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ARTICLE

Population pharmacokinetics and exposure-response modeling analyses of guselkumab in patients with psoriatic arthritis

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Abstract

Guselkumab is an anti-interleukin-23 human monoclonal antibody effective in treating psoriatic arthritis (PsA). To characterize the pharmacokinetics (PKs) and exposure-response relationship of guselkumab in PsA, population PKs, and exposure-response modeling, analyses were conducted using data from pivotal phase III studies of subcutaneous guselkumab in patients with PsA. The observed serum concentration-time data of guselkumab were adequately described by a one-compartment linear PK model with first-order absorption and elimination. Covariates identified as contributing to the observed guselkumab PK variability were body weight and diabetes comorbidity; however, the magnitude of the effects of these covariates was not considered clinically relevant, and dose adjustment was not warranted for the patient population investigated. Positive exposure-response relationships were demonstrated with landmark and longitudinal exposure-response analyses between guselkumab exposure and clinical efficacy end points (American College of Rheumatology [ACR] 20%, 50%, and 70% improvement criteria and Investigator's Global Assessment [IGA] of psoriasis) at weeks 20 and/or 24, with no clinically relevant differences observed in improvement of PsA signs and symptoms between the two guselkumab treatment regimens evaluated (100 mg every 4 weeks or 100 mg at weeks 0 and 4, then every 8 weeks). Baseline Disease Activity Score in 28 joints (DAS28), Psoriasis Area and Severity Index (PASI) score, and/or C-reactive protein level were identified as influencing covariates on guselkumab exposure-response model parameters. These results provide a comprehensive evaluation of subcutaneous guselkumab PKs and exposure-response relationship that supports the dose regimen of 100 mg at weeks 0 and 4, then every 8 weeks in patients with PsA.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Guselkumab, an IL-23 antagonist, is approved for use in adults with psoriasis or psoriatic arthritis (PsA). Subcutaneous guselkumab concentration data in patients with psoriasis are adequately described by a one-compartment linear pharmacokinetic (PK) model with first-order absorption and elimination, and systemic exposure is associated with clinical measures of treatment response in these patients.

WHAT QUESTION DID THIS STUDY ADDRESS?

These analyses aimed to describe subcutaneous guselkumab PKs in adults with PsA based on data from two phase III studies, quantify the effects of intrinsic or extrinsic factors that may contribute significantly to PK variability, characterize the relationships between guselkumab exposure and clinical efficacy measures in adults with PsA, and evaluate the impact of covariates on clinical efficacy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This is the first report of population PK and exposure-response analyses of guselkumab in patients with PsA. The observed guselkumab concentration-time data were adequately described by a one-compartment linear population PK model with first-order absorption and elimination. The major model parameters were consistent with those previously reported for guselkumab in patients with psoriasis. As in patients with psoriasis, the covariates identified as significantly contributing to guselkumab PK variability were body weight and diabetes comorbidity, with similar effects, which were not considered clinically relevant. Subcutaneous guselkumab 100 mg every 4 or 8 weeks resulted in similar improvements in the signs and symptoms of PsA, with no dose adjustment warranted for any of the subgroups identified in the covariate analyses.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These results were used to support the approval of guselkumab for use in adults with PsA and inform the product label.

INTRODUCTION

Interleukin-23 (IL-23) is critical in driving chronic inflammation associated with psoriatic arthritis (PsA).[1–4] Guselkumab, a fully human immunoglobulin G1 λ monoclonal antibody that binds to the p19 protein subunit of human IL-23, is approved for the treatment of adults with PsA or psoriasis. The results of population pharmacokinetic (PK) and exposure-response modeling analyses of guselkumab in patients with psoriasis have been previously reported.[5] This paper describes the results of population PK and exposure-response modeling analyses using data from two phase III studies of subcutaneous (s.c.) guselkumab in adults with active PsA (DISCOVER-1 and DISCOVER-2).[6,7] The objectives of these analyses were to describe the PKs of subcutaneous guselkumab in adults with active PsA and quantify the effects of intrinsic or extrinsic factors that may contribute significantly to the PK variability of s.c. guselkumab, and characterize the relationships between guselkumab exposure and clinical efficacy measures in adults with active PsA following treatment with s.c. guselkumab and evaluate the impact of covariates on clinical efficacy.

METHODS

Pooled data from pivotal phase III guselkumab studies in patients with active PsA (DISCOVER-1 [NCT03162796] and DISCOVER-2 [NCT03158285]) were used for population PK analysis and exposure-response modeling analyses.[6,7] Both were randomized, double-blind, placebo-controlled, multicenter studies in patients with active PsA randomized (1:1:1) to s.c. guselkumab 100 mg every 4 weeks (q4w) or at weeks 0 and 4, then every 8 weeks (q8w) or s.c. placebo q4w. Data through week 24 were included in population PK and exposure-response modeling analyses. Clinical efficacy end points included the proportion of patients achieving 20%, 50%, and 70% improvement in American College of Rheumatology (ACR20,

ACR50, and ACR70, respectively) response criteria and Investigator's Global Assessment (IGA) of psoriasis scores (0/1 for IGA score ≤1 [almost clear or better] and 0 for IGA score 0 [clear]).

The population PK base model was selected following comparisons among several structural models, including one and two-compartment linear models and a one-compartment model with parallel linear and nonlinear Michaelis-Menten elimination. Covariate model selection was conducted using a full-model approach with backward elimination at the nominal significance level ($p < 0.001$).[8] The final model was obtained by removing covariates with effect sizes less than 10% of the typical values of the respective PK parameters from the covariate model. The final population PK model was used to predict exposure metrics, including area under the drug concentration-time curve from week 0 to 24 (AUC_{0-24w}) and average concentration at steady state ($C_{ave,ss}$), to support the landmark exposure-response analyses. Additional simulations were conducted to assess covariate effect on guselkumab exposure.

