ARTICLE

Evaluating Potential Disease-Mediated Protein-Drug Interactions in Patients With Moderate-to-Severe Plaque Psoriasis Receiving Subcutaneous Guselkumab

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This open-label, multicenter, phase I therapeutic protein-drug interaction study was designed to evaluate the potential effect of guselkumab, a fully human anti-interleukin-23 immunoglobulin G1 lambda monoclonal antibody, on the pharmacokinetics of a cocktail of representative cytochrome P450 (CYP) probe substrates (midazolam (CYP3A4), S-warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and caffeine (CYP1A2)). Fourteen participants with psoriasis received a single subcutaneous dose of guselkumab 200 mg on day 8 and an oral probe cocktail on days 1, 15, and 36. Blood samples were collected for measuring plasma concentrations of these probe substrates on days 1, 15, and 36. No consistent trends in observed maximum plasma concentration and area under the curve from time 0 to infinity values of each probe CYP-substrate before (day 1) and after guselkumab treatment (days 15 and 36) could be identified in each individual patient, suggesting that the use of guselkumab in patients with psoriasis is unlikely to influence the systemic exposure of drugs metabolized by CYP isozymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2). The probe cocktail was generally well-tolerated when administered in combination with guselkumab in patients with psoriasis. Clinicaltrials.gov Identifiers: NCT02397382.

Psoriasis is a chronic inflammatory disease affecting 1–3% of the world’s population.4 Traditional systemic therapies for psoriasis have not fully met patients’ needs.5 Highly effective antibody-based or fusion protein-based biologics targeting key inflammatory mediators have been developed for psoriasis treatment.6 Based on their mechanisms of action, biological psoriasis therapies can be classified as: (i) T-cell modulating agents, (ii) tumor necrosis factor (TNF)-α antagonists, (iii) interleukin (IL)-12/23 and/or IL-23 inhibitors, and (iv) IL-17 inhibitors.4,7

Guselkumab (Tremfya, Janssen Research & Development, Spring House, PA) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds and inhibits IL-23, a critical driver of pathogenic T

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Therapeutic proteins (TPs) that modulate cytokine concentrations and activity can indirectly influence expression of cytochrome P450 (CYP) isoenzymes and may alter CYP-mediated metabolism of concomitantly administered small molecule drugs. An in vitro study1 and two phase I studies2,3 were previously conducted to assess if interleukin (IL)-23 modulates the expression or activity of multiple CYP isoenzymes (including CYP1A2, 2C9, 2C19, 2D6, and 3A4). These results suggest that potential TP-drug interactions between guselkumab and drugs metabolized by CYP450 could be low.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Subcutaneous administration of guselkumab to patients with psoriasis has no effect on the pharmacokinetics (PK) of the evaluated CYP substrates.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These results suggest that guselkumab can be used for the treatment of psoriasis without significant PK interactions with drugs metabolized by CYP3A4, CYP2C9, CYP2C19, CYP2D6, or CYP1A2.

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cells in chronic plaque psoriasis. Clinical trials have demonstrated that guselkumab had favorable efficacy and safety profiles for the treatment of moderate-to-severe plaque psoriasis.\textsuperscript{9–10}

As a fully human IgG1\(\lambda\) mAb, guselkumab is expected to be metabolized in the same manner as any other endogenous IgG antibody (degraded into small peptides and amino acids via catabolic pathways) and subject to similar routes for elimination.\textsuperscript{11} Therefore, the likelihood of direct therapeutic protein (TP)-drug interaction occurring during co-administration of guselkumab and other concomitant small molecule medications is assumed to be low. In line with this, clinically relevant information has been published about potential TP-drug interactions,\textsuperscript{12–16} and supports that mAbs do not elicit a direct effect on the metabolic/clearance pathways of small molecular therapeutics. However, the immunomodulatory properties of mAbs may indirectly alter the clearance of certain small molecules through noncatabolic hepatic metabolism pathways.\textsuperscript{14,15}

An \textit{in vitro} study\textsuperscript{1} using cryopreserved human hepatocytes to assess whether IL-12 and/or IL-23 modulate the expression or activity of multiple cytochrome P450 (CYP) enzymes (i.e., CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) suggested that TP-drug interactions between guselkumab and CYP450 substrates are unlikely. However, \textit{in vitro} studies may have limitations in predicting clinical interactions between TPs and small molecule drugs.\textsuperscript{17}

To confirm these findings, we conducted a phase I study in patients with moderate-to-severe plaque psoriasis to determine if blocking IL-23 with guselkumab for treatment of psoriasis would clinically alter the metabolism of probe substrates metabolized by CYP isozymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, or CYP1A2).

