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Modulation of Interleukin-23 Signaling With Guselkumab in Biologic-Naive Patients Versus Tumor Necrosis Factor Inhibitor–Inadequate Responders With Active Psoriatic Arthritis

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Objective. We assessed and compared immunologic differences and associations with clinical response to guselkumab, a fully human interleukin (IL)–23p19 subunit inhibitor, in participants with active psoriatic arthritis (PsA) who were biologic-naive or had inadequate response to tumor necrosis factor inhibitors (TNFi-IR).

Methods. Serum biomarker levels at baseline and after treatment with guselkumab 100 mg every 8 weeks were compared between biologic-naive (n = 251) and TNFi-IR (n = 93) subgroups identified in the pooled DISCOVER-1/DISCOVER-2/COSMOS data set. Baseline biomarker levels determined by achievement of week 24 clinical responses (≥75%/90% improvement in Psoriasis Area and Severity Index [PASI 75/90], Investigator's Global Assessment [IGA] of psoriasis score 0/1 and ≥2-point improvement], ≥20% improvement in American College of Rheumatology criteria [ACR20]) were compared between prior treatment subgroups.

Results. Baseline IL-22, TNFα, and beta defensin-2 (BD-2) levels were significantly lower in biologic-naive than in TNFi-IR participants. With guselkumab, week 24 IL-17A, IL-17F, IL-22, serum amyloid A, C-reactive protein, IL-6, and BD-2 levels were significantly reduced from baseline in biologic-naive and TNFi-IR participants (≥1.4-fold difference, nominal $P < 0.05$). Clinical responders to guselkumab exhibited significantly higher baseline levels of several biomarkers than nonresponders (IL-17A, IL-17F, BD-2 in biologic-naive PASI 90 responders; IL-17A, BD-2 in TNFi-IR IGA 0/1 responders; IL-22, BD-2 in TNFi-IR PASI 90 responders [nominal $P < 0.05$]) and trended higher in TNFi-IR ACR20 responders.

Conclusion. Guselkumab modulates IL-23 signaling and provides consistent pharmacodynamic effects in both biologic-naive and TNFi-IR PsA patients. Significantly elevated baseline IL-22, TNFα, and BD-2 levels and associations between baseline IL-22, IL-17A, and BD-2 levels and skin responses to guselkumab suggest greater dysregulation of IL-23/Th17 signaling in patients with TNFi-IR.

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The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at https://yoda.yale.edu/.

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, heterogeneous, inflammatory disease with multiple musculoskeletal and dermatologic manifestations.[1] Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are typically used as first-line treatments for patients with active peripheral arthritis involvement, while biologic DMARDs (bDMARDs) or targeted synthetic DMARDs are often used for those with an inadequate response to csDMARDs. Although advanced therapies, including bDMARDs targeting interleukin-17A (IL-17A), IL-12/23, or IL-23, may be appropriate for some patients, tumor necrosis factor inhibitors (TNFi) have historically been used as first-line biologics.[2,3] Despite this, ≥40% of patients receiving TNFi do not achieve ≥20% improvement in the American College of Rheumatology response criteria (ACR20) with 6 months of treatment.[4] Previous research has found that patients with PsA who switch TNFi therapy experience diminished responses with each successive TNFi agent[5,6] and decreased persistence with subsequent bDMARDs.[7,8] Thus, patients with PsA who have had an inadequate response, defined herein as lack of efficacy, to TNFi (TNFi-IR) represent a difficult-to-treat population. A better understanding of the immunologic characteristics of patients with PsA who are biologic-naive or have TNFi-IR and the differences between these patient types may help optimize treatment strategies.

IL-23, a heteromeric cytokine comprising p19 and p40 protein subunits, regulates expansion and maintenance of Th17 cells and stimulates several other cell types that collectively produce and secrete proinflammatory cytokines.[9–11] IL-23 signaling is a key driver of IL-17A, IL-17F, IL-22, IL-6, and tumor necrosis factor alpha (TNFα) production,[12,13] which has been associated with pathogenic changes in both skin and the musculoskeletal system in patients with psoriatic disease.[14–16] Production of the Th17-type signature cytokines IL-17A, IL-17F, and IL-22 contributes to pannus formation, the key feature underlying PsA pathogenesis.[17,18] Beta defensin-2 (BD-2), a protein secreted by epithelial cells that possesses a broad spectrum of antimicrobial activity, has also been identified as a biomarker of IL-17A-driven skin pathology in psoriasis[19,20] and has been shown to be upregulated in keratinocytes via IL-23 signaling.[21]