For the ACR landmark exposure-response analyses, the probability of achieving ACR20, ACR50, or ACR70 was simultaneously modeled by regrouping the ACR response variable to one ordered categorical variable with four possible outcomes: 0 if ACR70 was achieved; 1 if ACR50, but not ACR70, was achieved; 2 if ACR20, but not ACR50, was achieved; and 3 if ACR20 was not achieved. For the IGA landmark analyses, the probability of achieving IGA0/1 or IGA0 was simultaneously modeled by regrouping the IGA score to 1 ordered categorical variable with three possible outcomes: 0, 1, or 2 if the IGA score was 0, 1, or greater than or equal to 2, respectively. The probability of achieving each ACR or IGA response was modeled using a standard ordinal logistic regression. For the longitudinal exposure-response analyses, the PK-related parameters were set to their corresponding empirical Bayesian estimates (EBEs) from the final population PK model, and a latent variable indirect response model was developed to evaluate the relationship between PK and ACR responses.[9]

For both exposure-response analysis approaches, covariate models were developed using a forward addition followed by backward elimination using NONMEM (version 7.4).[10] Covariates tested were selected based on experience with similar biologics, assumptions about potential relevance to efficacy, or significance in the final population PK model. Simulation results from the landmark exposure-response models were summarized to evaluate the effects of the identified covariates on predicted outcomes.

Detailed methods for all analyses are presented in the Supplementary Information.

RESULTS

Demographic characteristics

Demographic and baseline clinical characteristics of patients in the population PK and exposure-response analyses are summarized in Table S1. Median baseline body weight was 84 kg, diabetes comorbidity was present in 9% of patients, the majority of patients were White, and ~11% had previously used antitumor necrosis factor α therapy. In the population PK analysis dataset, 2.0% of patients were positive for antidrug antibodies. Median baseline Psoriasis Area and Severity Index (PASI) and Disease Activity Score in 28 joints (DAS28) scores were the same in both exposure-response datasets (5.8 and 5.1, respectively).

Population pharmacokinetic modeling analysis

Base model

The base population PK model was a one-compartment linear PK model with first-order absorption and first-order elimination with interindividual variability (IIV) on first-order absorption rate constant (K_a), apparent clearance (CL/F), and apparent volume of distribution (V/F) to reasonably describe the observed data. The correlation between CL/F and V/F was significant and accounted for using a variance-covariance omega block matrix. The residual error was best described by a combined additive and proportional error model.

Covariate model

A covariate model, including body weight, baseline albumin, diabetes comorbidity, and white blood cell (WBC) count on CL/F and body weight on V/F was developed from the stepwise covariate selection (Figure 1). Baseline albumin and WBC count on CL/F had effect sizes less than 10% and were removed from the covariate model,[11,12] resulting in the final population PK model with effects of body weight on both CL/F and V/F and diabetes comorbidity status on CL/F.

Final model

Model parameters were estimated reasonably well with percent relative standard error (%RSE) less than 17% (Table 1). The typical population value for CL/F in patients with a median weight of 84 kg was 0.596 L/day, and the estimated typical population value for V/F was 15.5 L. The

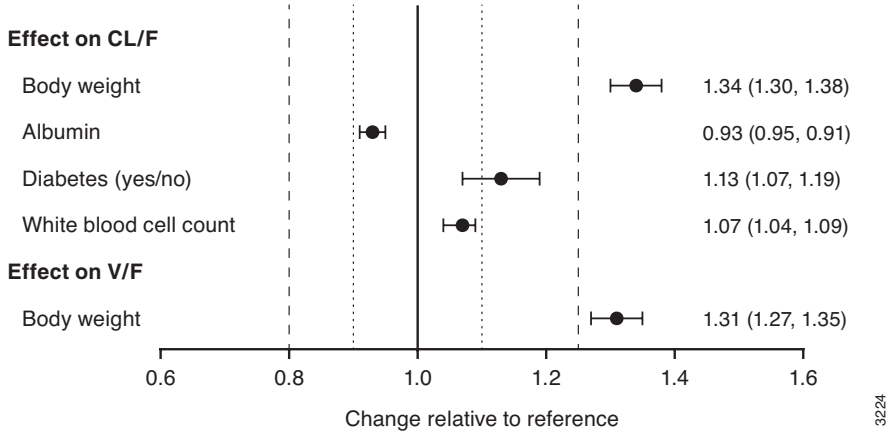

FIGURE 1 Effects of covariates on CL/F and V/F from the population pharmacokinetic (PK) covariate model. The effect sizes for discrete covariates (less common category/the most common category) were the parameter estimates of the less common category relative to the most common category. The effect size for continuous covariates (covariate values at 75th percentile/covariate values at 25th percentile) were calculated as the ratio of E75/E25, where E75 and E25 were PK parameter values with covariate values at 75th percentile and 25th percentile of the population, respectively. Circles represent model predictions, and line segments are the corresponding 90% confidence intervals. The associated values are shown on the right column. The dashed and dotted vertical lines are the 80% to 125% and the 90% to 110% boundaries, respectively. CL/F, apparent clearance; V/F, apparent volume of distribution

TABLE 1 Parameter estimates in the final population pharmacokinetic model

Parameters	Estimate[a]	95% CI[b]	Magnitude of change[c]
CL/F (L/day)[d]	0.596 (1.66)	0.573–0.616	–
Baseline body weight on CL/F	0.926 (7.17)	0.781–1.06	−14.4 to 14.5
Diabetes on CL/F	1.15 (3.54)	1.08–1.22	15%
V/F (L)[e]	15.5 (1.65)	14.9–16.1	–
Baseline body weight on V/F	0.861 (7.65)	0.719–0.978	−13.5 to 13.5
K_a (1/day)	0.572 (8.69)	0.491–0.761	–
IIV of CL/F (%)	38.9 (6.09) [3.51]	36.1–41.4	–
IIV of V/F (%)	33.3 (10.6) [14.3]	29.4–36.8	–
IIV of K_a (%)	93.4 (16.8) [61.7]	74.8–112.0	–
Correlation between IIV of CL/F and V/F	0.101 (8.40)	–	–
Proportional residual error (CV%)	19.1 (2.89)	17.9–20.2	–
Additive residual error (μg/ml)	0.00289 (–)	–	–

Abbreviations: –, not calculated; BWT, body weight; CI, confidence interval; CL/F, apparent clearance; CV%, percentage of coefficient of variance; DIAB, diabetes; IIV, interindividual variability; K_a, first-order absorption rate constant; PK, pharmacokinetic; RSE, relative standard error; V/F, apparent volume of distribution.