\section*{METHODS}
\subsection*{Study design}
This was an open-label, multicenter, phase I drug interaction study (ClinicalTrials.gov identifier: NCT02397382) designed to evaluate the potential effect of a single subcutaneous (s.c.) dose of guselkumab 200 mg on the pharmacokinetics (PK) of a cocktail of representative probe substrates of CYP isozymes (midazolam (CYP3A4), S-warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and caffeine (CYP1A2)). All participants were to receive a single s.c. dose of guselkumab 200 mg on day 8 and an oral probe cocktail on days 1, 15, and 36 (\textbf{Figure 1}). The 200-mg guselkumab dose was selected because it was twofold higher than the 100-mg dose selected for the guselkumab phase III psoriasis studies,\textsuperscript{8,9} and serum guselkumab concentrations were expected to be maintained at a high level through week 4. All components of the probe cocktail included in this study were reported to be systemically cleared within 7 days after a single oral administration. Therefore, the likelihood of systemic probe CYP-substrate exposures carried over from previous probe cocktail administrations (i.e., on day 15 following administrations on day 1, and on day 36 following administrations on day 15) is low. The day-15 visit (i.e., 1 week after guselkumab administration) was chosen because this time point was expected to reflect the approximate time to reach the maximum observed concentration (\(T_{\text{max}}\)) following guselkumab

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{study_design.png}
\caption{Study design.}
\end{figure}

PK: pharmacokinetics; SC: subcutaneous

Probe cocktail: oral doses of 0.03 mg/kg midazolam, 10 mg warfarin (+10 mg of vitamin K), 20 mg omeprazole, 30 mg dextromethorphan, 100 mg caffeine
s.c. administration on day 8, which would allow time for occurrence of any potential CYP isozyme induction or inhibition. The day-36 visit (i.e., 4 weeks after guselkumab administration) was chosen because, based on the terminal half-life ($t_{1/2}$) of $\sim$18 days for guselkumab, serum guselkumab concentrations would still be high enough to provide additional time to detect any potential indirect effect of guselkumab on CYP isozyme induction or inhibition.

There was no formal hypothesis to be tested for this trial. Therefore, no formal sample-size power calculation was performed. Approximately 18 patients were planned to be enrolled in this study such that at least 12 patients would be anticipated to complete the day-40 assessments for the PK of probe CYP-substrates. The total duration of study participation was $\sim$17 weeks, including a screening visit up to 4 weeks prior to first probe cocktail administration, 4 inpatient visits during the study (1 each on days 1, 8, 15, and 36), and study visits on days 64 and 92. The study was conducted at seven investigational sites in the United States from June 2015 to August 2016. It was conducted in accordance with applicable laws and regulations, the current International Council for Harmonization guidelines for Good Clinical Practices, and the Declaration of Helsinki. The study protocol and amendments were reviewed and approved by institutional review board/governing ethical bodies. Written informed consent was obtained from all participants prior to enrollment.

**Patients**

Eligible participants were men or women age $\geq$ 18 years with a diagnosis of moderate-to-severe plaque-type psoriasis (with or without psoriatic arthritis) for at least 6 months before day 1. Other key inclusion criteria were Psoriasis Area and Severity Index (PASI) $\geq$ 12, Investigator’s Global Assessment (IGA) $\geq$ 3, involved body surface area $\geq$ 10% at screening, and patients had to be candidates for phototherapy or systemic treatment for psoriasis (either naïve or history of previous treatment).

Patients were excluded if they had a history of or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, bleeding disorder, rheumatologic, psychiatric, or metabolic disturbances; had previously received guselkumab; had received any anti-TNF therapy within the longer of 3 months or 5 half-lives; had received any therapeutic agent directly targeted to inhibit. The day-36 visit (i.e., 4 weeks after guselkumab s.c. administration on day 8, which would allow time for occurrence of any potential CYP isozyme induction or inhibition. The day-36 visit (i.e., 4 weeks after guselkumab administration) was chosen because, based on the terminal half-life ($t_{1/2}$) of $\sim$18 days for guselkumab, serum guselkumab concentrations would still be high enough to provide additional time to detect any potential indirect effect of guselkumab on CYP isozyme induction or inhibition.