Guselkumab, a fully human monoclonal antibody targeting the IL-23p19 subunit, is approved to treat moderate-to-severe plaque psoriasis and active PsA.[22] In the phase 3 DISCOVER-1 (clinicaltrials.gov identifier: NCT03162796) and DISCOVER-2 (NCT03158285) trials, a significant benefit of guselkumab every 4 weeks (Q4W) or every 8 weeks (Q8W) was seen versus placebo in improving PsA signs and symptoms in adults with active PsA.[23,24] DISCOVER-1 included participants who were biologic-naive and TNFi-experienced, whereas DISCOVER-2 enrolled only biologic-naive individuals. Notably, significant disease improvement in multiple PsA manifestations was seen with guselkumab compared with placebo in both biologic-naive and TNFi-experienced participants.[23–25] The phase 3b COSMOS (NCT03796858) study of guselkumab Q8W versus placebo in participants with PsA with either inadequate efficacy or intolerance to TNFi corroborated the findings of the DISCOVER trials.[26]

The objectives of this exploratory analysis of data from the DISCOVER-1, DISCOVER-2, and COSMOS studies were to assess biologic-naive versus TNFi-IR participants with active PsA in terms of select serum biomarker levels at baseline both prior to and over the course of guselkumab treatment, as well as differences in baseline biomarker levels between clinical responders and nonresponders to guselkumab treatment.

MATERIALS AND METHODS

Participants. Study designs and participant populations of the multicenter, randomized, double-blind, placebo-controlled phase 3 DISCOVER-1[23] and DISCOVER-2[24] trials and the phase 3b COSMOS[26] trial have been described previously. In brief, DISCOVER-1 enrolled adults with active PsA (swollen joint count [SJC] ≥3, tender joint count [TJC] ≥3, and C-reactive protein [CRP] ≥0.3 mg/dL) despite standard therapies and who met ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening. Participants were biologic-naive or had prior exposure to one or two TNFi (limited to ∼30% of the study population); the latter could have discontinued their prior TNFi because of lack of benefit, intolerance, or other reasons. DISCOVER-2 enrolled biologic-naive adults with active PsA (SJC ≥5, TJC ≥5, and CRP ≥0.6 mg/dL) despite standard therapies. Participants in both DISCOVER trials were randomized 1:1:1 to receive subcutaneous guselkumab 100 mg Q4W; guselkumab 100 mg at weeks 0 and 4, then Q8W; or placebo with crossover to guselkumab 100 mg Q4W at week 24. COSMOS enrolled only adults with active PsA (SJC ≥3 and TJC ≥3, no minimum CRP requirement) who demonstrated inadequate efficacy or intolerance to one or two TNFi. COSMOS participants were randomized 2:1 to receive guselkumab 100 mg at weeks 0 and 4, then Q8W or placebo with crossover to guselkumab 100 mg Q8W at weeks 24 and 28, then Q8W. A TNFi washout period was required for TNFi-experienced participants in DISCOVER-1 and all COSMOS participants.[23,26]

Across the three studies, participants with <5% improvement from baseline in both SJC and TJC at week 16 qualified for early escape (EE). Those in DISCOVER-1 and DISCOVER-2 who met EE criteria continued their randomized dosing regimen and could initiate or increase the previously stable dose of a concomitant medication as specified per protocol. In COSMOS, participants meeting EE criteria could initiate or increase the dose of one concomitant medication up to the maximum allowed dose per protocol; those randomized to guselkumab received placebo at week 16 and guselkumab at week 20, then continued the Q8W dosing regimen, whereas those randomized to placebo initiated guselkumab 100 mg at weeks 16 and 20, then Q8W.

For these exploratory analyses, data from subgroups comprising TNFi-IR (defined in this analysis as lack of efficacy) participants (DISCOVER-1 and COSMOS) and biologic-naive participants (DISCOVER-1 and DISCOVER-2) with available biomarker data were evaluated. Baseline analyses in these biomarker cohorts included guselkumab Q4W–, guselkumab Q8W–, and placebo-randomized participants. Because the COSMOS study did not evaluate the guselkumab 100 mg Q4W regimen, postbaseline analyses assessing treatment effect included only guselkumab Q8W– and placebo-randomized participants within the biologic-naive and TNFi-IR subgroups from the DISCOVER trials. Additionally, because no minimum baseline CRP level was specified in the COSMOS inclusion criteria, only participants with serum CRP ≥0.3 mg/dL at the COSMOS screening visit were included in these post hoc analyses to align with the disease characteristics of DISCOVER-1 participants who had TNFi-IR.