[a]Mean (%RSE) [shrinkage %] estimates by nonlinear mixed effect modeling from the final PK dataset.

[b]95% CIs were obtained from 1000 bootstrap runs implemented in PsN, version 4.1 (https://uupharmacometrics.github.io/PsN/).

[c]The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from 25th percentile to 75th percentile of the population.

[d]$\frac{CL}{F} = 0.596 \times \left(\frac{BWT}{84}\right)^{0.926} \times 1.15^{DIAB}$.

[e]$\frac{V}{F} = 15.5 \times \left(\frac{BWT}{84}\right)^{0.861}$.

typical population value of K_a was ~0.572 per day. The ETA shrinkages for CL/F and V/F were small (3.51% and 14.3%, respectively), indicating reliable estimation of IIV and the associated covariate effects. However, the ETA shrinkage for K_a was relatively large (61.7%), likely due to the sparse sampling schemes in the studies; thus, the associated EBE of

ETA vs. covariates might not be informative. Nevertheless, characterization of K_a is of less importance because maintaining adequate exposure levels (e.g., trough plasma concentration [C_{trough}] or AUC) is mainly driven by CL/F. The estimated elimination half-life was approximately 18.1 days.

The final PK model consisted of the effects of body weight and diabetes comorbidity on CL/F. When body weight increased from the 25th (71.0 kg) to 75th percentile (97.3 kg) of the population values, the change in CL/F attributed to body weight ranged from −14.4% to 14.5% relative to the median CL/F estimate (a 29% difference), and the change in V/F attributable to weight ranged from −13.5% to 13.5% relative to the median V/F estimate (a 27% difference). In addition, after taking body weight effect into account, the model-predicted CL/F values for guselkumab were 15% higher in patients with diabetes comorbidity vs. those without.

As shown in the prediction-corrected visual predictive check (pcVPC; Figure S1a) and VPC (Figure S1b,c) plots, the final population PK model adequately captured the median guselkumab concentration-time profile and the associated variability across treatment groups, suggesting that the final model reasonably described the observed data. Additional diagnostic plots were also assessed, and no apparent bias was identified (data not shown), suggesting that the final model predictions were in good agreement with the observed data.

Simulation

The final population PK model was used to simulate concentration-time profiles following the two guselkumab regimens to make comparisons between covariate subpopulations. The model-predicted guselkumab median steady-state C_{trough} ($C_{trough,ss}$) and AUC during dosing interval (AUC_τ) were lower in patients with a body weight greater than or equal to 90 kg and with diabetes comorbidity, with similar effects regardless of treatment regimen (Figure S2a–d). In patients with a body weight greater than or equal to 90 kg vs. less than 90 kg, C_{trough} and AUC_τ were, respectively, 30.4% and 28.8% lower with the q4w regimen and 33.4% and 28.8% lower with the q8w regimen (Figure S2a,b). In patients with vs. without diabetes comorbidity, C_{trough} and AUC_τ were, respectively, 22.6% and 18.9% lower with the q4w regimen and 30.3% and 18.9% lower with the q8w regimen (Figure S2c,d).

Exposure-response modeling analyses

Landmark analyses

Landmark analyses were performed for ACR responses at week 24, the primary analysis time point, and week 20, a predose visit for both guselkumab regimens. The guselkumab exposure metrics used for week 24 included $AUC_{0–24w}$ and $C_{ave,ss}$. Observed trough serum concentration at week 20 ($C_{trough,wk20}$) was also linked to the ACR responses at the same visit. IGA responses were not evaluated at week 20, so landmark exposure-response analyses for IGA measures were only conducted for week 24 using $AUC_{0–24w}$ and $C_{ave,ss}$. Each landmark analysis included patients who had both exposure metrics and efficacy measurements at the selected timepoints. The ordinal logistic regression models with maximum drug effect (E_{max}) component were successfully developed in all five landmark analyses. Model parameter estimations in the final ACR models were reasonable, except that the %RSE for half-maximum drug effect (EC_{50}) was relatively high (ranging from 83.3% to 127%), likely due to a lack of data at the lower exposure range (Table 2). For the three ACR response exposure-response models using different exposure metrics ($AUC_{0–24w}$, $C_{ave,ss}$, and $C_{trough,wk20}$), the baseline DAS28 score was identified as a covariate with significant effects on the E_{max}, with a trend indicating that patients with lower baseline DAS28 scores would achieve higher maximum ACR20, ACR50, and ACR70 responses. The baseline PASI score was also identified as a covariate on E_{max} for the two landmark models using $C_{ave,ss}$ and $C_{trough,wk20}$ exposure metrics, with a trend indicating that patients with higher baseline PASI scores would achieve higher maximum ACR20, ACR50, and ACR70 responses. Overall, the modeling results for ACR responses at weeks 20 and 24, including the identified covariate effects, were consistent across exposure metrics, indicating that the landmark ACR models were robust.

Landmark analyses demonstrated that IGA responses were correlated with $AUC_{0–24w}$ and $C_{ave,ss}$. Model parameter estimations in the final IGA models were reasonable (Table 2). Baseline PASI score was the only covariate identified as having significant effects on both the intercept and E_{max}, suggesting that patients with lower baseline PASI scores had higher placebo IGA responses and higher maximum IGA responses with guselkumab treatment. As with the ACR response exposure-response analyses, the exposure-response modeling results for the IGA responses, including the covariate effects identified, were consistent using both model-predicted exposure metrics, indicating the models were robust.