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**Cytochrome P450 genotyping**

A single blood sample was obtained at screening from each patient to determine eligibility for the study. DNA samples were genotyped for common polymorphisms in the CYP2C9, CYP2C19, and CYP2D6 genes to identify poor metabolizers to CYP2C9, CYP2C19, and CYP2D6 (Covance Laboratory, Indianapolis, IN): for CYP2C9, patients were screened for the presence of *2 and *3 alleles; for CYP2C19, patients were screened for presence of *2, *3, and *4 alleles; and for CYP2D6, patients were screened for the presence of *9, *10, *17, *29, and *41 alleles. Genetically determined poor metabolizers of CYP2C9, CYP2C19, or CYP2D6 substrates (i.e., patients who did not have at least one functional allele for CYP2C9, CYP2C19, and CYP2D6) were excluded from participation because these patients had little or no catalytic activity to metabolize probe substrates.

**Interventions**

Guselkumab was supplied as a sterile, preservative-free, clear, colorless-to-light yellow solution assembled in a 1-mL single-use prefilled syringe assembled with a passive needle-guard. The formulation comprises 100 mg/mL guselkumab, containing L-histidine, L-histidine monohydrochloride monohydrate, polysorbate-80, sucrose, and water for injection at pH 5.8.

The probe cocktail consisted of oral doses of 0.03 mg/kg midazolam, 10 mg warfarin (+ 10 mg vitamin K), 20 mg omeprazole, 30 mg dextromethorphan, and 100 mg caffeine. The probe cocktail used in this study was expected to have no mutual interactions among the individual medications.

**Drug administrations**

Prior to each probe cocktail administration on days 1, 15, and 36, patients were to have fasted overnight for at least 8 hours; however, water was permitted until 2 hours prior to dosing. Each probe cocktail was to be administered orally with a total of 240 mL water, which was used to rinse the probe cocktail container prior to administration. Two hours after probe cocktail administration, consumption of nonprohibited food and beverages could resume. All patients had to remain in a semi-supine position (~ 30°
upper body elevation) for ~ 1 hour after ingesting the probe cocktail. Patients had to remain seated during and for a minimum of 4 hours after administration of the probe cocktail. On Day 8, guselkumab was administered as a single s.c. dose of 200 mg (2 injections, 100 mg each) at a recommended injection-site (lower abdomen, upper thigh, or upper arm).18

PK sample collection
Blood samples were collected for analysis of plasma concentrations of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine prior to administration of the probe cocktail and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours following the administration of the probe cocktail on days 1, 15, and 36. Additional blood samples were collected for analysis of plasma concentrations of S-warfarin at 48, 72, and 96 hours following each probe cocktail administration. Blood samples for analysis of serum guselkumab concentrations were collected prior to guselkumab administration on day 8, prior to probe cocktail administrations on days 1, 15, and 36, and on days 64 and 92.

Bioanalytical methods
Plasma samples were analyzed to determine concentrations of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine using validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry methods. The lower limits of quantitation (LLOQ) were 5, 20, 0.1, 0.05, and 1 ng/mL, respectively, for S-warfarin, caffeine, midazolam, dextromethorphan, and omeprazole; the accuracy (%Bias) values across the assays were within ± 12%; and the precision (percentage coefficients of variation (%CV)) values across the assays were ≤ 7.3% (Frontage Laboratories, Exton, PA). Serum guselkumab concentrations were quantified using a validated electrochemiluminescence immunoassay method. The lower quantifiable concentration for a sample was 0.01 µg/mL (LLOQ multiplied by the minimum required dilution of 1:10).20

PK analyses
The PK parameters of each probe CYP-substrate following each probe cocktail administration were calculated from the plasma drug concentration over time data using noncompartmental analyses21 implemented in Phoenix WinNonlin (version 6.3; Pharsight; a Certara Company, St. Louis, MO). All calculations were based on actual sampling times. For estimation of PK parameters, plasma concentrations below the LLOQ were assigned a value of 0 if they preceded the first quantifiable sample in the profile. Any other values below the LLOQ were set to "missing." The area under the curve (AUC) values were calculated using a combination of linear and logarithmic trapezoidal methods: the linear trapezoidal method was used before Tₘₐₓ, and the logarithmic trapezoidal rule was used after Tₘₐₓ. Linear regression of the log-linear portion of the terminal phase was used to estimate the terminal rate constant (λz). A minimum of three data points at the terminal phase, not including the maximum concentration (Cₘₐₓ), were used in calculating λz. Any measurable plasma concentration values occurring after consecutive samples that were below the LLOQ at the terminal portion of the profile, were not used for the estimation of λz. The calculated PK parameters for probe CYP-substrates included, but were not limited to, Cₘₐₓ, Tₘₐₓ, AUCₘₐₓ, area under the curve from time 0 to infinity (AUCₘₐₓ), and t₁/₂.