Serum sample collection. Serum samples were collected from randomized participants at baseline (week 0), week 4, and week 24, including from those who met the EE criteria. Serum samples from 43 healthy volunteers (no clinical evidence of active infection) were independently obtained (Bioreclamation and Biological Specialty Corporation) and were matched for age, sex, race, and ethnicity with participants of the clinical trials (as reported by the investigator).

Blood samples were allowed to clot for 30 minutes. Serum was separated by centrifugation at room temperature within one hour of collection (1,500 × *g* for 15 to 20 minutes). Aliquots of serum samples were frozen at –20°C or below before analysis.

Sample analysis. Serum samples were analyzed for selected IL-23/Th17 effector cytokines, acute phase proteins, and BD-2 in the biologic-naive and TNFi-IR subgroups and in healthy controls. Serum IL-17A levels were quantified by ultrasensitive single molecule array Simoa™ technology (Quanterix); IL-17F and IL-22 levels by Single Molecule Counting SMCxPRO Immunoassay Platform (Millipore); and serum amyloid A (SAA), CRP, IL-6, TNFα, and BD-2 levels by Meso Scale Discovery Platform.

Clinical response. Clinical responses were assessed among guselkumab Q8W– and placebo-randomized participants at week 24 as previously described.[23,24,26] In brief, improvements in joint symptoms were assessed using the ACR20 response criteria, the primary endpoint common to all three studies.[27] Among participants with an Investigator's Global Assessment of psoriasis (IGA) score ≥2 and ≥3% body surface area (BSA) affected at baseline, improvement in skin disease was assessed by achievement of IGA 0/1 response, defined as achieving an IGA score of 0 (clear) or 1 (minimal) with ≥2-point improvement from baseline.[28] Additionally, the proportions of participants achieving ≥75% or ≥90% improvement in the Psoriasis Area and Severity Index (PASI 75 or PASI 90, respectively)[29] were determined among individuals with a baseline PASI score >0, regardless of baseline IGA score or percent BSA affected by psoriasis.

Statistical analysis. Patient demographics, disease characteristics, and concomitant medication use reported at baseline among all randomized participants were compared between biologic-naive and TNFi-IR patient subgroups using either a chi-square test (categorical variables) or *t*-test (continuous variables). Significant differences between subgroups were defined by a nominal $P < 0.05$.

In these post hoc analyses, serum biomarker concentrations were log2-transformed to normalize distribution of the data. To assess differences in serum biomarker levels between biologic-naive and TNFi-IR patient subgroups, between these patient subgroups and healthy controls, and from baseline at weeks 4 and 24, general linear model analyses were performed assuming that the distributions for each group were normal. Differences in serum concentrations ≥1.4-fold and with nominal $P < 0.05$ were considered statistically significant. For the assessment of pharmacodynamic responses to study treatment over time, a contrast data set for within-participant changes in cytokine expression was generated from log2-transformed data, with the change from baseline and the specified time point(s) calculated for each participant. Associations between baseline serum biomarker levels and week 24 clinical responses (PASI 75, PASI 90, IGA 0/1, and ACR20) were assessed via a general linear model using the clinical response categorical variable as the fixed factor. Significant associations were defined by a nominal $P < 0.05$.

Week 24 clinical responses were derived from the primary analyses of DISCOVER-1,[23] DISCOVER-2,[24] and COSMOS[26] that applied the following treatment failure rules: discontinued study treatment, terminated study participation, initiated or increased csDMARD or oral corticosteroid use, initiated protocol-prohibited PsA treatment, or met EE criteria at week 16 and initiated or increased the dose of one of the permitted concomitant medications. Participants who met treatment failure rules or had missing data for any reason were classified as nonresponders at week 24.

Ethics. All studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The participants provided written informed consent before any study-related procedure was performed.