The performance of the final exposure-response models was assessed through the superposition of the observed response rates (binned into quartiles) and the model-predicted exposure-response trends. Overall, the ACR final model predictions were in good agreement with the observed data, and there was no apparent bias (Figure 2a). The wider 90% confidence intervals (CIs) of the model-predicted ACR responses in the lower exposure quartiles were consistent with the relatively higher %RSE of EC_{50}, indicating a lack

TABLE 2 Parameter estimates of the final landmark exposure-response models for ACR20, ACR50, and ACR70 responses at weeks 20 and 24 and IGA0/1 and IGA0 responses at week 24

Parameters	Week 24 using AUC_{0-24w}	Week 24 using $C_{ave,ss}$	Week 20 using $C_{trough,wk20}$
ACR responses			
β_1	−1.94 (6.62)	−1.92 (6.74)	−1.86 (6.94)
d_2	1.23 (5.35)	1.23 (5.45)	1.15 (6.02)
d_0	0.979 (7.64)	1.00 (7.66)	1.09 (7.77)
E_{max}	1.44 (19.7)	1.53 (18.2)	1.26 (12.9)
DAS28 on E_{max}	−0.847 (27.1)	−0.827 (27.5)	−0.981 (21.5)
PASI on E_{max}	–	0.142 (35.9)	0.169 (30.2)
EC_{50}[a]	134 (127)	1.06 (100)	0.150 (83.3)
IGA responses			
β_1	−0.450 (27.6)	−0.447 (27.8)	–
PASI on β_1	−0.779 (16.6)	−0.785 (16.4)	–
d_0	1.91 (5.45)	1.93 (5.51)	–
E_{max}	3.05 (10.9)	3.09 (9.27)	–
PASI on E_{max}	0.217 (27.9)	0.214 (27.8)	–
EC_{50}[a]	166 (48.3)	0.922 (39.5)	–

Note: Values are parameter estimate (%RSE).

Abbreviations: –, not calculated; ACR, American College of Rheumatology; ACR20/ACR50/ACR70, 20%, 50%, or 70% improvement in arthritis activity relative to baseline; AUC_{0-24w}, area under the concentration-time curve from week 0 to week 24 (unit: day*μg/ml); β_1, baseline response rate for ACR50 or IGA score ≤1 in logit scale; $C_{ave,ss}$, average concentration at steady state (unit: μg/ml); $C_{trough,wk20}$, trough serum concentration at week 20 (unit: μg/ml); d_0, rate of achieving ACR50 but not ACR70 or rate of IGA score = 1; d_2, rate of achieving ACR20 but not ACR50; DAS28, baseline Disease Activity Score in 28 joints; EC_{50}, guselkumab exposure at half-maximum drug effect (unit: same as the respective exposure metrics in the exposure-response analysis); E_{max}, maximum drug effect in logit scale; IGA, Investigator's Global Assessment score; IGA0, IGA score of cleared (0); IGA0/1, IGA score of ≤1 (almost clear or better); PASI, baseline Psoriasis Area and Severity Index score; RSE, relative standard error.

[a]EC_{50} units: day*μg/ml for AUC_{0-24w}; μg/ml for $C_{ave,ss}$ and $C_{trough,wk20}$.

of efficacy data in the lower exposure range. The goodness-of-fit plot for the IGA model using AUC_{0-24w} as the exposure metric demonstrates that the model predictions were also in good agreement with the observed IGA responses (Figure 2b). The 90% CIs of the IGA model-predicted responses were narrower than the ACR model, consistent with the overall lower %RSE of parameter estimations, especially for EC_{50}. Similar results were observed with the goodness-of-fit plots for the models using $C_{trough,wk20}$ and/or $C_{ave,ss}$ for ACR and IGA responses (Figure S3a–c).

Longitudinal modeling

The longitudinal exposure-response analysis was performed using pooled data through week 24 from a total of 1116 patients who received study treatment (placebo or guselkumab q4w or q8w) and had PK and ACR assessments. For the base model, a sequential modeling approach achieved by fixing individual PK parameters at their EBE from the population PK model was used to fit the longitudinal model equations to the observed ACR responses. Two covariates, disease duration and baseline PASI score, were identified as statistically significant and included in the final longitudinal exposure-response model. All parameters were well-estimated by this final model, except for parameters associated with EC_{50} due to lack of data in the lower exposure range (Table 3).

The model predicted that a higher baseline PASI score and/or C-reactive protein (CRP) level would be associated with a lower EC_{50} and, consequently, with a slightly higher probability of achieving an ACR20, ACR50, or ACR70 response. This was confirmed by observed data, where patients with baseline PASI greater than 5.8 (median baseline score) and/or baseline CRP greater than 0.94 mg/dl (median baseline level) appeared to be more sensitive to guselkumab and, consequently, had greater ACR response rates (data not shown). The model also predicted that a higher baseline DAS28 score would be associated with a higher intercept (α) value, resulting in a lower ACR response rate. Observations confirmed this prediction, with lower ACR response rates observed in patients with higher baseline DAS28 scores (>6.1, the population median; data not shown).