Statistical analysis
Descriptive statistics, including arithmetic mean and standard deviation (SD), were used to summarize plasma concentration-time data and derived PK parameters of each probe CYP-substrate. Concentrations below LLOQ were to be treated as zero in the summary statistics. For the descriptive statistics, PK parameters, including Cₘₐₓ, Tₘₐₓ, AUCₘₐₓ, and t₁/₂, were to be excluded if: (i) the dose amount of the probe CYP-substrate could not be verified; (ii) the baseline (predose) concentration was > 10% of the Cₘₐₓ value; (iii) the concentration-time profiles were abnormal; (iv) the concentration-time data points were insufficient for noncompartmental analysis; and/or (v) the probe CYP-substrate concentration values were identified as outliers using the Dixon test22 at a significance level of 0.01. In addition, PK parameters of AUCₘₐₓ and t₁/₂ were to be excluded from descriptive statistics if: (i) the adjusted coefficient of determination (R²) values of the terminal data points were < 0.80; or (ii) the percentage of extrapolated AUC after the last quantifiable plasma concentration (%AUCₘₐₓ,ex) exceeded 25% of the AUCₘₐₓ value. The geometric mean ratios (GMRs) of Cₘₐₓ and AUCₘₐₓ were calculated and the 90% confidence intervals (CIs) were estimated for each probe CYP-substrate: day 15 (1 week after guselkumab treatment) vs. day 1 (before guselkumab treatment) and day 36 (4 weeks after guselkumab treatment) vs. day 1. Only patients with available paired data (both before and after guselkumab administration) were included in the comparisons. The P values for exact median tests23 were provided to evaluate the difference in median Tₘₐₓ values between day-15/day-36 and day 1. Of note, this was not a statistically powered study; therefore, the results from the statistical analysis should be interpreted with caution.

Clinical efficacy and safety evaluations
Efficacy assessments, such as IGA and PASI, were conducted from the screening period through day 64 for all patients who received at least one dose of guselkumab. Safety assessments, such as type, incidence, and severity of treatment-emergent adverse events (TEAEs), injection-site reactions, vital sign measurements, clinical laboratory test results, pulse oximetry, electrocardiogram, and physical examinations, were performed from the screening period through day 92 (~ 12 weeks after guselkumab administration) for all patients who received at least 1 dose of probe cocktail or guselkumab.

RESULTS
Patient disposition and demographics
A total of 16 patients with moderate-to-severe psoriasis, genotyped to exclude poor metabolizers of CYP2C9, CYP2C19, and CYP2D6 were enrolled and received probe cocktail on day 1. Overall, patients had a mean age
and received probe cocktail administration on day 1.

Among these patients, 14 received azolam on day 36. PK parameters of midazolam from these patients were, therefore, excluded from the analyses. In

PK parameters for any probe CYP-substrate were excluded from the analyses if the parameters met any of the exclusion criteria described in the Methods section.

Overall, the mean plasma concentration-time profiles before and after guselkumab treatment were superimposed for each individual probe CYP-substrate, and the estimated PK parameters for each individual probe CYP-substrate were also generally comparable before and after guselkumab treatment. Of note, the interpatient variability in PK parameters of omeprazole was moderate-to-large (%CV up to 53% for Cmax and 68% for AUCinf). The interpatient variability in PK parameters of dextromethorphan were even larger (%CV for Cmax and AUCinf were >100%). Nevertheless, considering interpatient variability in PK, the plasma concentration-time profiles and estimated PK parameters for omeprazole and dextromethorphan were generally comparable before and after guselkumab treatment.