RESULTS

Baseline clinical and molecular characteristics. In this pooled biomarker cohort, 90 (84 biologic-naive, 6 TNFi-IR), 147 (84 biologic-naive, 63 TNFi-IR), and 107 (83 biologic-naive, 24 TNFi-IR) participants were randomized to guselkumab Q4W, guselkumab Q8W, or placebo, respectively. Across randomized

groups, baseline participant demographics, disease characteristics, and concomitant medication use were generally comparable between the 251 biologic-naive participants pooled across DISCOVER-1 (n = 101) and DISCOVER-2 (n = 150) and the 93 TNFi-IR participants pooled across DISCOVER-1 (n = 17) and COSMOS (n = 76). Statistically significant differences were observed between subgroups for SJC (higher among biologic-naive participants), PsA and psoriasis durations (longer among TNFi-IR participants), and PASI score at baseline (higher among TNFi-IR participants; Supplementary Table S1). Within the TNFi-IR subgroup, 76 and 17 participants, respectively, had received one or two TNFi before initiating study treatment.

Baseline serum IL-17A, IL-17F, SAA, CRP, IL-6, and BD-2 levels were significantly higher in both biologic-naive and TNFi-IR participants with active PsA than in healthy controls (Table 1 and Supplementary Figure S1). IL-22 and TNFα levels were significantly lower in healthy controls and in biologic-naive participants than in TNFi-IR participants, with no significant differences observed between healthy controls and biologic-naive participants. BD-2 levels were significantly higher in biologic-naive and TNFi-IR participants than in healthy controls, levels in biologic-naive participants were significantly lower than in TNFi-IR participants.

Among guselkumab Q8W– and placebo-randomized participants, baseline biomarker levels were similar between treatment groups in the biologic-naive subgroup. In the TNFi-IR subgroup, baseline levels of IL-22 and acute phase proteins were similar across randomized treatment groups. However, levels of IL-17A, IL-17F, and BD-2 were significantly higher in guselkumab Q8W– than in placebo-randomized participants (Figure 1).

Table 1. Differences in baseline serum biomarker levels, pharmacodynamic effects of GUS Q8W, and associations of clinical response with baseline serum biomarker levels*

	Biomarker							
	IL-17A	IL-17F	IL-22	SAA	CRP	IL-6	TNFα	BD-2
Baseline serum levels[a]								
TNFi-IR vs HC	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.001$**
Biologic-naive vs HC	**$P < 0.05$**	**$P < 0.05$**	NS	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	NS	**$P < 0.001$**
Biologic-naive vs TNFi-IR	NS	NS	**$P < 0.05$**	NS	NS	NS	**$P < 0.05$**	**$P < 0.05$**
Pharmacodynamic effects of GUS Q8W[b]								
Biologic-naive participants								
W4 GUS vs W0 GUS	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	NS	NS	NS	NS	**$P < 0.001$**
W24 GUS vs W0 GUS	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	NS	**$P < 0.001$**
W4 GUS vs W4 PBO	NS	**$P < 0.05$**	NS	NS	NS	NS	NS	**$P < 0.01$**
W24 GUS vs W24 PBO	**$P < 0.05$**	**$P < 0.05$**	NS	**$P < 0.05$**	NS	**$P < 0.05$**	NS	**$P < 0.001$**
TNFi-IR participants								
W4 GUS vs W0 GUS	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	NS	NS	**$P < 0.01$**
W24 GUS vs W0 GUS	**$P < 0.05$**	**$P < 0.05$**	**$P < 0.05$**	**$P <0.05$**	**$P < 0.05$**	**$P < 0.05$**	NS	**$P < 0.001$**
W4 GUS vs W4 PBO	NS	NS	NS	NS	NS	NS	NS	NS
W24 GUS vs W24 PBO	**$P < 0.05$**	NS	**$P < 0.05$**	NS	NS	NS	NS	**$P < 0.05$**
Association of baseline serum levels with W24 clinical response to GUS Q8W								
Biologic-naive participants								
PASI 75	NS	**$P < 0.05$**[c]	NS	NS	NS	NS	NS	NS
PASI 90	**$P < 0.05$**[c]	**$P < 0.01$**[c]	NS	NS	NS	NS	NS	**$P < 0.05$**[c]
IGA 0/1	NS	NS	NS	NS	NS	**$P < 0.05$**[d]	NS	NS
ACR20	NS	NS	NS	NS	NS	NS	NS	NS
TNFi-IR participants								
PASI 75	NS	NS	**$P = 0.06$**[b]	NS	NS	NS	NS	**$P < 0.01$**[c]
PASI 90	NS	NS	**$P < 0.05$**[c]	NS	NS	NS	NS	**$P < 0.01$**[c]
IGA 0/1	**$P < 0.05$**[c]	NS	NS	NS	NS	NS	**$P < 0.05$**[d]	**$P < 0.01$**[c]
ACR20	NS	NS	**$P = 0.07$**	NS	NS	NS	NS	**$P = 0.05$**