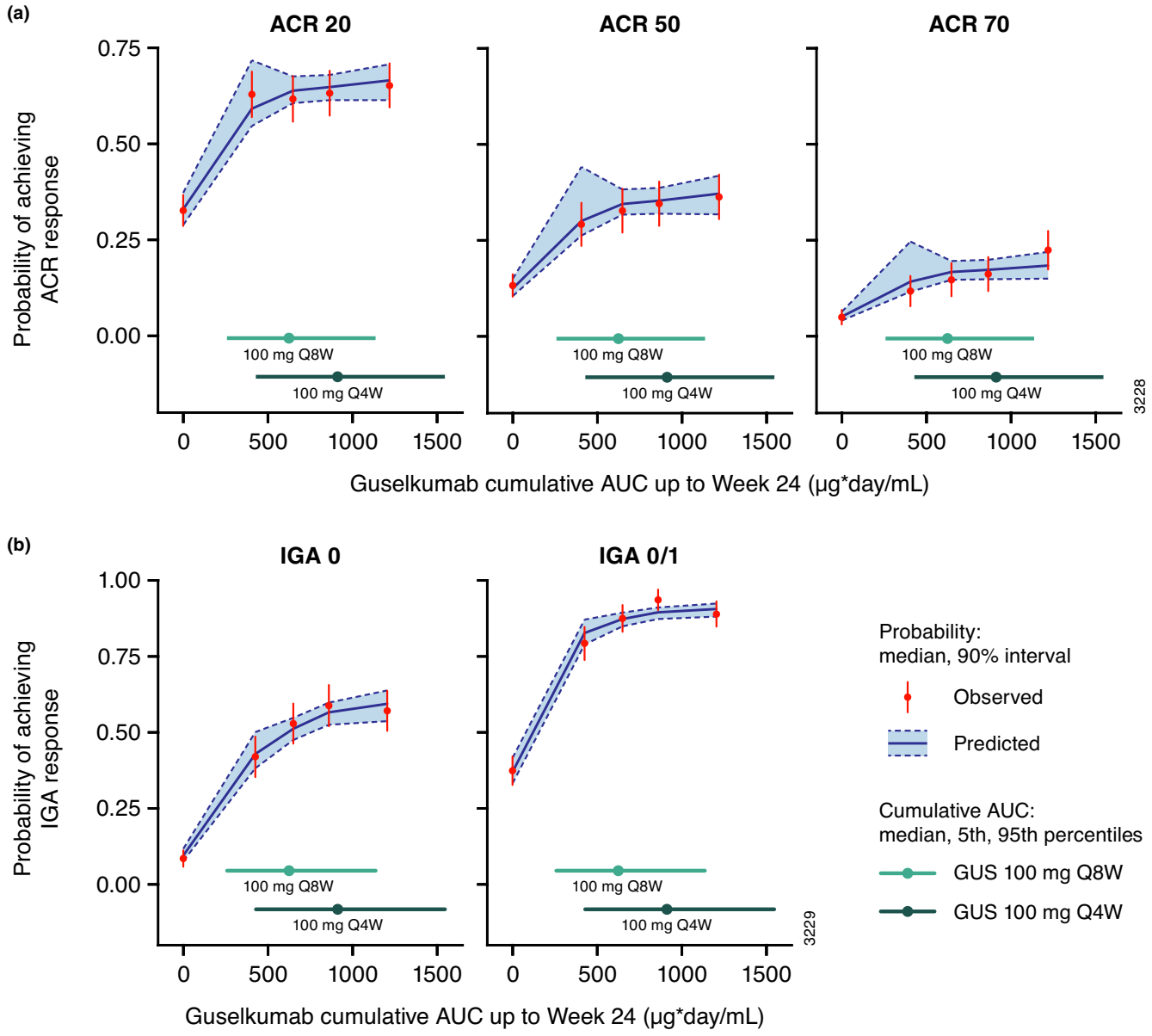

FIGURE 2 Goodness-of-fit plots for landmark exposure-response models of ACR20, ACR50, and ACR70 responses at week 24 using AUC_{0-24w} as an exposure metric (a) and of IGA0/1 and IGA0 responses at week 24 using AUC_{0-24w} as an exposure metric (b). The observed response rates and corresponding 90% confidence intervals were determined according to the bins for the model-predicted guselkumab exposure metrics and were plotted as the median exposure for each bin. The simulated 90% prediction intervals are from 1000 simulations incorporating model parameter uncertainties.[15] ACR, American College of Rheumatology; ACR20/ACR50/ACR70, 20%, 50%, or 70% improvement in arthritis activity relative to baseline; AUC, area under the concentration-time curve; AUC_{0-24w}, AUC from week 0 to week 24; GUS, guselkumab; IGA, Investigator's Global Assessment; IGA0, IGA score of cleared (0); IGA0/1, IGA score of cleared (0) or minimal (1); Q4W, every 4 weeks; Q8W, every 8 weeks

Visual predictive check results demonstrated that the longitudinal model-predicted ACR20, ACR50, and ACR70 response rates and the corresponding observed response rates were in good agreement, with almost all observed response rates within the 90% CIs of the model predictions (Figure 3). Similar results were observed when VPC results were stratified by baseline PASI, CRP, and DAS28 subgroups (data not shown).

Simulations

To quantify the differences in ACR and IGA responses with the dose regimens (q8w and q4w) and in different covariate subpopulations, the final landmark exposure-response models were used to simulate ACR and IGA responses, taking into account the model parameter uncertainties. The ACR20, ACR50, and ACR70 response

rates at week 24 predicted by the landmark model using $C_{ave,ss}$ were stratified by baseline DAS28 score (≤5.1 vs. >5.1) or baseline PASI score (≤5.8 vs. >5.8) for the q8w and q4w regimens.

The $C_{ave,ss}$ landmark model predicted that ACR20 and ACR50 response rates were 7%–9% higher and ACR70 response rates were 5%–6% higher in patients with baseline DAS28 scores less than or equal to 5.1 vs. greater than 5.1 following treatment with the q8w or q4w regimen (Figure 4a). Similarly, the model predicted that ACR20 and ACR50 response rates were 6%–7% higher and ACR70 response rates were 4% to 5% higher in patients with baseline PASI scores less than or equal to 5.8 vs. greater than 5.8 (Figure 4b). The $C_{ave,ss}$ landmark simulation results also suggest that the q4w regimen would result in minor increases in ACR responses vs. the q8w regimen, with differences of less than or equal to 5% for the overall population and any of the covariate subgroups. Similar results were predicted by the other ACR landmark models using $AUC_{0–24w}$ or $C_{trough,wk20}$ as exposure metrics (data not shown).

TABLE 3 Parameter estimates of the final longitudinal exposure-response model

Parameter	Estimate	%RSE
α_1	−8.31	3.99
DAS28 5.1 on α_1	−0.368	26.3
α_1-α_0	1.95	4.14
α_2-α_1	2.60	2.74
PB_{MX}	4.94	7.54
k (1/day)	0.0160	13.8
k_{out} (1/day)	0.0218	24.9
EC_{50} (μg/ml)	0.173	257
PASI 5.8 on EC_{50}	−0.535	91.4
CRP 0.93 μg/ml on EC_{50}	−2.19	88.8
DE_{MX}	2.75	11.5
ω^2 (interpatient variability of intercept)	6.69	6.94

Abbreviations: $\alpha_0/\alpha_1/\alpha_2$, intercept for ACR70/ACR50/ACR20; ACR, American College of Rheumatology; ACR20/ACR50/ACR70, 20%, 50%, or 70% improvement in arthritis activity relative to baseline; CRP, baseline C-reactive protein; DAS28, baseline Disease Activity Score in 28 joints; DE_{MX}, maximum drug effect; EC_{50}, guselkumab exposure at half-maximum drug effect; k, rate of placebo effect onset; k_{out}, disease amelioration rate; PASI, baseline Psoriasis Area and Severity Index score; PB_{MX}, maximum placebo effect; RSE, relative standard error.

