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ORIGINAL RESEARCH

Population Pharmacokinetics and Exposure–Response Analyses for Risankizumab in Patients with Active Psoriatic Arthritis

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ABSTRACT

Introduction: Risankizumab is an anti-IL23 monoclonal antibody approved for the treatment of moderate to severe plaque psoriasis and active psoriatic arthritis (PsA). This work characterizes the pharmacokinetics of risankizumab in PsA compared with psoriasis and evaluates the efficacy and safety exposure–response relationships in PsA.

Methods: The population pharmacokinetic analyses included data from 1527 participants that originated from one phase 1 healthy participant study, one phase 2 dose-ranging study in patients with PsA with an open-label extension study, and two pivotal phase 3 studies in patients with PsA, where the clinical regimen of risankizumab 150 mg administered subcutaneously (SC) at weeks 0, 4, and every 12 weeks thereafter was compared with placebo. Pharmacokinetics were analyzed using nonlinear mixed-effects modeling. Simulation analyses using the final model were conducted to evaluate the impact of covariates on exposure. Data from 1407 patients with PsA from the phase 3 studies were included in the exposure–response analyses. Graphical analyses were used to evaluate efficacy and safety exposure–response relationships, and logistic regression was conducted for further assessment of efficacy exposure–response relationships.

Results: Risankizumab pharmacokinetics were well described by a two-compartment model with first-order SC absorption and elimination. None of the evaluated covariates showed clinically relevant impact on exposure. On the basis of the final model, systemic clearance, steady-state volume of distribution, and terminal phase elimination half-life were estimated to be ~ 0.31 L/day, 11.1 L, and 26.3 days, respectively, for a typical 90 kg patient with PsA. Absolute SC bioavailability was estimated to be 83.5%. Exposure–response quartile analyses suggested that exposures associated with the clinical regimen maximized efficacy across the endpoints evaluated. No exposure dependency was observed for key safety endpoints.

Conclusions: Risankizumab exhibited linear and time-independent pharmacokinetics in patients with PsA and was comparable to patients with plaque psoriasis. Efficacy and safety exposure–response analyses support that the clinical regimen achieved robust efficacy

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with a favorable safety profile for patients with active PsA.**Clinical Trials:** NCT02596217, NCT02719171, NCT02986373, NCT03671148, and NCT03675308.
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Keywords: ACR20/50/70; Efficacy; PASI 90/100; Minimal disease activity; Pharmacokinetics; Psoriatic arthritis; Risankizumab

Key Summary Points
Risankizumab exhibited linear pharmacokinetics in patients with active PsA with pharmacokinetic parameters consistent with those observed in plaque psoriasis.
Under the clinical regimen (150 mg SC at weeks 0 and 4, and every 12 weeks thereafter), steady-state systemic concentrations of risankizumab were achieved by approximately week 16.
None of the covariates evaluated in the population pharmacokinetic analyses resulted in a clinically relevant impact on risankizumab exposure.
Exposure–response analyses for efficacy and safety indicated that this clinical regimen for risankizumab achieved robust efficacy responses with no apparent relationship between risankizumab exposure and key safety variables in patients with active PsA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease classified as a subtype of spondylarthritis and is associated with peripheral joint inflammation, enthesitis, dactylitis, and cutaneous manifestations. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, disability, and a reduced quality of life [1, 2]. For most patients, skin manifestations predate the arthritis [1].

Risankizumab (ABBV-066) is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that selectively binds with high affinity to the p19 subunit of the human cytokine interleukin-23 (IL-23) [3]. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23 dependent cell signaling and the release of pro-inflammatory cytokines, and thus has potential to treat immune-mediated inflammatory diseases. Risankizumab is currently approved for the treatment of moderate to severe chronic plaque psoriasis [4] and PsA [5, 6], and is being developed for other inflammatory diseases, including Crohn's disease [7, 8] and ulcerative colitis [8].

Risankizumab pharmacokinetics were well characterized in healthy participants and patients with plaque psoriasis, exhibiting typical IgG1 mAb linear pharmacokinetics with biexponential disposition and a long terminal elimination half-life ($t_{1/2}$) [9, 10]. In plaque psoriasis, none of the covariates identified in the population pharmacokinetic analyses had a clinically meaningful impact on risankizumab efficacy. Efficacy and safety exposure–response analyses in patients with psoriasis using pooled data from phase 1–3 studies supported the approved clinical regimen of risankizumab 150 mg administered subcutaneously (SC) at weeks 0 and 4, and every 12 weeks (q12w) thereafter [9].

Following the initial development and approval in plaque psoriasis, risankizumab was also evaluated in phase 2 and pivotal phase 3 studies in patients with active PsA where risankizumab exhibited superior efficacy versus placebo in key disease outcomes and was well tolerated [5, 6, 11, 12]. Leveraging these data, population pharmacokinetic and exposure–response analyses were conducted for risankizumab in PsA. Results from the analyses reported herein demonstrated that the same clinical regimen (150 mg SC at weeks 0 and 4, and q12w thereafter) as approved in plaque psoriasis is

appropriate for patients with active PsA and supported the approval for PsA.

METHODS

Data Sources

Five clinical studies were utilized in the population pharmacokinetic analyses, namely one phase 1 (NCT02596217 [10], study 1) study in healthy participants, one phase 2 study (NCT02719171 [11], study 2) with an extension study (NCT02986373 [12], study 3), and two pivotal phase 3 studies (NCT03675308/KEEPsAKE 1 [5] and NCT03671148/KEEPsAKE 2 [6], study 4 and study 5, respectively). The latter four studies were all in patients with active PsA. The two phase 3 studies (studies 4 and 5) were utilized in the exposure–response analyses. Safety and efficacy data as well as detailed descriptions of these studies have been reported previously [5, 6]. Brief summaries of these studies with details pertinent to the analyses herein are provided in Supplementary Material (Supplementary Table S1).

All studies 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 ethics committee or institutional review boards at each site, and all participants provided written informed consent prior to any study-related procedures.

Pharmacokinetic Sampling and Analysis

A summary of blood sample collection times for analysis of risankizumab and anti-drug antibody (ADA) concentrations for each study is provided in Supplementary Table S1. Risankizumab plasma or serum concentrations were determined by a validated enzyme linked immunosorbent assay with a lower limit of quantitation (LLOQ) of 5, 10, and 4.34 ng/mL for the phase 1, 2, and 3 studies, respectively [13]. The presence of ADAs to risankizumab was assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate) [14]. All samples positive for ADA were further characterized in a validated neutralizing antibody (NAb) assay [13, 14].

