 30 mg q.d. (extended-release formulation) were selected for evaluation in global phase III studies in subjects with moderate to severe RA. The 15 mg q.d. extended-release dose was predicted to approximate the plateau of response in RA while the 30 mg q.d. dose was to ensure that the efficacy is maximized across the RA subpopulations if a more refractory subpopulation needed a higher dose.[6] The exposure–response analyses reported herein were conducted using the combined data from two phase IIb and five subsequently conducted phase III studies in patients with RA to (i) characterize the relationships between upadacitinib plasma exposure and efficacy and select safety parameters using the totality of the data in subjects with RA; (ii) identify any potential influence of subject-specific covariates on the exposure response relationships of efficacy and safety variables; and (iii) predict changes in upadacitinib efficacy response or safety variables under certain scenarios of increased upadacitinib exposures to support overall benefit–risk and dose recommendation in moderate to severe RA.

RESULTS

Data from 3,685 subjects with moderate to severe RA from the phase IIb studies BALANCE I and II[6] and four of the five phase III studies—SELECT-NEXT,[3] SELECT-BEYOND,[4] SELECT-COMPARE,[19] and SELECT-MONOTHERAPY[5]—were included in the exposure–response efficacy analyses. Data from the phase III SELECT-EARLY[2] were not included in the exposure–response efficacy analyses due to the lack of placebo control arm to inform the placebo response (therefore the net treatment effect in this early disease population). For safety analyses, the phase III study SELECT-EARLY was included (total 4,577 subjects with RA). Summaries of the demographics and baseline characteristics of subjects with RA included in the efficacy and safety analyses are provided in **Tables S1** and **S2**, respectively. Mean baseline disease activity score 28–C-reactive protein (DAS28-CRP) was 5.7, mean baseline high-sensitivity CRP was 15–17 mg/L, mean age was 55 years, and mean body weight was 76 to 78 kg across the efficacy and safety analyses data sets. The majority of subjects (~80%) were females. Overall, baseline demographic characteristics were consistent with typical demographics for an RA population. Median (95% prediction interval) model-predicted average plasma concentration over a dosing interval at steady state (C_{avg}) values for the 15 mg and 30 mg q.d. dosing regimens were 15.1 (9.65, 25.5) and 30.3 (19.3, 51.1) ng/mL, respectively.

Exposure–efficacy modeling and simulation results

Two continuous-time first-order Markov chain models were developed to describe the placebo response and exposure–response relationship between upadacitinib plasma exposures and ACR20/50/70 response in one model and low disease activity (LDA; defined as DAS28-CRP ≤ 3.2)/clinical remission (CR; defined as DAS28-CRP < 2.6) responses in a second model. Schematics for the Markov chain models used for analyses of ACR and LDA/CR responses are provided in **Figure S1**. Representative individual profiles of 25 patients are shown in **Figures S2 and S3**.

The selected ACR base model included a placebo model described by forward (transition from nonresponder to responder or from lower response to higher response) and backward placebo transition rates that differed between the different RA populations to reflect different placebo response across the different patient populations (e.g., MTX-inadequate responders vs. biologic disease-modifying anti-rheumatic drug–inadequate responders). A lower dropout rate was observed in ACR20/50/70 responders compared with nonresponders and in most studies after rerandomization of placebo patients to active treatment arms. In order to adequately account for the change in dropout rate, different dropout rates were used in the model: separate dropouts for nonresponders and ACR20/50/70 responders, a different dropout for MTX-inadequate responders/csDMARD-inadequate responder patients who were on MTX or csDMARD (any csDMARD other than MTX) background therapy, and a decrease in dropout after the placebo-controlled treatment period. The relationship between upadacitinib plasma concentration and ACR responses was best described by the maximum drug effect (E_{max}) function with one half maximal effective concentration (EC_{50}) parameter and one E_{max} parameter on all forward transitions rates (increase in the forward transition with increasing upadacitinib plasma concentration). Models with different EC_{50} or E_{max} parameters for the different

forward transition rates did not provide any improvement in model predictive performance. Early onset of upadacitinib (as early as Week 1; **Figure 1**) was observed in clinical studies, which was empirically captured in the model through inclusion of a time-dependent reduction in E_{max} for the first 8 weeks of upadacitinib treatment.

Statistically significant covariate effects in the final model for ACR were the effects of: "South/Central America" region (higher estimates for forward and backward transition rates compared with other regions), black race (higher backward transition rates compared with other race categories), anti-cyclic citrullinated peptide (CCP) negative status (higher backward transition rates and higher EC_{50} compared with anti-CCP positive status), baseline DAS28-CRP (decreased backward transition rates with higher baseline DAS28-CRP), and body weight (higher EC_{50} with higher body weight).

The LDA/CR placebo responses were adequately described by a Markov model structure that was similar to the ACR model structure. Different LDA/CR placebo responses were observed in subjects who were on background treatment of MTX or csDMARDs (except for MTX) compared with subjects who were not (placebo without background medications). This was adequately captured in the model through an exponentially increasing transition rate from nonresponder to LDA response state with time in subjects who were on background treatment of MTX or csDMARD. The effect of upadacitinib plasma concentrations on the transitions from nonresponder to LDA and CR states was best described by E_{max} function with separate E_{max} parameters for transition from nonresponder to LDA and from LDA to CR states and one EC_{50} parameter for both forward transition rates. Onset of upadacitinib effect on LDA and CR was noted as early as Week 1 of treatment, which was adequately described by the model (**Figure 2**). In addition, Visual predictive checks (VPCs) for dropouts are provided in **Figures S4 and S5**. Overall, the models adequately described the dropouts, despite some nonsystematic bias for some treatment groups in some studies. Additional VPCs stratified by significant covariates as well as phase II vs. phase III studies are provided in **Figures S6–S11**.