The GMRs (day-15/day-1 and day-36/day-1) with 90% CIs for exposure parameters (Cmax and AUCinf) of each probe CYP-substrate are summarized in Table 3. Of note, only patients with available paired data (i.e., both days 1 and 15, or days 1 and 36) were included in the comparisons. The GMRs for Cmax and AUCinf of midazolam, S-warfarin, omeprazole, and caffeine ranged from 0.90–1.14 and 0.96–1.19, respectively. These ratios indicate that changes in Cmax and AUCinf values of these probe CYP-substrates were within ±20% before and after guselkumab treatment. The GMRs for Cmax and AUCinf of dextromethorphan for day-36/day-1 were 1.33 (90% CI 0.55–3.18) and 1.24 (90% CI 0.46 – 3.31), respectively. The numerically higher Cmax and AUCinf values of dextromethorphan were generally comparable before and after guselkumab treatment.

Exposure to guselkumab

A total of 14 patients received a single s.c. administration of guselkumab 200 mg on day 8. The mean serum guselkumab concentrations were 15.47 μg/mL (range 7.47–23.77 μg/mL; N = 14) on day 15 and 5.69 μg/mL (range 0.01–11.03 μg/mL; N = 12) on day 36, indicating that patients were exposed to guselkumab when receiving the CYP probe cocktail. Serum guselkumab concentrations were still quantifiable (mean: 0.53 μg/mL (range 0.01–1.34 μg/mL) on day 92. Of note, the t1/2 of guselkumab is ~18 days in patients with psoriasis.

PKs of probe CYP450 substrates

Mean plasma concentration-time profiles for each probe CYP-substrate following probe cocktail administrations on day 1 (1 week prior to guselkumab treatment), and on days 15 and 36 (1 and 4 weeks, respectively, after guselkumab treatment) are plotted on a semilogarithmic scale in Figure 2. Descriptive statistics for the derived PK parameters of each probe CYP-substrate before and after probe cocktail administrations are summarized in Table 2. Of note, among the 16 patients who received probe cocktail on day 1, 3 patients received an unverified dose of midazolam on day 1; 2 patients received unverified doses for midazolam on day 15; and 1 patient received an unverified dose of midazolam on day 36. PK parameters of midazolam from these patients were, therefore, excluded from the analyses. In

of 43 years (range 18–68 years), body weight of 96 kg (range 58–150 kg), and body mass index of 35 kg/m² (range 21–51 kg/m²). Among these patients, 14 received guselkumab and 12 completed the study. Four patients discontinued for various reasons (Table 1).

PK parameters for each individual probe CYP-substrate, including dextromethorphan, before (day 1) and after guselkumab treatment (days 15 and 36; Figure 3). Similarly, no consistent trend could be identified for individual Cmax values of each probe CYP-substrate, including dextromethorphan, before and after guselkumab treatment (data on file).

Clinical efficacy

The PASI and IGA data from this study indicated that the majority of patients experienced substantial clinical improvement in their psoriasis after a single s.c. administration of guselkumab 200 mg (Table 4). On day 64 (i.e., 8 weeks following guselkumab administration), 9 of 12 patients (75.0%) achieved at least 75% improvement in PASI score from baseline (PASI 75) and 8 of 11 patients (72.7%) achieved an IGA score of clear (0) or minimal (1).

Safety and tolerability

The probe cocktail was generally well-tolerated when administered alone or in combination with guselkumab to patients with psoriasis. A total of 10 patients reported at
least 1 TEAE: 4 patients who received probe cocktail only (after day 1 but before receiving guselkumab on day 8), 1 patient who received guselkumab only (received guselkumab on day 8 but before receiving probe cocktail on day 15), and 5 patients who received probe cocktail after receiving guselkumab (after receiving probe cocktail on day 15; data on file). The rate of TEAEs reported during the period of treatment with probe cocktail in combination with guselkumab (38.5%) was slightly higher than that for treatment with probe cocktail alone (25.0%); overall, there was no pattern suggestive of a meaningful difference in TEAEs between treatment with probe cocktail alone and in combination with guselkumab. The majority of TEAEs were mild or moderate in intensity. No clinically significant changes were observed for vital signs, electrocardiogram, physical examinations, and/or laboratory parameters.