Population Pharmacokinetics Analyses

A population pharmacokinetic model developed using data from healthy participants and patients with moderate to severe chronic plaque psoriasis [10] was leveraged and refined using data from patients with active PsA.

Comparison of Risankizumab Pharmacokinetics in Psoriasis and Psoriatic Arthritis

To demonstrate the appropriateness of leveraging the psoriasis population pharmacokinetic model in PsA, graphical comparisons were carried out as follows:

- The observed risankizumab concentrations in patients with plaque psoriasis treated with the approved clinical regimen of 150 mg SC at weeks 0 and 4, and q12w thereafter (referred to hereafter as “clinical regimen”) in phase 3 psoriasis studies were compared graphically with the observed risankizumab concentrations in patients with active PsA enrolled in phase 2 and 3 studies and treated with the same clinical regimen.
- A simulation-based comparison using the parameter estimates from the previously developed psoriasis model [10] and the patient-specific information in PsA phase 2 and 3 studies was performed through simulations of 1000 replicates of the plasma concentration data for the PsA phase 2 and 3 studies based on the actual dose administered and sampling time. Median and 5th and 95th percentiles of the observed data were compared graphically with the 95% confidence intervals (CIs) of the corresponding percentiles of the simulated data.

Population Pharmacokinetic Model Development for Psoriatic Arthritis

The psoriasis population pharmacokinetic model (described as "starting model" hereafter) was fit to the data. This was a two-compartment model with first-order processes describing SC absorption and elimination, and with risankizumab clearance correlated with weight, baseline serum albumin, baseline serum creatinine, baseline high-sensitivity C-reactive protein (hsCRP), and relatively high ADA titers. Model parameters were estimated using the first-order conditional estimation method with interaction between interindividual variability (IIV) and residual variability [FOCE with η–ε INTERACTION].

For each of the covariate effects included in the starting model, the relationship was retained if the 95% CIs did not overlap with 0 and its removal from the model rendered a statistically significant worsening in the model fit (at $\alpha = 0.001$; similar to the criteria used in the development of the starting model). The resulting "base model" was refined in a stepwise forward inclusion ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$) covariate search [15] as implemented in Perl Speaks NONMEM (PsN Version 4.8.1) to evaluate the statistical significance of other covariates that could be relevant to the PsA population. Covariates tested included: age, sex, race, baseline levels of alanine transaminase, aspartate transaminase, total bilirubin, creatinine clearance, baseline Disease Activity Score in 28 joints (DAS28 score), baseline Health Assessment Questionnaire-Disability Index (HAQ-DI) score, Psoriasis Area Severity Index (PASI) score, duration of disease, presence of axial spondylitis, number of prior biologic therapies, number of prior conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), concomitant use of methotrexate, and immunogenicity. The cutoff value identified in the previous analyses [10] for the ADA effect on risankizumab clearance was adjusted depending on the dilution factor used for the ADA assay in each of the studies.

After establishing the final model structure, the fixed and random effects parameter estimates were updated; goodness-of-fit plots, bootstrap analyses, and visual predictive checks (VPCs) were used to support model evaluation and selection. After identifying statistically significant covariates for risankizumab pharmacokinetic parameters, simulations were carried out for 10,000 virtual subjects, with IIV, without residual error to evaluate their impact on risankizumab steady-state concentration at the end of a dosing interval (C_{trough}) and area under the concentration–time curve over a dosing interval (AUC_{tau}).

Risankizumab exposures [maximum concentration (C_{max}), AUC_{tau}, and C_{trough}] were simulated using the final population pharmacokinetic model for virtual subjects with active PsA who were administered the clinical regimen. Exposures were summarized over the first (weeks 0–4), second (weeks 4–16), and third (weeks 16–28, representing steady-state values) dosing intervals.

Exposure–Response Analyses for Efficacy and Safety

The exposure–response analyses for efficacy evaluated the following endpoints: proportions of patients with PsA achieving American College of Rheumatology (ACR) 20, ACR50, and ACR70 responses at week 24, PASI75 [for patients with ≥ 3% body surface area (BSA) psoriasis at baseline] at week 24, and minimal disease activity (MDA) evaluated at week 24, in the phase 3 studies (studies 4 and 5).

Since pharmacokinetic samples for phase 3 studies were collected predose in week 28 only, post-hoc individual pharmacokinetic parameter estimates were not used to simulate individual exposure predictions for patients enrolled in phase 3 studies because of the limited information available on an individual level. Given that risankizumab reaches steady state by week 16 for the approved clinical regimen [9], observed C_{trough} at week 28 for patients who received risankizumab from the beginning of the phase 3 studies was assumed to be correlated with exposure levels at week 24, and therefore was used to assess relationships with efficacy endpoints evaluated at week 24. The correlation between observed concentrations at week 24 and week 28 for the phase 2 study was evaluated

(correlation coefficient 0.961) to confirm the appropriateness of the assumption. The relationships between efficacy endpoints at week 24 and observed risankizumab C_{trough} at week 28 for phase 3 studies were evaluated graphically using exposure-quartile plots. In these plots, patients who received placebo in period 1 (weeks 0–24) of either phase 3 study were binned together. Patients who received risankizumab were binned into quartiles according to their individual observed exposures, and vertical bars represented the percent of responders for a given efficacy endpoint per quartile for ACR20/50/70, PASI 90/100, and MDA responses.

For each of the efficacy endpoints at week 24, logistic regression models with treatment effect (yes/no) and exposure effect (observed C_{trough} at week 28) were first evaluated and compared after accounting for stratification factors. An exposure and/or a treatment effect were included in the model only if proven to be statistically significant ($\alpha = 0.01$). For patients who received placebo at the beginning of each study, concentrations were assumed to be zero for the exposure–response analyses. The logistic regression models were constructed as follows:

$$\log\left(\frac{P(Y_i = 1)}{1 - P(Y_i = 1)}\right) = \alpha + \beta_{\text{Ctrough}} * C_{\text{trough},i} + \beta_{\text{TRT}} * \text{RZB}_i + \sum_j \left(\beta_j * x_{j,i}\right) \quad (1)$$

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 (reflecting placebo response), β_{Ctrough} is the slope for C_{trough} at week 28, $C_{\text{trough},i}$ is the observed risankizumab concentration in subject i. β_{TRT} is the estimated magnitude of treatment effect, RZB_i is an indicator of receiving risankizumab in subject $_i$ (yes = 1/no = 0). The β_j are the coefficients for prespecified stratifying factors (and potential additional covariates) with respective values $x_{j,i}$ in subject i.