Similar to the ACR model, significant covariates in the final LDA/CR model were: baseline DAS28-CRP (lower forward transition rates with higher baseline DAS28-CRP), "South/Central America" and "Western Europe" regions (higher forward transition rates compared with other regions), "Eastern Europe" region (lower backward transition rates compared with other regions).

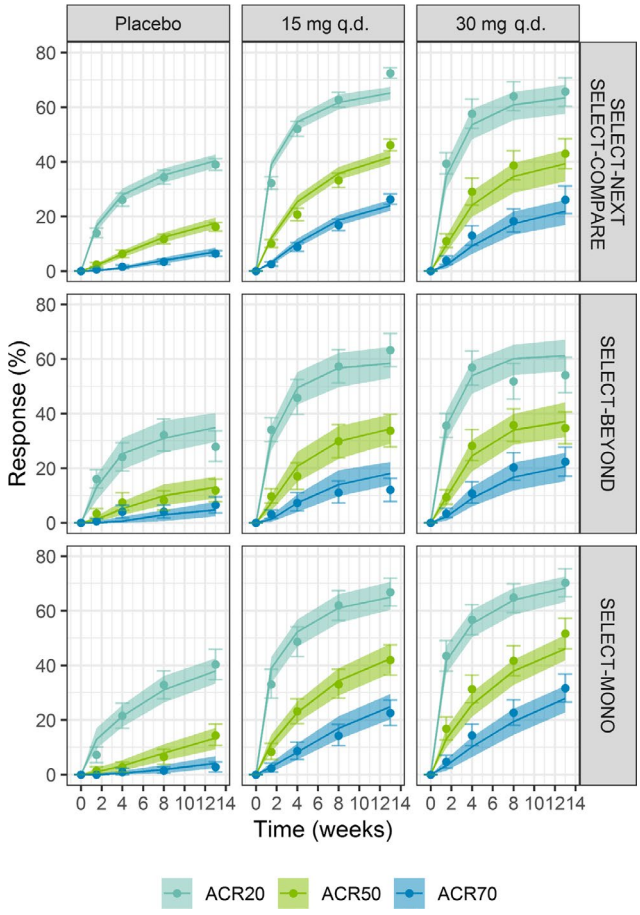

Figure 1 Visual predictive checks (VPCs) for ACR responses based on the final ACR model. Symbols and error bars, observed response, and 90% confidence interval at respective time bin; lines/shaded regions: median ± 90% confidence interval (CI) for predicted responses. ACR, American College of Rheumatology.

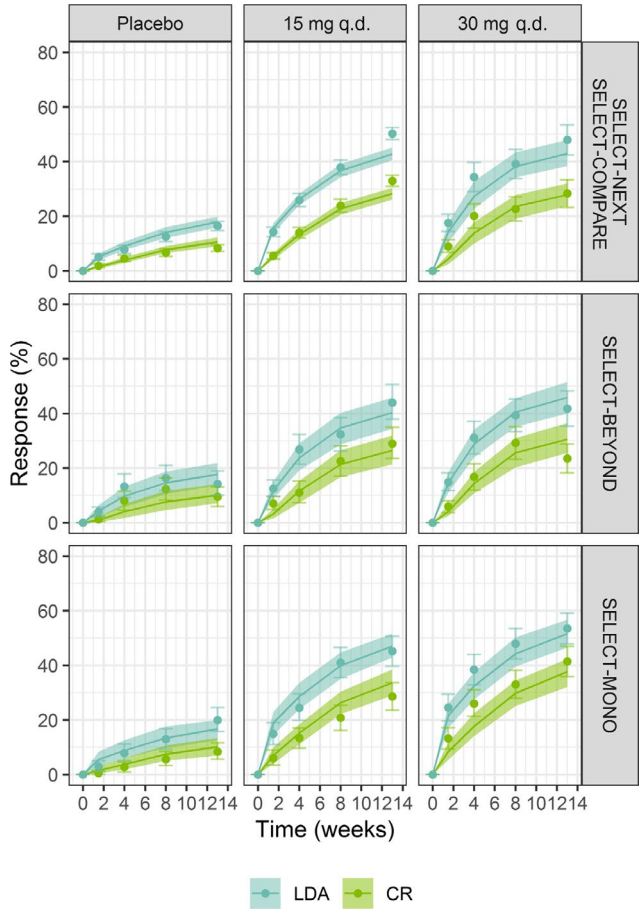

Figure 2 Visual predictive checks (VPCs) for low disease activity / clinical remission (LDA/CR) responses based on the final LDA/CR model. Symbols and error bars = observed response and 90% confidence interval at respective time bin; lines/shaded regions: median ± 90% confidence interval (CI) for predicted responses.

Additionally, anti-CCP negative status, larger body weight, and higher baseline DAS28-CRP were associated with higher EC_{50}.

The final model parameter estimates together with bootstrap evaluation results for ACR and LDA/CR models are summarized in **Tables S3** and **S4**, respectively. Ninety-six percent of bootstrap runs for each model converged successfully; and the median parameter estimates were in line with the final model estimates, and the confidence intervals did not contain the neutral values for lack of significance.

Figures 1 and 2 show the VPCs for the final ACR and LDA/CR models, respectively, and demonstrate adequate model predictive performance across all studies and RA patient populations.