* Analyses conducted at baseline include data from all randomized participants of the DISCOVER-1, DISCOVER-2, and COSMOS biomarker cohorts. Analyses conducted postbaseline include data only from GUS Q8W– and placebo-randomized participants of the DISCOVER-1, DISCOVER-2, and COSMOS biomarker cohorts. Bold values indicate statistical significance or trending associations. All *P* values are nominal. ACR20, ≥20% improvement in the American College of Rheumatology response criteria; BD-2, beta defensin-2; CRP, C-reactive protein; GUS, guselkumab; HC, healthy control; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (minimal) with ≥2-point improvement from baseline (among patients with an IGA score ≥2 and ≥3% body surface area affected at baseline); IL, interleukin; NS, not significant; PASI 75/90, ≥75%/90% improvement from baseline in Psoriasis Area and Severity Index; PBO, placebo; Q8W, every 8 weeks; SAA, serum amyloid A; TNFα, tumor necrosis factor alpha; TNFi-IR, tumor necrosis factor inhibitor–inadequate response; W, week.

[a] *P* values indicate higher biomarker levels in biologic-naive participants versus TNFi-IR participants, biologic-naive participants versus HCs, and TNFi-IR participants versus HCs. Significant differences between groups are defined by ≥1.4-fold difference and $P < 0.05$.

[b] *P* values indicate lower biomarker levels in GUS-treated participants versus PBO participants and at W4/W24 versus W0. Significant differences with GUS versus PBO and from W4/W24 versus W0 are defined by ≥1.4-fold difference and $P < 0.05$.

[c] *P* values indicate higher baseline biomarker levels associated or trending toward association with clinical responses. Significant associations were defined by $P < 0.05$.

[d] *P* values indicate lower baseline biomarker levels associated with clinical responses. Significant associations were defined by $P < 0.05$.