For the phase 3 studies, stratification factors used for randomizations and accounted for in the models included: number of prior biologic therapies (0 versus ≥ 1, study 5), number of csDMARDs (0 versus ≥ 1, studies 4 and 5), psoriasis surface area (PSA; $\geq 3\%$ BSA versus $< 3\%$ BSA, studies 4 and 5) at baseline, presence of dactylitis (yes versus no, study 4), and presence of enthesitis (yes versus no, study 4) at baseline. Only efficacy endpoints exhibiting a statistically significant exposure (C_{trough}) effect (p value < 0.01 for β_{Ctrough}) were evaluated further for identification of additional covariates. If a statistically significant exposure effect was observed for an endpoint, the potential effect of the demographic covariates of body weight, age, sex, and race was tested as well as the disease covariates of extent of disease at baseline (DAS28 and PASI), duration of PsA, with or without axial spondylitis at baseline and concomitant use of methotrexate.

Exposure–response analyses for safety evaluated the following safety variables graphically: any adverse event (AE), any serious AE (SAE), any infection, and any serious infection. Proportions of patients who experienced these safety events across period 1 (weeks 0–24) of phase 3 studies were determined among patients who received placebo and in each observed risankizumab exposure quartile at week 28.

Software

The population pharmacokinetic model was developed using nonlinear mixed-effects modeling based on NONMEM (Version 7.4.4) compiled with the GNU Fortran compiler (Version 7.5.5). R (Version 3.6.3) was used for the exposure–response analyses.

RESULTS

Data

Data from patients with active PsA ($N = 1460$) and healthy participants ($N = 67$) who received risankizumab and had at least one post-treatment measurable concentration were included in the population pharmacokinetic analyses.

Data from patients with active PsA enrolled in phase 3 studies [study 4 (N = 964) and study 5 (N = 443)], who received placebo or at least one dose of risankizumab, were included in the efficacy and safety exposure–response analyses. Summaries of demographic variables and other intrinsic factors are presented in Supplementary Table S2.

In total, 3875 risankizumab plasma concentration measurements from 1546 individuals were acquired across all studies. Data from 19 individuals were excluded owing to the lack of a valid dose or concentration record, and 214 measurements were made prior to the first risankizumab dose. Out of the remaining 3642 measurements, 11 (0.3%) measurements were below the LLOQ, which were also excluded (resulting in exclusion of no additional individual's data), leaving a total of 3631 concentration measurements from 1527 individuals included in the analyses. The total number of individuals included in the dataset for studies 1, 2/3, 4, and 5 are 67, 177, 391, and 892, respectively, yielding 683, 1663, 391, and 894 pharmacokinetic observations, respectively.

Population Pharmacokinetic Analyses

Comparison of Risankizumab Pharmacokinetics in Psoriasis and Psoriatic Arthritis to Support the Use of the Psoriasis Population Pharmacokinetic Model

The similarity of risankizumab exposure levels between psoriasis and PsA patient populations was demonstrated by graphical comparison of the observed concentrations at week 28 (Fig. 1a) for the clinical regimen. Simulation-based comparisons (Fig. 1b and c) showed that the model based on patients with psoriasis adequately captured the observed data in patients with PsA. On the basis of these graphical comparisons, the previously developed psoriasis population pharmacokinetic model [10] was deemed appropriate for characterizing risankizumab pharmacokinetics in PsA.

Model Refinement Using Psoriatic Arthritis Data

The psoriasis population pharmacokinetic model was fit to the data from four phase 2 and 3 studies in patients with active PsA and one phase 1 study in healthy participants. Relationships for the effect of high ADA titers on clearance (CL) and weight on peripheral volume of distribution (V_2) did not meet the criteria for retaining the covariates (described above in Population Pharmacokinetic Model Development for Psoriatic Arthritis) and was therefore removed. A single estimate for bioavailability was made [10], and the term for IIV on bioavailability was removed. This model served as a base model for the covariate search (retaining the effects of body weight on CL and central volume of distribution [V_1], the effects of baseline serum creatinine, baseline serum albumin, and hsCRP on CL). The forward-inclusion backward-elimination covariate search identified only age as an additional statistically significant covariate on CL. The covariate–parameter relationships for CL and V_1 using the final model are shown in Eqs. (2) and (3), respectively.

$$\mathrm{CL} = 0.248 * \left(\frac{\mathrm{WTKG}}{70}\right)^{0.869} * \left(\frac{\mathrm{ALB}}{45}\right)^{-0.703} * \left(\frac{\mathrm{CRE}}{70.73}\right)^{-0.201} * \left(\frac{\mathrm{CRPHS}}{5.21}\right)^{0.0471} * \left(\frac{\mathrm{AGE}}{52}\right)^{-0.138} \quad (2)$$

$$V_1 = 4.71 * \left(\frac{\mathrm{WTKG}}{70}\right)^{1.46} \quad (3)$$

The effect of ADA on CL [evaluated as time invariant flag (yes/no), time variant flag (yes/no)], and NAb on CL [evaluated as time invariant flag (yes/no), time variant flag (yes/no)] were found not to be statistically significant. Furthermore, similar exposure levels at week 28 concentrations across patients and participants grouped by their ADA titer levels using different ADA titer thresholds confirmed the lack of an apparent relationship between ADA titers and CL (data on file at AbbVie).