Simulations were performed to predict the efficacy responses following dosing with placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d. regimens. Results of the exposure–efficacy simulations demonstrate that upadacitinib 30 mg q.d. regimen provides only a small incremental efficacy benefit (< 5%) compared with 15 mg q.d. regimen across the different RA patient populations (**Table 1**), indicating that the 15 mg q.d. regimen achieved the plateau of response in treatment of RA. Additional simulations of efficacy response (ACR20 and LDA) across the different covariate categories (for the significant covariates on upadacitinib EC_{50}) in the final models showed that upadacitinib 15 mg q.d. is predicted to provide adequate efficacy across the different covariate categories such as body weight, baseline anti-CCP status, and baseline DAS28-CRP (**Figures S12 and S13**).

Exposure–safety modeling and simulation results

With the small number of observed safety events, no clear relationships were observed between upadacitinib plasma exposure (assessed as C_{avg}) and pneumonia, herpes zoster infection, changes in platelet count (platelets ≥ 600×10^9/L with baseline ≤ 400×10^9/L), lymphopenia (Grade 4 or higher), and neutropenia (Grade 3 or higher) at Week 12/14 or Week 24/26 (**Figure 3**). Shallow exposure–response relationships were observed between upadacitinib C_{avg} and lymphopenia Grade 3 or higher at Week 12/14,> 2 g/dL decrease in hemoglobin from baseline at Week 12/14 and Week 24/26, and serious infections at Week 24/26, which were adequately described by logistic regression models (**Figure 4**). At Week 12/14, there was a statistically significant relationship between increasing upadacitinib C_{avg} and the percentage of subjects experiencing > 2 g/dL decrease in hemoglobin, or lymphopenia Grade ≥ 3 at Week 12/14. A logistic regression model with linear drug effect function best described the probability of experiencing lymphopenia Grade 3 or higher. On the other hand, sigmoid E_{max} models best described the drug effect on the probability of experiencing > 2 g/dL decrease in hemoglobin.

At Week 24/26, there was a statistically significant relationship between increasing upadacitinib C_{avg} and the percentage of subjects experiencing > 2 g/dL decreases in hemoglobin as well as the percentage of subjects having serious infections. A logistic regression model with linear drug effect function best described the drug effect on the probability of experiencing > 2 g/dL decrease in hemoglobin and on the probability of experiencing serious infection. On the other hand, there was no statistically significant relationship between upadacitinib C_{avg} and the percentage of subjects experiencing lymphopenia Grade 3 or higher at Week 24/26.

Significant covariate in the exposure–safety models (**Table S5**) were baseline hemoglobin (higher values are associated with higher percentage of subjects, independent of upadacitinib treatment, experiencing a > 2 g/dL decrease from baseline hemoglobin at Week 12/14 and Week 24/26), baseline lymphocyte counts (higher values associated with lower percentage of subjects, independent

Table 1 Model-simulated clinical efficacy responses (% responders) at Week 12 following placebo and upadacitinib 15 mg and 30 mg q.d. regimens

Population	Clinical efficacy response variable[a]	Upadacitinib dosing regimen		
		Placebo	15 mg q.d.	30 mg q.d.
MTX-IR on background MTX	ACR20	40 (34, 47)	66 (60, 71)	68 (62, 74)
	ACR50	17 (12, 22)	41 (35, 48)	45 (39, 52)
	ACR70	6 (3, 11)	23 (18, 29)	26 (21, 33)
	LDA	19 (13, 24)	45 (40, 52)	50 (44, 57)
	CR	11 (8, 16)	31 (25, 36)	34 (29, 41)
bDMARD-IR on background MTX	ACR20	36 (30, 43)	58 (52, 65)	61 (54, 67)
	ACR50	14 (8, 19)	34 (27, 42)	38 (32, 45)
	ACR70	5 (2, 9)	18 (13, 24)	21 (16, 26)
	LDA	18 (14, 24)	40 (34, 47)	45 (39, 51)
	CR	11 (7, 15)	27 (21, 33)	31 (25, 36)
MTX-IR on upadacitinib monotherapy	ACR20	36 (29, 44)	65 (58, 72)	68 (61, 75)
	ACR50	12 (8, 16)	42 (36, 49)	45 (38, 52)
	ACR70	3 (1, 7)	24 (18, 30)	27 (20, 33)
	LDA	17 (12, 23)	50 (44, 58)	55 (48, 62)
	CR	11 (7, 16)	36 (31, 44)	40 (34, 47)

ACR, American College of Rheumatology; bDMARD-IR, biologic disease-modifying anti-rheumatic drug inadequate responder; CR, clinical remission; LDA, low disease activity; MTX-IR, methotrexate inadequate responder.
[a]Data are presented as median (5^{th}, 95^{th} percentiles).