Longitudinal model-predicted ACR20, ACR50, and ACR70 responses at week 24 were similar to those predicted by the landmark models. The difference in ACR responses between the q8w and q4w regimens was less than 2% in the overall population (Figure S4) and less than 3% in any covariate subgroup (baseline PASI, DAS28, and CRP; data not shown). The longitudinal model also predicted differences of similar magnitude between PASI and DAS28 covariate subgroups (≤8%) following treatment with the q8w or q4w regimen. When compared by baseline CRP levels (≤0.94 mg/dl vs. >0.94 mg/dl), the differences between model-predicted ACR response rates were 1% to 4% higher in patients with higher baseline CRP levels following guselkumab treatment.

For IGA responses, the $C_{ave,ss}$ landmark model-predicted differences in IGA0/1 response between the

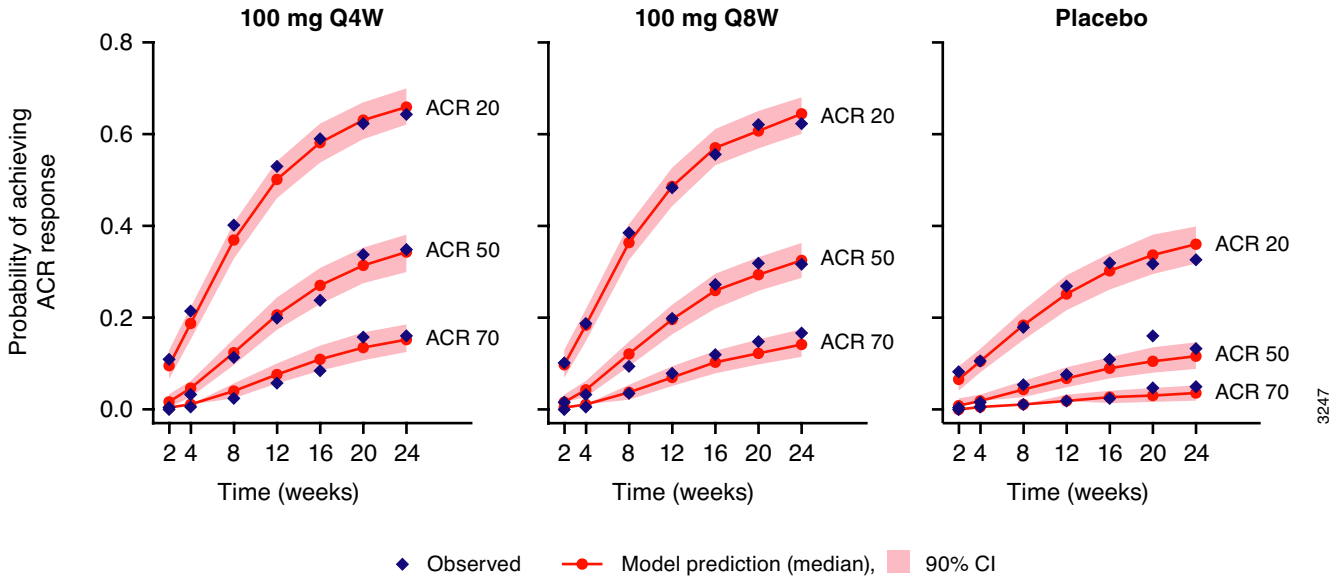

FIGURE 3 Overall visual predictive check of the final longitudinal exposure-response model. ACR, American College of Rheumatology; ACR20/ACR50/ACR70, 20%, 50%, or 70% improvement in arthritis activity relative to baseline; CI, confidence interval; Q4W, every 4 weeks; Q8W, every 8 weeks