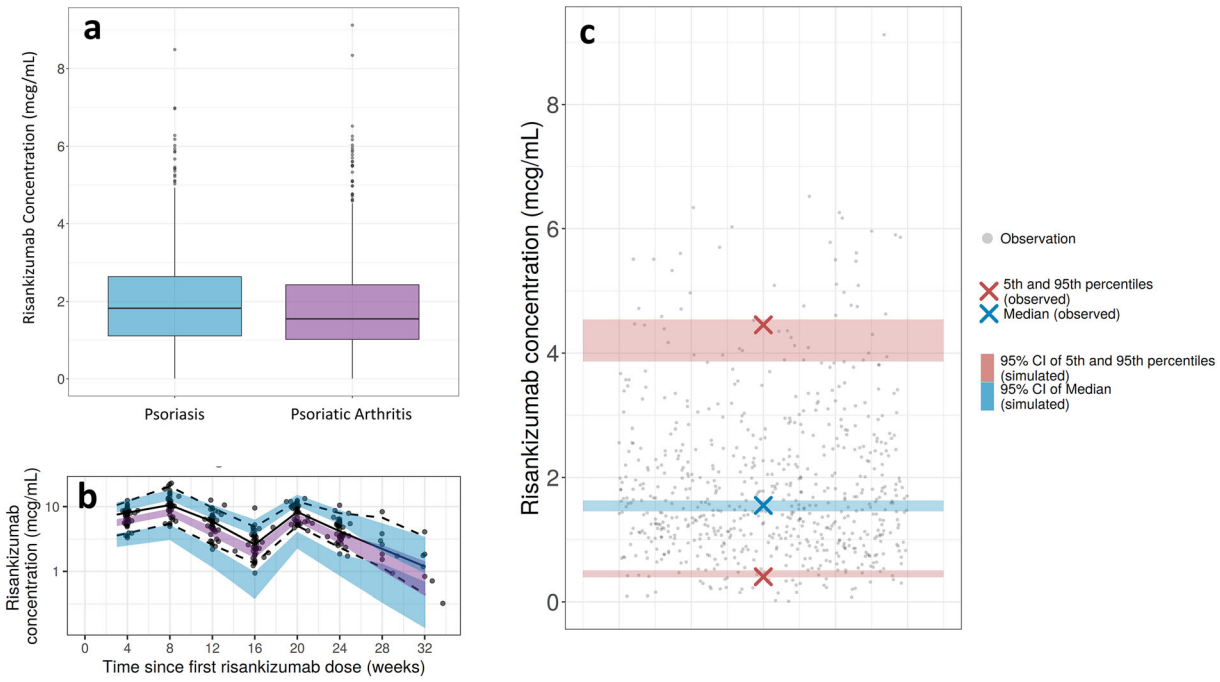

Fig. 1 Comparison of risankizumab pharmacokinetics in psoriasis and psoriatic arthritis to support the use of the psoriasis population pharmacokinetic model. Graphical comparisons of risankizumab exposure levels for psoriasis and PsA patient populations on the clinical regimen of 150 mg SC at weeks 0, 4, and q12w thereafter are shown for **a** week 28 predose observed risankizumab concentrations in patients with PsA and psoriasis, **b** simulated risankizumab concentrations as a function of time since first dose using psoriasis population pharmacokinetic model and observed concentration in patients with PsA in the phase 2 study, and **c** simulated and observed risankizumab predose concentrations at week 28 in the phase 3 studies. The shaded regions show the 95% CIs around median and 5th and 95th percentiles of simulated risankizumab concentrations. The gray dots denote the observed risankizumab concentration in the PsA studies, and the lines/dashed lines in (**b**) and the crosses in (**c**) show the median and 5th and 95th percentile of the observed risankizumab concentration in the PsA studies. PsA, psoriatic arthritis; SC, subcutaneous; q12w, every 12 weeks

The estimated pharmacokinetic parameter values and their associated variability for the final pharmacokinetic model are listed in Table 1. The computed η-shrinkages for CL, V_1, and k_a were 16.0%, 46.7%, and 79.2%, respectively. Bootstrap analyses confirmed robustness of model, with 998 out of 1000 runs converging successfully with all parameters in good agreement with the final model parameters and relatively narrow 95% CIs. On the basis of the final population pharmacokinetic model, risankizumab systemic CL, V_1, V_2, volume of distribution at steady state (V_{ss}), and $t_{1/2}$ were estimated to be approximately 0.31L per day, 6.8 L, 4.3 L, 11.1 L, and 26.3 days, respectively, for a typical 90 kg patient with PsA. Risankizumab absolute SC bioavailability (pooling drug substances utilized in earlier and later stages of development [10]) was estimated to be 83.5%.

Model Evaluations and Simulations

The goodness-of-fit for the final model, based on data from the phase 2 and 3 studies, was evaluated graphically and is shown in Supplementary Fig. S1. The plots of the population predicted and individual predicted concentrations versus the observed concentrations indicated that the model adequately described the data over the entire range of risankizumab systemic concentrations. The conditional weighted residuals did not show any trends when plotted against time or population predictions, indicating lack of bias in the model. VPCs for

Table 1 Fixed and random effects parameter estimates for final psoriatic arthritis risankizumab population pharmacokinetic model

	Population estimate	%RSE[a]	95% CI
Clearance (CL; L/day)	0.248	6.2	0.218, 0.278
Central volume of distribution (V_1; L)	4.71	12.7	3.54, 5.88
Intercompartmental clearance (Q; L/day)	0.839	8.2	0.705, 0.973
Peripheral volume of distribution (V_2; L)	4.26	5.9	3.77, 4.75
Absorption rate constant (k_a; /Day)	0.218	10.4	0.174, 0.262
Absolute SC bioavailability (F)	0.835	6.3	0.732, 0.938
Exponent for the effect of body weight on risankizumab clearance (CL)	0.869	5.1	0.781, 0.957
Exponent for the effect of body weight on risankizumab central volume of distribution (V_1)	1.46	9.7	1.18, 1.74
Exponent for the effect of serum albumin on risankizumab clearance (CL)	−0.703	17.2	−0.940, −0.466
Exponent for the effect of serum creatinine on risankizumab clearance (CL)	−0.201	18.3	−0.273, −0.129
Exponent for the effect of c-reactive protein on risankizumab clearance (CL)	0.0471	12.9	0.0352, 0.0590
Age on risankizumab clearance (CL)	−0.138	21.2	−0.195, −0.0808
Variance of IIV on CL, %CV[b]	0.0943, 31.4	5.8	0.0835, 0.105
Variance of IIV on V_1, %CV[b]	0.171, 43.2	18.9	0.107, 0.235
Variance of IIV on k_a, %CV[b]	0.164, 42.2	29.3	0.0699, 0.258
Covariance between IIV on CL and V_1, %correlation[c]	0.0836, 65.8	12.0	0.0640, 0.103
Variance of proportional residual error	0.0382	1.4	0.0372, 0.0392

CI, confidence interval; IIV, interindividual variability; RSE, relative standard error; SC, subcutaneous

[a]% Relative standard error (%RSE) was estimated as the standard error of the estimate divided by the population estimate multiplied by 100

[b]$\%CV = SQRT[\exp(\omega 2)-1] \times 100$

[c]$\%correlation = 100^{*}(\omega_{CL,V1}/(\omega_{CL} \times \omega_{V1}))$

the risankizumab systemic concentration showed that the model described the central tendency and variability in the observed data adequately for different single and multiple dose regimens in phase 2 and 3 studies (for regimens, see Supplementary Table S1). VPCs for the clinical regimen for phase 2 and 3 studies are shown in Supplementary Fig. S2.

On the basis of the simulations, the impact of covariates included in the final model on risankizumab model-predicted, steady-state C_{trough} and AUC_{tau} (weeks 16–28 dosing interval) for the clinical regimen is depicted in Fig. 2.