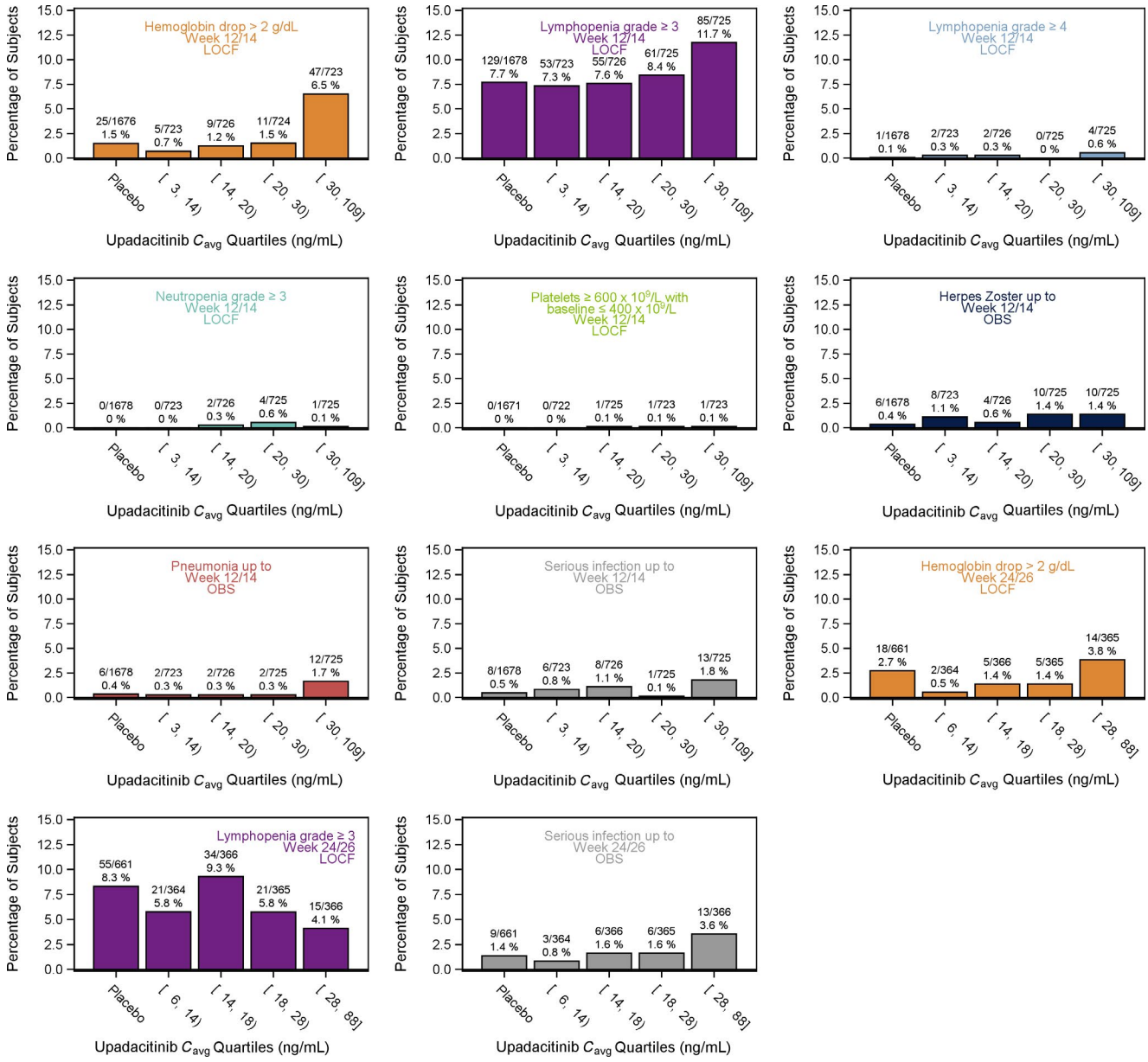

Figure 3 Exposure–response quartile plots for select safety variables at Week 12/14 and Week 24/26. C_{avg}, average plasma concentration over a dosing interval at steady state; HGB, hemoglobin; LOCF, last observation carried forward; OBS, observed. [Colour figure can be viewed at wileyonlinelibrary.com]

of upadacitinib treatment, experiencing lymphopenia Grade 3 or higher at Week 12/14), baseline use of csDMARD and older age (associated with higher percentage of subjects experiencing lymphopenia Grade 3 or higher). Similarly, older age was associated with higher incidence of > 2 g/dL decrease from baseline hemoglobin at Week 12/14 and Week 24/26. A summary of the final model parameters estimates for the logistic regression models is provided in **Table S5**. **Figure 4** shows the VPCs for the final models, indicating adequate model predictive performance across all evaluated safety variables.

Differences in the incidence of safety end points among the different covariate subcategories were further evaluated through simulations using the final exposure–safety models. Results of the simulations showed that the differences in age or baseline use of csDMARDs are not expected to result in clinically relevant changes in upadacitinib safety profile associated with the 15 mg q.d. regimen (**Figure S14**).

The final logistic regression models were used to perform simulations to predict impact on safety variables following placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d. at Week 12 or Week 24; as well as the effect of increasing upadacitinib exposures (e.g., due to hepatic or renal impairment; coadministration with strong CYP3A inhibitors), relative to 15 mg q.d., on the probability of occurrence of clinically relevant safety variables. The simulated percentages of subjects for each variable under placebo, upadacitinib 15 mg q.d., and upadacitinib 30 mg q.d. regimens