DISCUSSION

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, and interferon) during chronic inflammation. For example, sirukumab, which targets IL-6 directly, and tocilizumab, which targets the IL-6 cell surface receptor, could reverse suppression of CYP enzyme activity in vitro or in vivo. In patients with rheumatoid arthritis, effects of sirukumab on midazolam (CYP3A4-substrate), omeprazole (CYP2C19-substrate), and S-warfarin (CYP2C9-substrate) were observed, and effects of tocilizumab on simvastatin (CYP3A4-substrate) and omeprazole (CYP2C19-substrate) were also reported. Consequently, TP-drug interaction studies are important for determining the effects of therapeutic monoclonal antibodies that target or modulate cytokines on CYP enzymes. Although recent studies reported that tildrakizumab and risankizumab (other IL-23p19 inhibitors) did not have any clinically meaningful effects on CYP metabolism, the implication of these study results to guselkumab is questionable because guselkumab has different binding affinity to the p19 subunit of human IL-23, distinct PK profile, and different dosing regimen when compared with tildrakizumab and risankizumab.

This study was conducted in patients with psoriasis to evaluate whether blocking IL-23p19 with guselkumab would alter the metabolism of probe substrates for CYP isozymes. Although a single-dose of guselkumab was used, the dose selected (200 mg) was twofold higher than the therapeutic dose level (100 mg) approved in patients with psoriasis.
A sufficiently high level of serum concentration was maintained through week 4. Therefore, the activity of IL-23 ligand would be fully blocked during the 4-week study period, which is deemed to be adequate to restore the activities of CYP-enzymes. Effects of cytokines on CYP-enzymes were evident following 24–48 hours of incubation of human hepatocytes with known influential cytokines.29 Overall, results from this exploratory TP-drug interaction study demonstrate that there were no clinically relevant changes in systemic exposure (C_max and AUC_τ) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine (probe substrates of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2, respectively) after a single s.c. dose of guselkumab. These results confirm in vitro findings that IL-23 inhibition does not modulate the expression or activity of multiple CYP450 enzymes,1 and indicate that drug interactions between guselkumab and substrates of various CYP enzymes are unlikely in patients with psoriasis. Our findings also suggest that the metabolic activity of CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2 was not affected by the decreased inflammation associated with improvement in disease achieved by blocking IL-23 in patients with psoriasis.

Dextromethorphan, a substrate of CYP2D6 (and also CYP3A4), has been widely used as a probe substrate for the measurement of CYP2D6 activity, as assessed by dextromethorphan exposure in plasma, or metabolic ratios of dextromethorphan to dextrorphan (its major metabolite) in urine or plasma.30 Due to the large sample size required and the low correlation of urinary metabolic ratio of dextromethorphan to dextrorphan with oral clearance of dextromethorphan,31 urine samples were not collected in this study. Large interpatient variability in PK parameters due to the large sample size required and the low correlation of urinary metabolic ratio of dextromethorphan to dextrorphan with oral clearance of dextromethorphan,31 urine samples were not collected in this study. Large interpatient variability in PK parameters

Table 2 PK parameters of probe CYP450 substrates before and after treatment with guselkumab