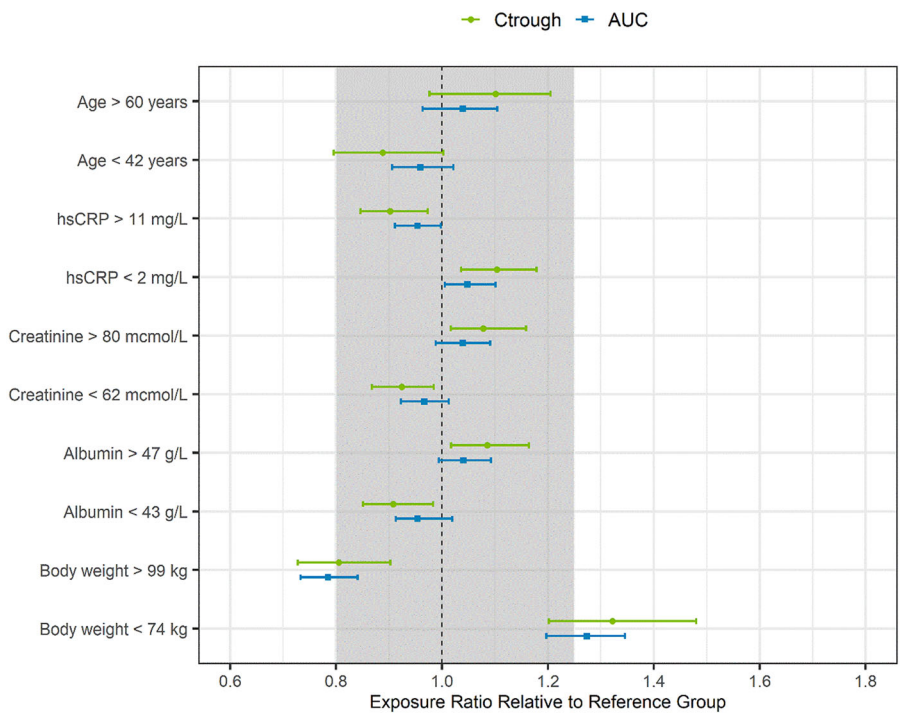

Fig. 2 Simulated impact of statistically significant covariates identified in the population pharmacokinetic analyses on risankizumab exposures for patients with psoriatic arthritis. Points represent medians and error bars represent 95% confidence intervals of the normalized exposure ratios across 200 simulation replicates. The vertical black dashed line shows exposure ratio of 1 relative to the reference group, and the shaded area represents the 0.8–1.25 default equivalence boundaries. AUC, area under the concentration–time curve between weeks 16 and 28 (AUC_{tau}); C_{trough}, concentration after a dosing interval at week 28; hsCRP, high-sensitivity C-reactive protein

Body weight was found to have a modest impact on risankizumab exposure. Patients with PsA with relatively high body weight (> 75th percentile; 99 kg) and low body weight (< 25th percentile; 74 kg) were predicted to have ~ 20% lower and 30% higher exposures, respectively, compared with the reference group (74–99 kg). However, these modest exposure differences were not deemed clinically meaningful on the basis of the lack of exposure–response relationships for safety and efficacy over the exposure range associated with the clinical dosing regimen (see Discussion section). None of the other statistically significant covariates showed a meaningful impact on risankizumab exposures (Fig. 2). Simulated risankizumab exposures following administration of the clinical regimen in a virtual population are summarized in Table 2.

Exposure–Response Analyses for Efficacy

ACR

Exposure–response quartile plots for ACR20/50/70 responses at week 24 for the phase 3 studies are shown in Fig. 3a–c. For all ACR response endpoints, patients treated with risankizumab showed higher response rates compared with placebo at week 24. The upper exposure quartiles consistently showed numerically higher response rates compared with the lower exposure quartiles across all ACR response endpoints, including ACR20 (the primary endpoint for the pivotal phase 3 studies).

Logistic regression analyses that accounted for study stratification factors for ACR20/50/70 at week 24 revealed a statistically significant treatment effect ($p < 0.01$), but no statistically significant exposure–response relationship. Parameter estimates are provided in Table 3. Of

Table 2 Model-simulated risankizumab exposures at selected dosing intervals using the final population pharmacokinetic model

Exposure	First dosing interval (weeks 0–4)	Second dosing interval (weeks 4–16)	Third dosing interval (weeks 16–28)
C_{max} (μg/mL)			
Mean (SD)	9.63 (3.05)	14.7 (5.02)	11.6 (4.36)
Median	9.40	14.1	11.0
2.5th, 97.5th percentile	4.50, 16.2	6.60, 25.9	5.00, 21.8
C_{trough} (μg/mL)			
Mean (SD)	5.95 (2.09)	2.32 (1.55)	1.88 (1.34)
Median	5.68	1.93	1.52
2.5th, 97.5th percentile	2.66, 10.7	0.530, 6.44	0.420, 5.44
AUC_{tau} (μg·day/mL)			
Mean (SD)	215 (69.9)	608 (252)	482 (218)
Median	207	565	439
2.5th, 97.5th percentile	98.9, 368	244, 1218	186, 1031

Simulation was performed for the risankizumab clinical regimen of 150 mg subcutaneous injection at weeks 0 and 4, and every 12 weeks thereafter

AUC_{tau}, area under the concentration–time curve over a dosing interval; C_{max}, maximum concentration; C_{trough}, concentration at the end of the dosing interval; SD, standard deviation

the stratification factors, patients with no prior biologic treatment showed higher probability of achieving ACR20 and ACR50 at week 24, whereas patients with PSA of < 3% of their BSA at baseline had lower probability of achieving ACR20 and ACR50 responses at week 24.

PASI

The PASI 90/100 responses were evaluated only for patients with PSA ≥ 3% of BSA at baseline. Exposure–response quartile plots for PASI 90/100 responses at week 24 are presented in Fig. 3d, e. Similar to ACR responses, patients treated with risankizumab showed higher response rates for PASI 90/100 at week 24 compared with patients treated with placebo. For PASI 90, all exposure quartiles showed a similar response rate, whereas for PASI 100 the upper two quartiles showed numerically higher response rates as compared with the lower exposure quartiles. Like ACR responses, logistic regression analyses with models that accounted for study stratification factors for PASI 90/100 at week 24 identified a statistically significant treatment effect for risankizumab, but no statistically significant exposure–response relationships. Consistent with the ACR responses, these data indicate that the selected clinical regimen evaluated in phase 3 provided robust efficacy across the exposure range as assessed by the PASI 90/PASI 100 responses at week 24.

MDA

Exposure–response quartile plots exploring the impact of observed risankizumab exposure at week 28 on MDA response at week 24 (Fig. 3f) showed numerically higher response rates with increasing risankizumab exposure. Logistic regression analyses with a treatment effect model that accounted for stratification factors revealed risankizumab treatment effect to be significant (Table 3). Risankizumab exposure did not have a statistically significant influence on MDA response at week 24. Of the stratification factors, patients with no enthesitis at baseline showed lower probability of achieving MDA response at week 24.