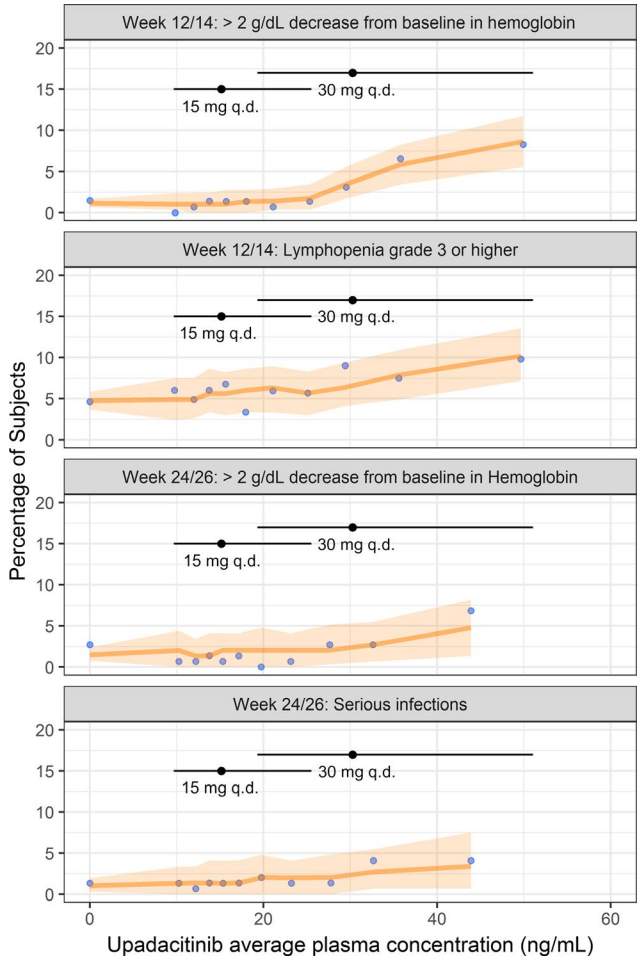

Figure 4 Visual predictive checks for final exposure–safety logistic regression models at Week 12/14 and Week 24/26. The blue dots denote observed responses within upadacitinib average plasma concentrations deciles, orange solid lines denote median predicted responses within upadacitinib average plasma concentrations deciles, and the orange shaded areas denote the 95% prediction interval. [Colour figure can be viewed at wileyonlinelibrary.com]

are shown in **Table 2**. Simulations for percentages of subjects experiencing serious infections or changes in clinically relevant laboratory parameters under scenarios of increased upadacitinib C_{avg} relative to the 15 mg q.d. regimen are shown in **Table 3**. Simulation results showed that increases in upadacitinib exposures up to 75% are predicted to result in only 0.67% increase in percentage of subjects experiencing serious infections up to Week 24 and only up to 1.33% increase in percentage of subjects experiencing lymphopenia Grade ≥ 3 or a decrease in hemoglobin of > 2 g/dL at Week 12 from baseline.

DISCUSSION

Exposure–response models were developed to describe the relationships between upadacitinib exposures and clinical efficacy and safety in subjects with RA using pooled data from two phase II dose-ranging and five phase III studies. Final models were used to predict efficacy and safety outcomes following different upadacitinib doses and exposure scenarios to support benefit–risk assessment for upadacitinib use in treatment of RA.

The efficacy of upadacitinib was exposure-dependent, and exposure–efficacy Markov chain models for ACR responses as well as for LDA/CR adequately described placebo responses as well as response to upadacitinib treatment in subjects with RA. No tolerance to upadacitinib efficacy was observed over time (**Figures 1 and 2**). The selected efficacy end points for the exposure–response analyses included the categorical end points of ACR20/50/70 and LDA/CR. Alternatively, the continuous scales could have been analyzed, then the cutoffs of interest could have been derived. Modeling the categorical efficacy and safety end points has the advantage of directly capturing the clinically relevant study end points of interest, hence allowing direct comparison to the study end points and assessment of clinical utility. Additionally, analysis of the continuous scores sometimes results in biased estimates of the cutoffs if there is some bias in capturing the true distribution of the data. Although the categorical analysis does not fully utilize the richness of the data captured with the continuous scales, this was mitigated in our analyses through simultaneously modeling ACR20/50/70 responses and, similarly, DAS LDA/CR.

Simulated clinical efficacy response shows that upadacitinib 15 mg q.d. regimen maximize upadacitinib efficacy (66%, 41%, and 23% for ACR20, ACR50, and ACR70, respectively, and 45% and 31% for LDA and CR, respectively); with the 30 mg q.d. regimen only providing small incremental benefit in subjects with RA (≤ 5% increase in ACR or LDA/CR responses from 15 mg q.d. to 30 mg q.d. across all studied populations). These results were

Table 2 Model-simulated percentage of subjects with serious infections or changes in laboratory parameters at Weeks 12 and 24 following placebo and upadacitinib 15 mg and 30 mg q.d. regimen

	Upadacitinib dosing regimen		
Safety variable[a]	Placebo	15 mg q.d.	30 mg q.d.
Week 12			
Percentage of subjects with Hgb > 2 g/dL decrease from baseline	1.33 (0.33, 2.00)	1.67 (0.33, 2.67)	4.00 (2.00, 6.00)
Percentage of subjects with lymphopenia Grade 3 or higher	5.67 (3.98, 7.67)	6.67 (4.67, 8.67)	8.33 (6.00, 10.30)
Week 24			
Percentage of subjects with Hgb > 2 g/dL decrease from baseline	1.33 (0.65, 2.67)	2.00 (0.67, 3.02)	2.33 (1.33, 4.00)
Percentage of subjects with serious infections	1.00 (0.333, 2.00)	1.67 (0.333, 3.33)	2.67 (1.33, 4.67)

Hgb, hemoglobin.
[a]Data are presented as median (5^{th}, 95^{th} percentiles).