| Substrate/parameter | Day 1 (1 week before initiating guselkumab) | Day 15 (1 week after initiating guselkumab) | Day 36 (4 weeks after initiating guselkumab) |
|---------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Midazolam           |                                             |                                             |                                             |
| N                   | 13                                          | 11                                          | 11                                          |
| C_max, ng/mL        | 13.2 (7.0)                                  | 14.6 (6.8)                                  | 15.2 (8.0)                                  |
| T_max, hour         | 1.0 (0.5; 3.0)                              | 0.5 (0.5; 1.1)                              | 1.0 (0.5; 1.6)                              |
| AUC_τ, ng·hour/mL   | 49.8 (24.0)                                 | 51.2 (22.9)                                 | 51.5 (23.1)                                 |
| t_1/2, hour         | 7.3 (1.9)                                   | 7.4 (2.7)                                   | 7.0 (2.0)                                   |
| S-Warfarin          |                                             |                                             |                                             |
| N                   | 16                                          | 13                                          | 12                                          |
| C_max, ng/mL        | 582.9 (159.7)                               | 618.7 (132.7)                               | 540.0 (142.5)                               |
| T_max, hour         | 1.8 (0.5; 3.0)                              | 1.5 (0.5; 4.0)                              | 1.6 (0.5; 3.1)                              |
| AUC_τ, ng·hour/mL   | 18398.2 (6037.8)^a                          | 20774.2 (5871.5)                            | 19522.5 (5726.0)^b                          |
| t_1/2, hour         | 34.1 (7.1)^a                                | 36.1 (6.7)                                  | 36.4 (6.7)^a                                |
| Omeprazole          |                                             |                                             |                                             |
| N                   | 15                                          | 12                                          | 11                                          |
| C_max, ng/mL        | 350.6 (132.6)                               | 331.3 (130.8)                               | 330.9 (175.5)                               |
| T_max, hour         | 2.8 (1.5; 4.1)                              | 3.0 (1.5; 4.0)                              | 3.0 (2.0; 7.7)                              |
| AUC_τ, ng·hour/mL   | 1029.9 (686.6)^b                            | 952.8 (646.8)^b                            | 795.6 (669.7)^d                             |
| t_1/2, hour         | 1.4 (0.6)^c                                 | 1.3 (0.5)^b                                 | 1.2 (0.3)^d                                 |
| Dextromethorphan    |                                             |                                             |                                             |
| N                   | 15                                          | 12                                          | 11                                          |
| C_max, ng/mL        | 1.8 (2.0)                                   | 2.1 (2.7)                                   | 2.5 (3.3)                                   |
| T_max, hour         | 3.0 (1.0; 4.1)                              | 3.2 (1.5; 4.3)                              | 3.1 (1.5; 4.0)                              |
| AUC_τ, ng·hour/mL   | 23.0 (29.6)^a                               | 17.2 (21.7)^d                               | 26.4 (33.8)^d                               |
| t_1/2, hour         | 6.5 (1.1)^a                                 | 6.6 (1.0)^d                                 | 6.9 (1.2)^d                                 |
| Caffeine            |                                             |                                             |                                             |
| N                   | 16                                          | 13                                          | 11                                          |
| C_max, ng/mL        | 2096.3 (533.5)                              | 2166.2 (358.9)                              | 2183.6 (499.9)                              |
| T_max, hour         | 1.5 (0.5; 4.0)                              | 1.5 (0.5; 4.0)                              | 1.0 (0.5; 3.0)                              |
| AUC_τ, ng·hour/mL   | 22766.7 (12312.0)                           | 21019.2 (8215.7)^a                          | 20856.9 (7874.5)                            |
| t_1/2, hour         | 6.4 (1.9)                                   | 6.2 (1.9)^a                                 | 6.5 (2.5)                                   |

AUC_τ, area under the plasma concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase; C_max, maximum observed plasma concentration; PK, pharmacokinetic; SD, standard deviation; T_max, terminal half-life; T_max, time to reach the maximum observed plasma concentration. Median (minimum, maximum) is reported for T_max; arithmetic mean (SD) is reported for other PK parameters. ^a n = 14; ^b n = 11; ^c n = 13; ^d n = 7; ^e n = 12; ^f n = 9; ^g n = 10. Patients were excluded from midazolam analysis because of unverified midazolam dose; patients were excluded from s-warfarin analysis because of the percentage of extrapolated AUC after the last quantifiable plasma concentration (%AUC_τ,ex ) exceeded 25% of the AUC_τ value; patients were excluded from omeprazole analysis because of (i) insufficient data points; (ii) R^2 < 0.80; and/or (iii) concentration values were outliers identified using Dixon test; patients were excluded from dextromethorphan analysis because of (i) insufficient data points; (ii) abnormal PK profile; and/or R^2 < 0.80; patients were excluded from caffeine analysis because of (i) %AUC_τ,ex > 25% of the AUC_τ value, and (ii) predose concentration (632 ng/mL) is > 10% of C_max.
of dextromethorphan has been reported, with CV% of plasma AUC values over 100% in extensive metabolizers,\textsuperscript{32} which might be related to the high interpatient variability in CYP2D6 hepatic intrinsic clearance (~60–70% CV% among extensive metabolizers).\textsuperscript{33} Dextromethorphan has also been reported to exhibit moderate-to-large intrapatient variability (37–56%) in metabolic ratios,\textsuperscript{34} which would further complicate the assessment of CYP2D6-related drug interactions using this probe substrate. The large interpatient variability in dextromethorphan PK observed in this study (CV% ~115–130% for $C_{\text{max}}$ and $AUC_{\text{inf}}$) was consistent with literature reports cited above.