Exposure–Response Analyses for Safety

The relationships between observed week 28 risankizumab C_{trough} (from studies 4 and 5) and percentage of patients who experienced any AE, SAE, infection, or serious infection over the first 24 weeks (placebo-controlled period) are shown in Fig. 4. Rates of incidence of the safety

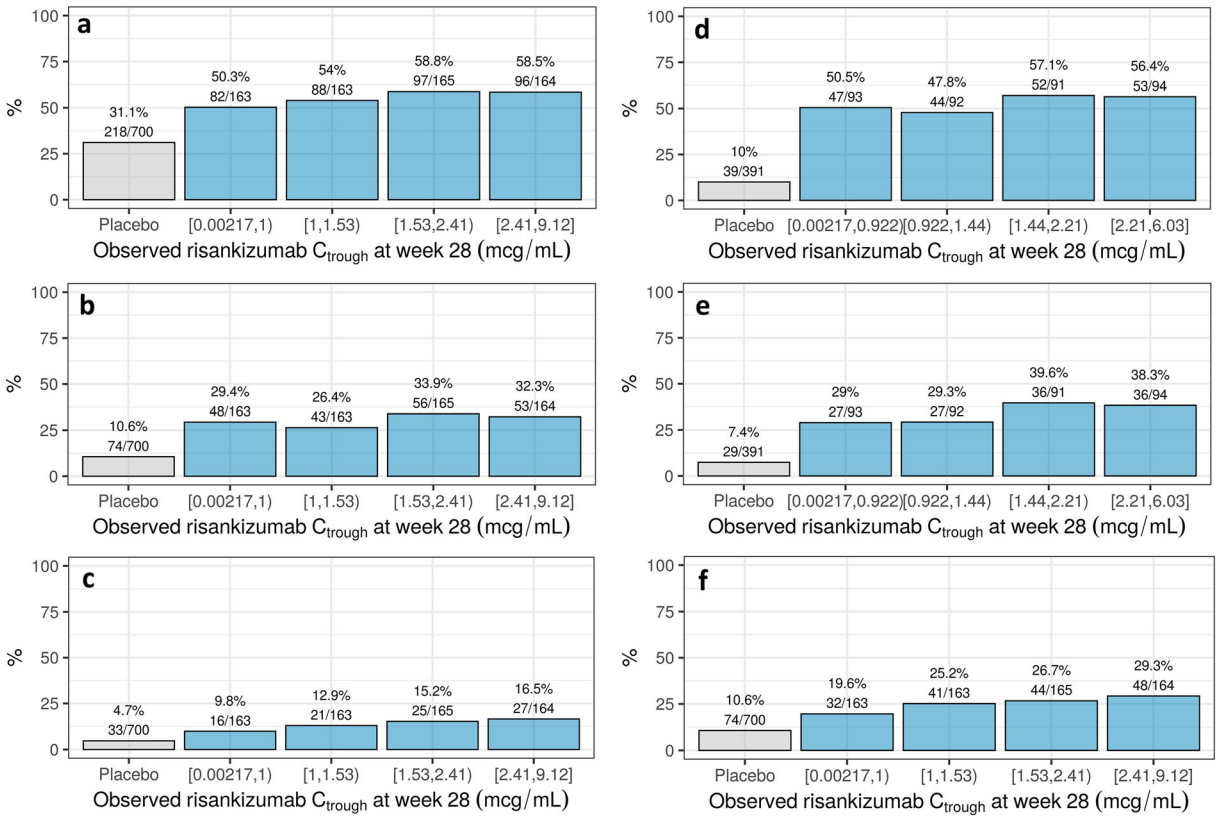

Fig. 3 Exposure–response relationships for efficacy endpoints at week 24 from phase 3 studies. Values on the *x*-axis represent range of the observed phase 3 risankizumab C_{trough} at week 28 for each quartile. Plots show %response (using nonresponder imputation) and *n*/*N*, where *n* represents number of responders and *N* represents total number of patients in each exposure-quartile bin. For ACR, PASI, and MDA analyses (at week 24), 52, 26, and 52 patients (*N*), respectively, from phase 3 studies were excluded from these analyses owing to missing C_{trough} values at week 28. Of these 52 patients for ACR, 28 (53.8%), 19 (36.5%), and 9 (17.3%) were ACR20 (**a**), ACR50 (**b**), and ACR70 (**c**) responders, respectively. Of the 26 patients for the PASI endpoint, 11 (42.3%) and 9 (34.6%) were PASI 90 (**d**) and PASI 100 (**e**) responders, respectively. Of these 52 patients for the MDA endpoint, 14 (26.9%) were MDA (**f**) responders at week 24. ACR20/50/70, at least 20%/50%/70% improvement in American College of Rheumatology response criteria; C_{trough}, concentration at the end of a dosing interval; PASI 90/100, at least 90%/100% improvement in Psoriasis Area and Severity Index relative to baseline; MDA, minimal disease activity

variables of interest over the first 24 weeks evaluated were comparable to placebo, with no apparent relationship with risankizumab exposure over the entire exposure range observed with the clinical regimen.

DISCUSSION

The analyses presented herein report the first assessment of risankizumab pharmacokinetics and exposure–response relationships in patients with active PsA. Results showed similarity in risankizumab pharmacokinetics between patients with plaque psoriasis and those with PsA. Furthermore, the same clinical regimen approved in chronic plaque psoriasis (150 mg SC at weeks 0 and 4, and q12w thereafter) provided robust efficacy across the different clinical endpoints in PsA with no exposure-dependent increase in safety risks for AE, SAE, infection, or serious infection when compared with placebo.