Table 3 Model-simulated percentage of subjects experiencing changes in clinically relevant laboratory parameters in scenarios of increased upadacitinib C_{avg} relative to 15 mg q.d. regimen

Scenario	Median C_{avg} (ng/mL)	Simulated percentage of subjects based on modeling: Median	Simulated percentage of subjects based on modeling: 90% confidence interval
Percentage of subjects with > 2 g/dL decrease from baseline in hemoglobin at Week 12			
Reference (15 mg q.d.)	15.1	1.67	0.33, 2.67
25% higher upadacitinib C_{avg}	18.9	1.67	0.67, 3.33
50% higher upadacitinib C_{avg}	22.7	2.33	1.00, 4.00
75% higher upadacitinib C_{avg}	26.5	3.00	1.67, 5.00
Percentage of subjects with lymphopenia Grade 3 or higher at Week 12			
Reference (15 mg q.d.)	15.1	6.67	4.67, 8.67
25% higher upadacitinib C_{avg}	18.9	6.67	4.98, 9.33
50% higher upadacitinib C_{avg}	22.7	7.33	5.00, 10.00
75% higher upadacitinib C_{avg}	26.5	8.00	5.67, 10.30
Percentage of subjects with > 2 g/dL decrease from baseline in hemoglobin at Week 24			
Reference (15 mg q.d.)	14.7	2.00	0.67, 3.02
25% higher upadacitinib C_{avg}	18.4	2.00	0.67, 3.33
50% higher upadacitinib C_{avg}	22.1	2.00	1.00, 3.67
75% higher upadacitinib C_{avg}	25.8	2.33	1.00, 3.67
Percentage of subjects with serious infections at Week 24			
Reference (15 mg q.d.)	14.7	1.67	0.33, 3.33
25% higher upadacitinib C_{avg}	18.4	1.67	0.67, 3.35
50% higher upadacitinib C_{avg}	22.1	2.00	1.00, 3.67
75% higher upadacitinib C_{avg}	25.8	2.33	1.00, 3.67

C_{avg}, average plasma concentration over a dosing interval at steady state; q.d., once daily.

consistent across csDMARD–inadequate responder (IR) and biologic disease-modifying anti-rheumatic drug–IR populations and whether upadacitinib is used as monotherapy or on background treatment of csDMARDs. These results were also consistent with the predictions from the phase II efficacy exposure–response analyses.[6] However, the present analyses provided greater precision in the efficacy estimates due to the increased power with the large sample size from the phase III trials. This is evident from the width of the prediction intervals in the VPCs from the present analyses (**Figures 2 and 3**) compared with the phase II analyses.[6]

Significant covariate effects in the final ACR and LDA/CR models included effects of baseline anti-CCP status, baseline DAS28-CRP, and baseline body weight on upadacitinib EC_{50}. All other significant covariates (e.g., study region, subject race, etc.) were only associated with parameters related to placebo response and hence are not expected to affect response to upadacitinib treatment in particular. It is worth noting that although body weight and anti-CCP status were identified as statistically significant covariates on EC_{50}, a sensitivity analysis (data not shown) demonstrated that an alternative parameterization with these covariates included on E_{max} instead of EC_{50} yields similar comparable objective function values. Therefore, the analyses do not support that a dose higher than 15 mg q.d. in certain patient subgroups will lead to a clinically meaningful increase in efficacy over 15 mg q.d. In addition, simulations using the final ACR and LDA/CR models demonstrated that the estimated differences in upadacitinib EC_{50} due to the statistically significant covariate effects are not expected to result in clinically relevant differences in response; therefore, the analyses do not support that a dose higher than 15 mg q.d. in certain patient subgroups may lead to a clinically meaningful increase in efficacy. Hence the 15 mg q.d. regimen is expected to provide adequate efficacy in all evaluated covariate categories. Recently, the 15 mg q.d. dose of upadacitinib was approved by the US Food and Drug Administration (FDA) for treatment of patients with moderated-to-severe RA.[26]

With the small number of observed safety events, no clear exposure–response relationship was observed between upadacitinib plasma exposures and occurrence of serious infections (Week 12/14), pneumonia, herpes zoster infections, changes in platelet count, or neutropenia (Week 12/14 or Week 24/26). Such results indicate that variability in upadacitinib exposures due to intrinsic or extrinsic factors among subjects receiving the same dose (e.g., 15 mg q.d.) may not result in clinically relevant changes in the incidence of these safety end points.

Exposure-dependent changes were observed for > 2 g/dL decrease in hemoglobin from baseline, lymphopenia Grade ≥ 3, and serious infections (Week 24/26). Simulations with Week 24/26 logistic regression models for decreases in hemoglobin yielded similar results, indicating no increase in upadacitinib-associated changes in hemoglobin levels between Weeks 12 and 24. The effects of upadacitinib exposures on the increased incidence of lymphopenia Grade 3 or higher were only evident at Week 12/14, while the relationship was not statistically significant at Week 24/26. Such results indicate that upadacitinib effects on lymphocyte counts may be transient. Upadacitinib exposures were associated with a slight increase in the incidence of serious infections at Week 24/26, but not at Week 12/14. However, the model-predicted incidence for occurrence of serious infections (1.67%) or clinically relevant changes in laboratory parameters (2% for hemoglobin decrease > 2 g/dL, and 6.7% for lymphopenia Grade ≥ 3) were generally low for upadacitinib 15 mg q.d. regimen.