**Table 3** GMRs with 90% CIs of exposure parameters of probe CYP450 substrates after treatment with guselkumab

| Substrate | Parameter       | Day 15/day 1 | Day 36/day 1 |
|-----------|----------------|--------------|--------------|
|           | $n^a$ GMR (90% CI) | $n^a$ GMR (90% CI) |
| Midazolam | $C_{\text{max}}$ (ng/mL) | 11 1.11 (0.75–1.65) | 11 1.14 (0.77–1.69) |
|           | $AUC_{\text{inf}}$ (ng·hour/mL) | 11 1.01 (0.70–1.45) | 11 1.04 (0.75–1.44) |
| S-warfarin| $C_{\text{max}}$ (ng/mL) | 13 1.07 (0.90–1.27) | 12 0.90 (0.74–1.11) |
|           | $AUC_{\text{inf}}$ (ng·hour/mL) | 13 1.12 (0.90–1.40) | 11 1.05 (0.82–1.36) |
| Omeprazole| $C_{\text{max}}$ (ng/mL) | 12 0.96 (0.72–1.28) | 11 0.96 (0.67–1.36) |
|           | $AUC_{\text{inf}}$ (ng·hour/mL) | 10 0.96 (0.61–1.52) | 6 1.19 (0.75–1.90) |
| Dextromethorphan | $C_{\text{max}}$ (ng/mL) | 12 1.06 (0.46–2.43) | 11 1.33 (0.55–3.18) |
|           | $AUC_{\text{inf}}$ (ng·hour/mL) | 8 1.13 (0.56–2.28) | 8 1.24 (0.46–3.31) |
| Caffeine  | $C_{\text{max}}$ (ng/mL) | 13 1.07 (0.94–1.22) | 11 1.06 (0.89–1.26) |
|           | $AUC_{\text{inf}}$ (ng·hour/mL) | 12 1.00 (0.77–1.31) | 11 1.02 (0.77–1.35) |

$AUC_{\text{inf}}$, area under the plasma concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase; CI, confidence interval; $C_{\text{max}}$, maximum observed plasma concentration; GMR, geometric mean ratio.

*aOnly patients with paired data were included in the comparison (i.e., patients who had both day 1 and day 15 pharmacokinetic (PK) parameters were included in comparison of day 15/day 1 and patients who had both day 1 and day 36 PK parameters were included in comparison of day 36/day 1).

**Figure 3** Individual $AUC_{\text{inf}}$ of: (a) midazolam, (b) S-warfarin, (c) omeprazole, (d) dextromethorphan, and (e) caffeine before and after treatment with guselkumab. $AUC_{\text{inf}}$, area under the curve; $AUC_{\text{inf}}$, $AUC$ from time 0 to infinity with extrapolation of the terminal phase.
Because increased cytokine levels may downregulate CYPs, blockade of cytokines may enhance CYP activity and consequently lead to reduction in systemic exposure of drugs metabolized by CYPs. In this study, however, the systemic exposure of dextromethorphan following guselkumab treatment seemed to be higher rather than lower. This cannot be explained by inhibition of the potentially downregulating effect of IL-23 on CYPs by guselkumab. The numerically higher mean $C_{\text{max}}$ and $AUC_{\text{inf}}$ values of dextromethorphan at 4 weeks following guselkumab treatment were more likely attributable to the large interpatient and intrapatient variability in the PK of dextromethorphan. Regardless of the numeric differences in the geometric mean values of $C_{\text{max}}$ and $AUC_{\text{inf}}$ for dextromethorphan before and after treatment with guselkumab, no consistent trend could be identified for the individual $C_{\text{max}}$ and $AUC_{\text{inf}}$ values of dextromethorphan before and after guselkumab treatment, further demonstrating that systemic exposure of dextromethorphan was not affected by treatment with guselkumab.

Based on the prespecified criteria, some PK parameters were excluded from statistical analyses (Table S1). Additional sensitivity analyses were conducted to include all paired PK parameters, including the outliers for omeprazole and dextromethorphan, in the statistical comparison. The results from the sensitivity analysis (data on file) were similar to those presented from the original analysis. With the inclusion of the outliers, the GMRs were slightly closer to 1, but the 90% CIs were slightly larger.

The efficacy of guselkumab for treatment of psoriasis observed in this study was expected and comparable to published results. Additional cocktail studies with a cocktail of substrates are generally not powered to use the strict bioequivalence criteria to determine the presence or absence of drug-drug interactions for all evaluated exposure parameters of each component of the cocktail. Based on the findings from this study, drug interactions between guselkumab and substrates of various CYP enzymes are unlikely. Consequently, dose adjustment for concomitant CYP substrates in patients treated with guselkumab does not seem to be necessary.

**Supporting Information.** Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

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**Author Contributions.** All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

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