Risankizumab pharmacokinetics has been well characterized in healthy participants and

Table 3 Logistic regression model parameters for all efficacy endpoints at week 24 with C_{trough} at week 28 as exposure metric

Efficacy endpoint	AIC	Variable	Estimate (SEE)	95% CI	*P*-value
ACR20	1748	Intercept	−0.151 (0.236)	−0.613 to 0.311	> 0.05
		Exposure	0.094 (0.065)	−0.033 to 0.221	> 0.05
		Placebo	−0.866 (0.165)	−1.189 to −0.543	< 0.01
		Number of prior csDMARDs = 0	−0.428 (0.478)	−1.364 to 0.508	> 0.05
		Number of prior biologic therapies = 0	0.610 (0.176)	0.265 to 0.955	< 0.01
		Psoriasis surface area < 3% BSA	−0.460 (0.117)	−0.689 to −0.230	< 0.01
		Presence of enthesitis at baseline = yes	−0.178 (0.132)	−0.436 to 0.081	> 0.05
		Presence of dactylitis at baseline = yes	0.082 (0.129)	−0.171 to 0.336	> 0.05
ACR50	1262	Intercept	−1.336 (0.300)	−1.923 to −0.748	< 0.01
		Exposure	0.071 (0.069)	−0.066 to 0.207	> 0.05
		Placebo	−1.214 (0.199)	−1.604 to −0.825	< 0.01
		Number of prior csDMARDs = 0	0.340 (0.553)	−0.743 to 1.423	> 0.05
		Number of prior biologic therapies = 0	0.713 (0.243)	0.237 to 1.190	< 0.01
		Psoriasis surface area < 3% BSA	−0.603 (0.149)	−0.895 to −0.311	< 0.01
		Presence of enthesitis at baseline = yes	−0.094 (0.161)	−0.409 to 0.222	> 0.05
		Presence of dactylitis at baseline = yes	0.252 (0.156)	−0.053 to 0.558	> 0.05
ACR70	783	Intercept	−2.625 (0.434)	−3.474 to −1.775	< 0.01
		Exposure	0.153 (0.088)	−0.021 to 0.326	> 0.05
		Placebo	−0.886 (0.276)	−1.427 to −0.346	< 0.01
		Number of prior csDMARDs = 0	0.273 (0.793)	−1.281 to 1.827	> 0.05
		Number of prior biologic therapies = 0	0.718 (0.358)	0.016 to 1.420	< 0.05
		Psoriasis surface area < 3% BSA	−0.516 (0.207)	−0.921 to −0.111	< 0.05
		Presence of enthesitis at baseline = yes	−0.122 (0.219)	−0.551 to 0.306	> 0.05
		Presence of dactylitis at baseline = yes	0.452 (0.205)	0.049 to 0.854	< 0.05
MDA	1208	Intercept	−1.047 (0.287)	−1.609 to −0.484	< 0.01
		Exposure	0.128 (0.070)	−0.009 to 0.265	> 0.05
		Placebo	−0.815 (0.204)	−1.215 to −0.414	< 0.01
		Number of prior csDMARDs = 0	−0.835 (0.763)	−2.332 to 0.661	> 0.05
		Number of prior biologic therapies = 0	0.232 (0.228)	−0.215 to 0.678	> 0.05
		Psoriasis surface area < 3% BSA	−0.150 (0.150)	−0.443 to 0.144	> 0.05
		Presence of enthesitis at baseline = yes	−0.519 (0.158)	−0.829 to −0.208	< 0.01
		Presence of dactylitis at baseline = yes	−0.130 (0.170)	−0.463 to 0.202	> 0.05

Table 3 continued

Efficacy endpoint	AIC	Variable	Estimate (SEE)	95% CI	*P*-value
PASI 90	776	Intercept	−0.045 (0.332)	−0.696 to 0.606	> 0.05
		Exposure	0.145 (0.093)	−0.038 to 0.329	> 0.05
		Placebo	−2.069 (0.254)	−2.568 to −1.570	< 0.01
		Number of prior csDMARDs = 0	0.282 (0.585)	−0.864 to 1.428	> 0.05
		Number of prior biologic therapies = 0	−0.042 (0.264)	−0.559 to 0.475	> 0.05
		Presence of enthesitis at baseline = yes	−0.088 (0.199)	−0.479 to 0.302	> 0.05
		Presence of dactylitis at baseline = yes	0.023 (0.197)	−0.363 to 0.409	> 0.05
PASI 100	691	Intercept	−1.068 (0.362)	−1.778 to −0.359	< 0.01
		Exposure	0.175 (0.094)	−0.009 to 0.360	> 0.05
		Placebo	−1.560 (0.279)	−2.107 to −1.013	< 0.01
		Number of prior csDMARDs = 0	−0.342 (0.693)	−1.701 to 1.017	> 0.05
		Number of prior biologic therapies = 0	0.057 (0.289)	−0.509 to 0.623	> 0.05
		Presence of enthesitis at baseline = yes	0.062 (0.216)	−0.362 to 0.486	> 0.05
		Presence of dactylitis at baseline = yes	0.051 (0.211)	−0.363 to 0.464	> 0.05

Note: All models were treatment effect models and converged successfully

ACR20/50/70, at least 20%/50%/70% improvement in American College of Rheumatology response criteria; C_{trough}, concentration at the end of a dosing interval; AIC, Akaike Information Criterion; BSA, bovine serum albumin; CI, confidence interval; csDMARDS; conventional synthetic disease-modifying antirheumatic drugs; PASI 90/100, at least 90%/100% improvement in Psoriasis Area and Severity Index relative to Baseline; MDA, minimal disease activity; SEE, standard error of estimate

patients with psoriasis [9, 10]. On the basis of the similarities between psoriasis and PsA, the population pharmacokinetic model previously developed for psoriasis [10] was refined and fit to data from patients with active PsA. This was supported by comparable risankizumab concentrations observed following the same dosing regimen (150 mg SC at weeks 0 and 4, and q12w thereafter) in both populations as well as the model simulation comparisons. The final population pharmacokinetic model in PsA is a two-compartment model with first-order SC absorption and first-order elimination. The parameters of the model were estimated with high precision (relative standard error ranging from approximately 5.1% to 29.3%). Model evaluation using goodness-of-fit plots, VPCs, and bootstrap analyses indicated that the model adequately described risankizumab pharmacokinetics. Parameter estimates in the PsA model were consistent with the original plaque psoriasis model [10], further confirming the comparability across both patient populations. Similar to patients with plaque psoriasis [10], risankizumab steady-state systemic concentrations were achieved by approximately week 16 in patients with active PsA following the administration of the same clinical regimen. The predicted mean steady-state (at the end of the third dosing interval, weeks 16–28) C_{max} and C_{trough} were 11.6 μg/mL and 1.88 μg/mL, respectively, also consistent with psoriasis patient findings [9].