Simulation results based on final exposure–safety models showed that none of the statistically significant covariates were predicted to result in clinically relevant changes in upadacitinib-related changes in hemoglobin, or the incidence of serious infections or lymphopenia Grade 3 or higher. Also, increases in upadacitinib exposures by 25% to 50% due to intrinsic or extrinsic factors (e.g., renal and hepatic impairment) are predicted to result in < 1% increase in the percentage of subjects who may experience > 2 g/dL decrease in hemoglobin from baseline, lymphopenia (Grade 3 or higher) at Week 12 or serious infections at Week 24. Even in scenarios of increased exposures by 75% (e.g., due to strong CYP3A inhibition.[24]), it is predicted that such

scenario would result in only 0.33%, 1.33%, and 0.67% increase in the percentage of subjects experiencing > 2 g/dL decrease from baseline hemoglobin, lymphopenia Grade 3 or higher, or serious infections, respectively, within up to 6 months of treatment compared with 15 mg q.d. exposures. These results indicate that scenarios that may be associated with up to 75% higher upadacitinib exposures are predicted to be associated with limited additional changes in hemoglobin and lymphocytes or the occurrence of serious infections compared with the typical 15 mg q.d. exposures. Consistent with the results of the exposure–response analyses and the expected small impact on upadacitinib exposure, no dose adjustments are needed for subjects with renal impairment or mild or moderate hepatic impairment.[26]

In summary, exposure–response analyses demonstrate that the upadacitinib 15 mg q.d. regimen using the extended-release formulation provides the optimal benefit–risk profile in patients with RA.

METHODS

Participants and design of the studies

The studies (BALANCE I, BALANCE II, SELECT-NEXT, SELECT-BEYOND, SELECT-COMPARE, SELECT-EARLY, SELECT-MONOTHERAPY) 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.

Details of the study designs for the two phase IIb and the five phase III studies have been previously described.[2–5,19] These studies represent all controlled upadacitinib phase IIb and III studies in subjects with rheumatoid arthritis with results available to date, which encompassed different populations (csDMARD-IR, MTX-IR, Biologics-IR and MTX-naïve patients) and treatment modalities (on background of MTX/csDMARDs or monotherapy). Data from the phase III SELECT-EARLY[2] were not included in the exposure–response efficacy analyses due to the lack of placebo control arm to inform the placebo response (therefore the net treatment effect in this early disease population). Briefly, men and women 18 years of age or older who were diagnosed with moderate to severe RA for at least 3 months and had active disease with at least 6 swollen joints (based on a 66-joint count) and at least 6 tender joints (based on a 68-joint count)) were eligible to enroll into the studies. **Table S6** summarizes the patient population, background therapy, evaluated doses, and pharmacokinetic/safety/efficacy assessments for each of the seven studies included in the analysis.

Pharmacokinetic, efficacy, and safety assessments

Blood samples for determination of upadacitinib plasma concentrations were collected at specific time points (**Table S6**). Plasma concentrations of upadacitinib were determined at AbbVie (North Chicago, IL) using a validated liquid chromatography method with mass spectrometric detection as previously described.[24]

Efficacy end points evaluated in the exposure–response efficacy analyses included proportions of patients achieving ACR20, ACR50, or ACR70 responses, as well as LDA and CR. ACR responses, LDA, and CR were defined as previously described in the original studies.

The adverse events and laboratory parameters evaluated for relationships with upadacitinib exposures included serious infections, pneumonia, herpes zoster infection, changes in platelet count (platelets ≥ 600×10^9/L with baseline ≤ 400×10^9/L), changes in hemoglobin (> 2 g/dL decrease from baseline, hemoglobin < 8 g/dL), lymphopenia (Grade 3 or higher: < 1×10^9/L, Grade 4: < 0.5×10^9/L), and neutropenia (Grade 3 or higher: < 1×10^9/L) at Week 12/14 and at Week 24/26.

Exposure–response analyses for efficacy end points

All subjects with at least a baseline and subsequent response assessment were included in the Markov exposure–response analyses for efficacy. For all studies except SELECT-EARLY and SELECT-COMPARE, data were included up to the time point of primary end-point evaluation (i.e., Week 12 or Week 14). In addition, longer term data up to Week 24 were included for SELECT-BEYOND. For SELECT-COMPARE, only data up to Week 14 were included in the analyses because rescue therapy was allowed after these time points based on subject response status, which could not be accounted for in the Markov model without the potential for introducing some bias. Data from the phase III SELECT-EARLY were not included in the exposure–response efficacy analyses due to the lack of placebo control arm to inform the placebo response (therefore the net treatment effect in this early disease population). Continuous-time Markov chain exposure–response models were developed in NONMEM (Version 7.4.1; Icon, Ellicott City, MD) for ACR20/50/70 responses (combined in one model) as well as LDA and CR (combined in one model). Upadacitinib individual predicted plasma concentration profiles, based on a previously developed population pharmacokinetic model[21] including the same studies, were used as input for the Markov models. The models were developed in a stepwise manner. First, a structural placebo model was developed to describe the transition rates only in subjects who received placebo. Second, upadacitinib effect was added in the model using data from all subjects and all parameters were reestimated. Lastly, the effects of covariates were assessed. The transition states of the Markov chain model for ACR were defined as no response, ACR20, ACR50, ACR70 response, and dropout. Likewise, the Markov model for LDA and CR included four model states defined as no response, LDA, CR, and dropout. Final exposure–response models were used to evaluate the effects of covariates on different placebo or upadacitinib-associated model parameters. Covariates evaluated on the final models included patient demographics, concomitant therapy, and patient population, as well as measures of disease severity and disease duration at baseline. Details of the exposure–response efficacy analyses including model structure, model building, model selection and evaluation, and covariate testing can be found in the **Supplementary Material**.