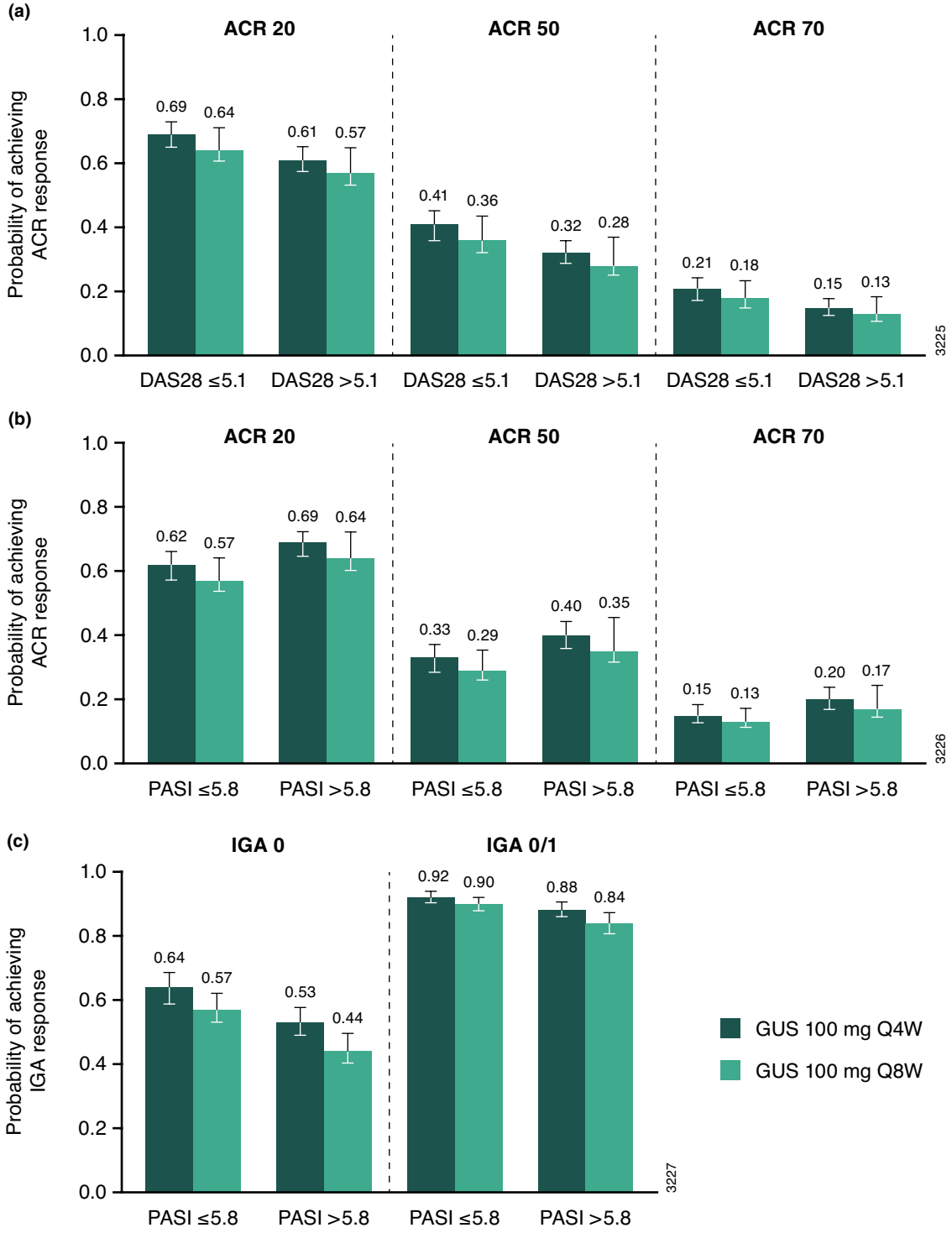

FIGURE 4 Landmark exposure-response model simulated ACR20, ACR50, and ACR70 responses at week 24 using $C_{ave,ss}$ stratified by baseline DAS28 score (≤5.1 vs. >5.1) (a) and baseline PASI score (≤5.8 vs. >5.8) (b) and simulated IGA0/1 and IGA0 responses at week 24 using $C_{ave,ss}$ stratified by baseline PASI score (≤5.8 vs. >5.8) (c). The error bars and the associated numbers are the model-predicted median responses with 90% confidence intervals from 1000 replicates. ACR, American College of Rheumatology; ACR20/50/70, 20%, 50%, or 70% improvement in arthritis activity relative to baseline; $C_{ave,ss}$, average concentration at steady state; DAS28, Disease Activity Score in 28 joints; IGA, Investigator's Global Assessment; GUS, guselkumab; IGA0, IGA score of cleared (0); IGA0/1, IGA score of cleared (0) or minimal (1); PASI, Psoriasis Area and Severity Index; Q4W, every 4 weeks; Q8W, every 8 weeks

q8w and q4w regimens were less than 5%; however, there was a 4% to 9% difference between treatment groups in IGA0 response, suggesting a small, incremental benefit with the higher dose regimen (Figure 4c). When stratified by baseline PASI score, the IGA0/1 and IGA0 model-predicted response rates were 4% to 6% and 11% to 13% higher, respectively, in patients with baseline PASI less than or equal to 5.8 vs. greater than 5.8 following treatment with the q8w or q4w regimen. Similar results were observed with the landmark model using AUC_{0-24w} as the exposure metric (data not shown).

Exposure-safety analyses

Analyses evaluating the relationship between systemic guselkumab exposure and the occurrence of selected safety events (i.e., adverse events [AEs], serious AEs, AEs leading to discontinuation of study agent, infections, and serious infections) demonstrated that safety was not associated with observed (Table S2) or model-predicted (Table S3) exposure metrics.

DISCUSSION

Population PK and exposure-response analyses are commonly used to inform drug development and product label. Here, we report the results of population PK and exposure-response modeling analyses for guselkumab in adults with PsA using data from two pivotal phase three studies, DISCOVER-1 and DISCOVER-2. These results were used to support guselkumab approval for use in adults with PsA.

The observed guselkumab concentration-time data were adequately described by a one-compartment linear population PK model with first-order absorption and first-order elimination. The major model parameters were consistent with those previously reported for guselkumab-treated patients with psoriasis.[5] No apparent differences in clearance were observed for guselkumab in patients with PsA vs. psoriasis (0.596 vs. 0.516 L/day), and volume of distribution (within 15%) and half-life are also similar. In this population PK analysis, the typical population estimate for K_a was lower than that reported for guselkumab in patients with psoriasis,[5] likely due to the highly sparse sampling utilized in the phase III studies for both indications, making it hard to accurately identify K_a, rather than different absorption rates in the patient populations. Comparable PK between patients with psoriasis and patients with PsA has also been reported for the anti-IL-12/IL-23 monoclonal antibody, ustekinumab.[13]

The covariates identified as significantly contributing to the observed guselkumab PK variability, body weight, and diabetes comorbidity, were also identified by population PK modeling in patients with psoriasis, with similar effects.[5] Body weight accounted for 28% and 32% of the proportion of variance for the IIV of CL/F and V/F, respectively, in the psoriasis population PK analysis compared with 29% and 27% in this PsA population PK analysis, and patients with diabetes had 12% higher CL/F values than those without in the psoriasis analysis compared with 15% higher in this PsA analysis.[5] Nevertheless, these effects are not considered clinically relevant, as no trend in clinical response (i.e., ACR and IGA response rates) and safety end points (data not shown) were identified. Therefore, dose adjustment based on body weight or diabetes comorbidity is not warranted. The psoriasis population PK analysis identified a marginal influence of race (non-White vs. White) on guselkumab PK.[5] In this PsA population PK analysis, race was not identified as an influencing covariate because non-White patients were only 3.9% of the population.