Covariate analyses demonstrated that baseline albumin, baseline hsCRP, baseline serum creatinine, and age were statistically correlated with risankizumab CL in patients with PsA. However, none of these covariates had a

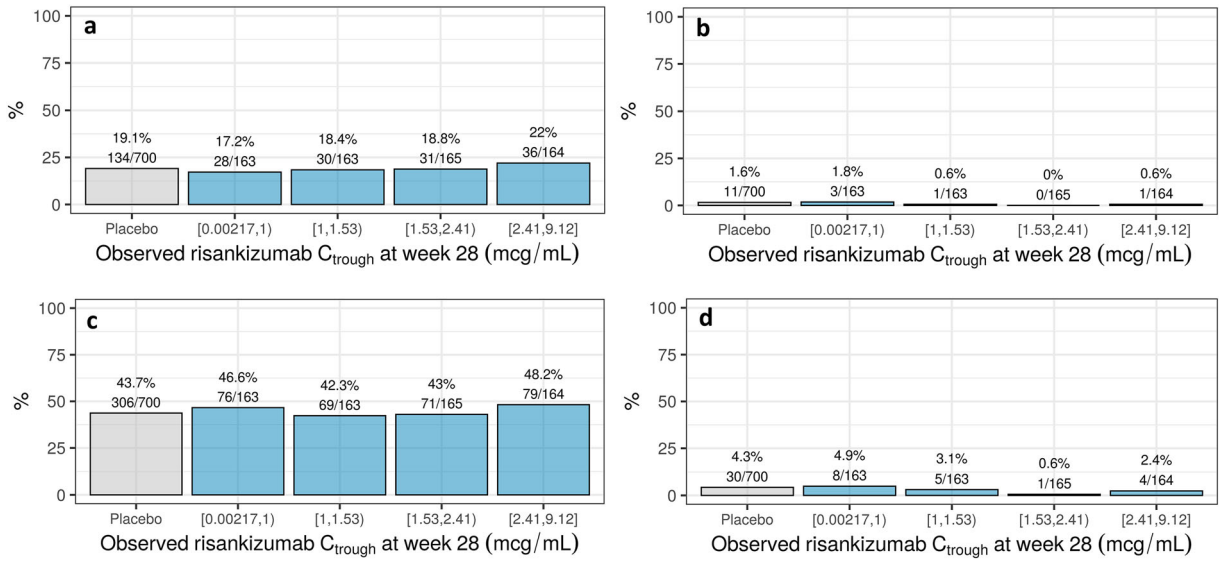

Fig. 4 Exposure–response quartile analyses for safety events of interest over weeks 0–24 in phase 3 studies. Values on the *x*-axis represent range of the observed phase 3 studies risankizumab C_{trough} at week 28 for each quartile. Plots show %response (using nonresponder imputation) and *n*/*N*, where *n* represents number of responders and *N* represents total number of patients in each exposure-quartile bin. In this analysis, 52 patients (*N*) from the phase 3 studies who had missing C_{trough} at week 28 were excluded. Of these 52 patients, 9 (17.3%), 2 (3.8%), 24 (46.2%), and 3 (5.8%) had **a** infections, **b** serious infections, **c** adverse events, and **d** serious adverse events, respectively, by week 24. C_{trough}, concentration at the end of a dosing interval

clinically meaningful impact over the range of covariate values observed in patients with PsA. Similar to other IgG1 mAbs and consistent with the psoriasis pharmacokinetic model [10], body weight was statistically correlated with risankizumab CL. Despite the modest differences in exposures across the body weight range, exposure–response analyses for all efficacy endpoints evaluated have shown the absence of a statistically significant effect of exposure. The incidences of safety events were similar across the entire range of risankizumab exposure and comparable to patients treated with placebo. Therefore, the modest differences in exposures because of differences in body weight were deemed clinically irrelevant. Other intrinsic factors, including sex, race, liver function markers (total bilirubin, alanine transaminase, and aspartate transaminase), did not impact risankizumab exposures. PsA disease-related characteristics, including presence of axial spondylitis, baseline DAS28 score, baseline PASI score, duration of disease, prior use of biologic therapy (0 versus ≥ 1), prior use of csDMARDs (≤ 1 versus > 1), and use of methotrexate (yes/no), had no impact on risankizumab pharmacokinetics. Treatment-emergent anti-risankizumab antibodies [evaluated either as a flag (positive/negative) or as a titer], showed no statistically significant effects on risankizumab CL. None of the patients in the phase 3 studies had NAbs [9, 10].

As is often the case for late-stage patient trials, the pharmacokinetic data in the two pivotal phase 3 PsA studies were limited to the predose samples collected at week 28 to accommodate for immunogenicity sample collections at the trough timepoint. The collection time at week 28 for pharmacokinetics is different from that for the primary endpoints at week 24. Additionally, the limited amount of pharmacokinetic data made it challenging to use the population pharmacokinetic model to simulate individual exposures. Nevertheless, because risankizumab is known to reach steady state by week 16 and exposures at week 24 and week 28 in patients recruited in the phase 2 PsA study were found to be highly correlated, observed

C_{trough} at week 28, instead of model-simulated individual exposure predictions, were used to investigate exposure–efficacy relationships for endpoints evaluated at week 24.

Exposure–response analyses of risankizumab efficacy endpoints at week 24 were carried out using data from the two phase 3 studies in patients with active PsA. Since the primary efficacy endpoints during the double-blind treatment period in the phase 2 study were evaluated up to week 16, data from this study were not included in the analyses. With the phase 3 data, exposure–response analyses consistently showed that the clinical regimen provided robust efficacy across the entire exposure range compared with placebo for all endpoints evaluated at week 24. Exposure–response quartile analyses showed that patients with relatively lower risankizumab exposures had numerically lower response rates compared with higher exposures observed for the efficacy endpoints at week 24. This suggests that further lowering exposures at doses less than 150 mg might cause lower efficacy response rates for these endpoints.

Logistic regression analyses at week 24 demonstrated that patients treated with risankizumab showed statistically significant higher response rates compared with placebo for all evaluated endpoints. After accounting for a treatment effect, risankizumab systemic exposures showed no statistically significant exposure–response relationships for all endpoints within the range of exposures evaluated in phase 3 studies. This indicates that further increasing exposures at doses greater than 150 mg is unlikely to provide additional efficacy. Analyses of the key safety variables of interest indicated no apparent relationship between risankizumab exposure and any AE, SAE, infection, or serious infection over the first 24 weeks in the phase 3 studies of risankizumab in patients with active PsA.

CONCLUSIONS

Risankizumab exhibited linear pharmacokinetics in patients with active PsA that was consistent with pharmacokinetics observed in patients with plaque psoriasis. None of the covariates evaluated were found to have a clinically meaningful impact on risankizumab exposures. The exposure–response for efficacy and safety analyses indicates that the clinical regimen of risankizumab (150 mg SC at weeks 0 and 4, and q12w thereafter) achieved robust efficacy responses with no apparent relationship between risankizumab exposure and key safety variables in patients with active PsA.

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Compliance with Ethics Guidelines. The studies reported herein were conducted in accordance with the International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical

study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Approval was granted by institutional review boards and independent ethics committees at participating institutions. All participants provided written consent prior to participation or study-related procedures. All individual participants signed informed consent regarding publishing their data.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis datasets), 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. 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 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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