Finally, the developed exposure–response models for ACR and LDA/CR were used to perform simulations to predict efficacy responses following upadacitinib 15 mg q.d. and 30 mg q.d. dosing regimens and to compare efficacy outcomes across different covariate subcategories. Two hundred replicates with 300 subjects each were simulated; and for each simulation, replicate median and 90% confidence intervals were calculated.

Exposure–response analyses for safety variables

All subjects with pharmacokinetic measurements and at least one safety assessment were included in the exposure–response safety analyses for Week 12/14. In addition, for Week 24/26 analyses, subjects from SELECT-BEYOND and SELECT-COMPARE were only included if they remained on the same treatment up to Week 24 and 26, respectively.

For the exposure–response safety analyses, upadacitinib individual predicted C_{avg} based on the empirical Bayesian individual estimates from the population pharmacokinetic model[21] was used as the exposure measure. Exploratory quartile plots were first evaluated using a pooled data set across all seven studies to identify safety variables at Week 12 (or 14) that appear to be related to upadacitinib exposure. For SELECT-EARLY, data for 15 mg and 30 mg q.d. only were included in safety analyses.

The following safety variables showed a trend for possible exposure–response relationship based on the quartile plots (**Figure 3**) and were assessed further through logistic regression exposure–response models: > 2 g/dL decrease in hemoglobin from baseline at Week 12/14 and Week 24/26, lymphopenia Grade 3 or higher at Week 12/14, serious infections at Week 24/26. All other evaluated safety variables did not show trends for

exposure-dependent changes with upadacitinib treatment (**Figure 3**) and hence were not evaluated further in exposure–response models.

Linear and nonlinear logistic regression analyses for the safety parameters were evaluated using the Laplacian estimation method within NONMEM. Final exposure–response models were used to evaluate the effects of covariates on different placebo or upadacitinib-associated model parameters. Covariates evaluated on the final models included patient demographics, concomitant therapy, and patient population, as well as measures of disease severity and disease duration at baseline. Details of the exposure–response safety analyses including model structure, model building, model selection and evaluation, and covariate testing can be found in the **Supplementary Material**.

Final models were then used to perform simulations to predict safety outcomes following upadacitinib 15 mg q.d. and 30 mg q.d. regimens and to compare the incidence of key safety end points across different covariate subcategories. In addition, the final models with upadacitinib C_{avg} as the exposure parameter were used to conduct simulations to predict the effect of changes in upadacitinib exposures (e.g., due to renal/hepatic impairment, drug interactions, etc.) on the probability of safety outcomes. Upadacitinib exposure increases of 25%, 50%, and 75% were simulated and results were compared with those predicted with upadacitinib 15 mg q.d. dosing regimen. Two hundred replicates of 300 subjects each were run; the percentage of simulated subjects experiencing the safety outcome was calculated for each replicate and median, and 90% confidence intervals were calculated across the 200 replicates.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. Markov chain models for (**a**) American College of Rheumatology (ACR) and (**b**) low disease activity/clinical remission (LDA/CR) responses.
Figure S2. Representative individual profiles of American College of Rheumatology (ACR) 20/50/70 responses for 25 subjects.
Figure S3. Representative individual profiles of low disease activity/clinical remission (LDA/CR) responses for 25 subjects.
Figure S4. Visual Predictive Checks (VPCs) for dropouts based on final American College of Rheumatology (ACR) model.
Figure S5. Visual Predictive Checks (VPCs) for dropouts based on final low disease activity/clinical remission (LDA/CR) model.
Figure S6. Visual Predictive Checks (VPCs) for American College of Rheumatology (ACR) responses based on final ACR model (stratified by study phase).
Figure S7. Visual Predictive Checks (VPCs) for American College of Rheumatology (ACR) responses based on final ACR model (stratified by subject weight).
Figure S8. Visual Predictive Checks (VPCs) for American College of Rheumatology (ACR) responses based on final ACR model (stratified by anti-CCP status).
Figure S9. Visual Predictive Checks (VPCs) for low disease activity/clinical remission (LDA/CR) responses based on final LDA/CR model (stratified by study phase).
Figure S10. Visual Predictive Checks (VPCs) for low disease activity/clinical remission (LDA/CR) responses based on final LDA/CR model (stratified by subject weight).
Figure S11. Visual Predictive Checks (VPCs) for low disease activity/clinical remission (LDA/CR) responses based on final LDA/CR model (stratified by anti-CCP status).
Figure S12. Model-predicted American College of Rheumatology (ACR) responses across different covariate subcategories.
Figure S13. Model-predicted low disease activity/clinical remission (LDA/CR) responses across different covariate subcategories.
Figure S14. Model-predicted changes in clinically relevant safety end points across the different covariate subcategories.
Table S1. Demographic and baseline characteristics for subjects included in the exposure–efficacy analyses.
Table S2. Demographic and baseline characteristics for subjects included in the week 12/14 and week 24/26 exposure–safety analyses.
Table S3. Final parameter estimates for the exposure–response final model for American College of Rheumatology (ACR).
Table S4. Final parameter estimates for the exposure–response final model for low disease activity/clinical remission (LDA/CR).
Table S5. Final model parameter estimates for logistic regression models of upadacitinib C_{avg} (average plasma concentration over a dosing interval at steady state) and select safety variables.
Table S6. Summary of studies and data included in the exposure–response analyses for efficacy and safety.
Methods S1. Supplemental Methods.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

A.N., M.-E.F.M., I.W., E.D., P.N., and A.A.O. performed the research; A.N., M.-E.F.M., I.W., E.D., P.N., A.L.P., and A.A.O. designed the research, analyzed the data, and wrote the manuscript.

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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