Landmark and longitudinal exposure-response analyses are commonly used to explore the relationship between drug exposure and clinical response.[14] The landmark analysis approach links exposure metrics to a clinical end point at a selected time point. Usually, a linear or E_{max} model is used in this approach, assuming that drug exposure directly drives the clinical response. Because landmark analysis is relatively easy to conduct and the interpretation of the results is straightforward, it has been widely used and is well accepted in support of drug development. The landmark approach requires both exposure metrics and clinical end point measures to be available for inclusion in the analysis. In addition, a wide exposure range along the exposure-response curve is needed to accurately define the exposure-response relationship and identify the model parameters.

Because it was not clear which exposure metric was most influential on the clinical end points, multiple metrics were used to link the two clinical end points, ACR and IGA responses, at or close to the primary analysis time point. The consistent modeling results, including the covariate effects identified, using different exposure metrics indicate that the landmark ACR and IGA models were robust. In the three landmark models for ACR response, the high uncertainties in EC_{50} estimation were likely due to lack of low-exposure data as 100 mg q8w was the lowest dose regimen studied in patients with PsA. Indeed, the observed and model-predicted differences in ACR responses between the two regimens used in the studies (q8w and q4w) were less than or equal to 5% for the overall population and for any covariate subgroup, suggesting that both regimens are at or near the dose level that achieves a maximum effect. In the two landmark models for IGA responses, compared with the landmark models

for ACR responses, the uncertainties in EC_{50} estimation were relatively smaller and the 90% CIs in the model predictions considering model parameter uncertainties were narrower, suggesting better data distribution for informing the exposure-response relationship. Consistently, the model predicts that the q4w regimen would achieve a higher IGA0 response rate (up to 9%) compared with the q8w regimen. As shown in the goodness-of-fit plots, the placebo data were essential for defining the exposure-response relationship and parameter estimation, especially for the ACR responses.

The longitudinal exposure-response analysis approach using an indirect response model is a semi-mechanism-based modeling approach that uses PK and efficacy data at different timepoints to characterize the time course of the clinical end point that is assumed to be driven by drug exposure.[12] In this longitudinal analysis for ACR response, the results were consistent with those of the landmark analyses. Both approaches confirmed that the two guselkumab regimens studied similarly improved PsA signs and symptoms as measured by ACR response rates in the overall and covariate subpopulations, suggesting that 100 mg q8w is an appropriate dose regimen for PsA treatment.

In both the landmark and longitudinal analyses, baseline DAS28 and PASI scores were identified as significant covariates. Baseline DAS28 is an indicator of arthritis disease activity. The landmark analyses results suggest that a higher baseline DAS28 score, which is associated with more severe arthritis, may result in a lower maximum drug effect. The longitudinal analyses results suggest that patients with a higher baseline DAS28 score may have a lower placebo effect and, consequently, lower ACR responses. Although the effects of baseline DAS28 were on different model parameters, because both investigated regimens are at or near the plateau of the ACR dose-response relationship, both model approaches predict that patients with higher baseline DAS28 may have lower ACR response rates following guselkumab treatment.

Baseline PASI score is an indicator of psoriasis disease activity. The landmark analyses suggested that patients with a higher baseline PASI score may achieve higher maximum ACR response rates. In the longitudinal analysis, the baseline PASI score effect was on EC_{50}, which indicates that arthritis symptoms in patients with a higher baseline PASI score are more sensitive to treatment, with higher ACR response rates predicted at a lower dose. In general, the covariate effects identified by the two exposure-response modeling approaches were consistent and point in the same direction. The longitudinal model also identified baseline CRP level as a covariate on EC_{50}, but the effect size was small (<5% in patients with a higher baseline CRP level). Likely due to the minor effect and data limitation for landmark analyses (only PK and efficacy data for certain timepoints were used), the CRP effect was not identified in the landmark models. The explanation for the covariate influence on the exposure-response relationship is unclear and pending future confirmation.

In the landmark analyses for IGA responses, baseline PASI score was the only covariate identified on both the intercept and E_{max}, with a trend suggesting that patients with lower baseline PASI scores, which are associated with less severe baseline psoriasis disease activity, may achieve higher IGA response rates with guselkumab treatment. The simulation results suggest that the q4w regimen may provide a small incremental benefit over the q8w regimen in achieving an IGA0 response.

Overall, the observed guselkumab concentration data were adequately described by a one-compartment linear PK model with first-order absorption and first-order elimination with IIV on CL/F, V/F, and K_a. Body weight and diabetes comorbidity were identified as significant covariates contributing to the observed guselkumab PK variability, but the magnitude of the effects of these covariates was not considered clinically relevant. The results of landmark and longitudinal exposure-response analyses demonstrate that guselkumab 100 mg q8w and q4w result in similar improvements in PsA signs and symptoms as measured by ACR and IGA response rates, with no dose adjustment warranted for any subgroup identified in the covariate analyses. These results, together with the exposure-safety analyses, support the use of an s.c. guselkumab treatment regimen of 100 mg at weeks 0 and 4, then q8w thereafter in patients with active PsA.

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CONFLICT OF INTEREST

Yang Chen and Chyi-Hung Hsu were employees of Janssen Research & Development, LLC, a wholly owned subsidiary of Johnson & Johnson, at the time the work was conducted, and own stock and/or stock options in Johnson & Johnson. Xin Miao, Yanli Zhuang, Alexa Kollmeier, Zhenhua Xu, Honghui Zhou, and Amarnath Sharma are employees of Janssen Research & Development, LLC, a wholly owned subsidiary of Johnson & Johnson and may own stock and/or stock options in Johnson & Johnson.

AUTHOR CONTRIBUTIONS

Y.C., X.M., C.-H.H., Y.Z., A.K., Z.X., H.Z., and A.S. wrote the manuscript. Y.C., X.M., C.-H.H., Y.Z., and A.S. designed the research. Y.C., X.M., C.-H.H., Y.Z., A.K., Z.X.,

H.Z., and A.S. performed the research. Y.C., X.M., and C.-H.H. analyzed the data.

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SUPPORTING INFORMATION

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

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