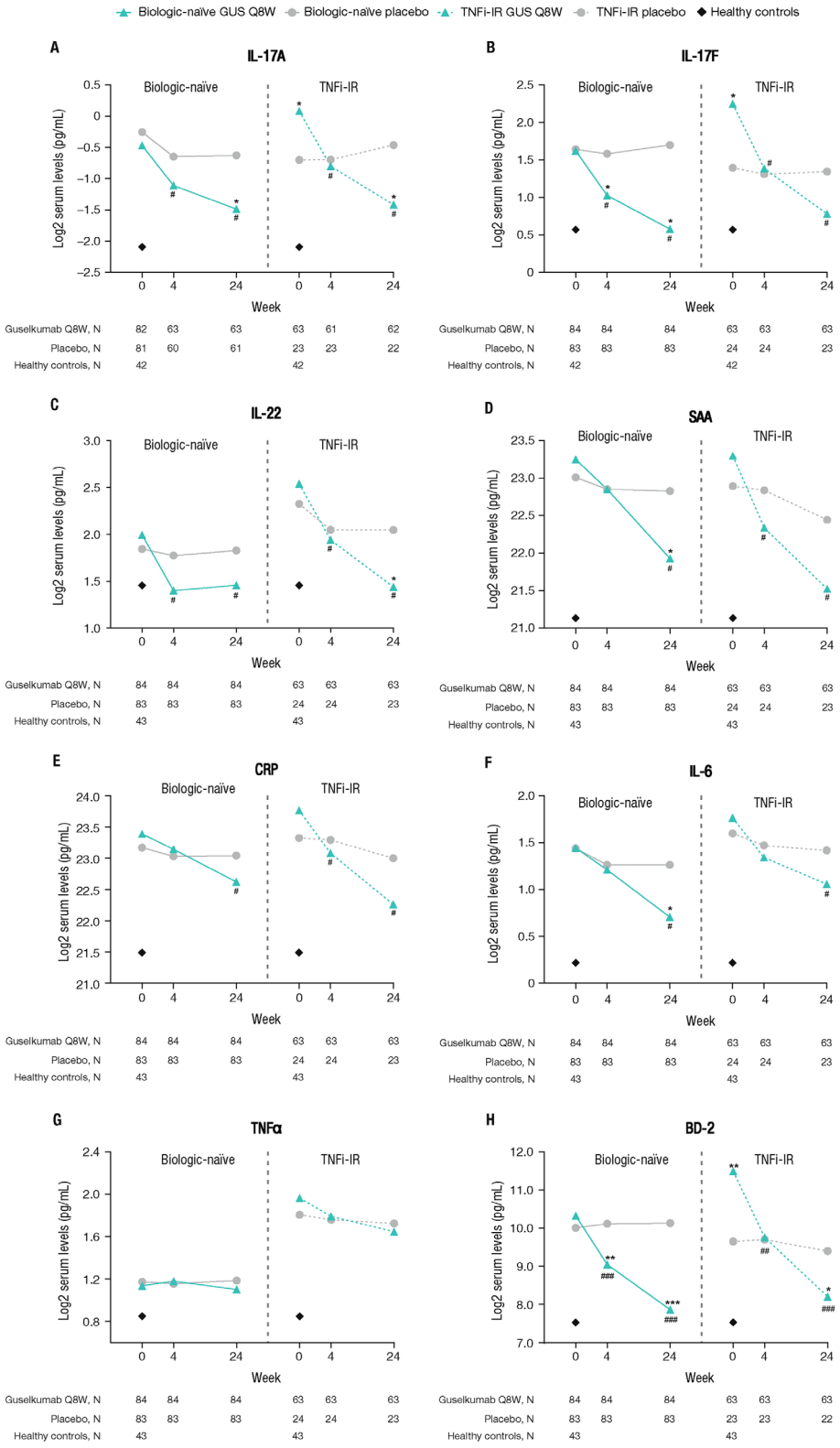

Figure 1. Mean serum A) IL-17A, B) IL-17F, C) IL-22, D) SAA, E) CRP, F) IL-6, G) TNFα, and H) BD-2 levels over time with GUS Q8W or placebo in biologic-naive and TNFi-IR subgroups pooled across the DISCOVER-1, DISCOVER-2, and COSMOS clinical trials. A total of 16 biologic-naive (GUS Q8W, n = 2; placebo, n = 14; all DISCOVER) and 8 TNFi-IR (GUS Q8W, n = 0; placebo, n = 8; all COSMOS) qualified for EE at W16. $^{*}P < 0.05$ versus placebo; $^{**}P < 0.01$ versus placebo; $^{***}P < 0.001$ versus placebo; $^{\#}P < 0.05$ versus W0; $^{\#\#}P < 0.01$ versus W0; $^{\#\#\#}P < 0.001$ versus W0. All *P* values are nominal. Differences in serum concentrations ≥1.4-fold from baseline at each time point and with nominal $P < 0.05$ were considered statistically significant. BD-2, beta defensin-2; CRP, C-reactive protein; EE, early escape; GUS, guselkumab; IL, interleukin; Q8W, every 8 weeks; SAA, serum amyloid A; TNFα, tumor necrosis factor alpha; TNFi-IR, tumor necrosis factor inhibitor–inadequate response; W, week.

Pharmacodynamic effect of guselkumab Q8W. Guselkumab treatment showed early and sustained pharmacodynamic effects across biologic-naive and TNFi-IR subgroups (Table 1 and Figure 1). Among participants receiving placebo, no significant changes in biomarker levels occurred through week 24 (placebo-controlled period) (Figure 1).

By week 4, guselkumab treatment significantly lowered levels of IL-23/Th17 effector cytokines (IL-17A, IL-17F, and IL-22) and BD-2 from baseline in both biologic-naive and TNFi-IR participants (Figure 1A, B, C, and H and Table 1). Levels of these biomarkers generally continued to decrease through week 24 across subgroups. After rapidly reaching levels similar to those in healthy controls, reduced IL-22 levels were maintained from week 4 to week 24 in biologic-naive participants (Figure 1C). TNFα levels, which are not exclusively IL-23 dependent, did not decrease significantly in response to guselkumab in either subgroup (Figure 1G). Levels of SAA, CRP, and IL-6 were significantly reduced from baseline at week 24 of guselkumab treatment in both biologic-naive and TNFi-IR participants (Figure 1D–F). In addition, levels of IL-17A, IL-17F, BD-2, SAA, and IL-6 were significantly lower with guselkumab than with placebo at week 24 among biologic-naive participants, as were levels of IL-17A, IL-22, and BD-2 in TNFi-IR participants.

Baseline biomarker levels and clinical responses. Evaluation of the relationships between baseline biomarker levels and week 24 clinical response within each subgroup revealed several associations in guselkumab-, but not placebo-, treated participants (Table 1 and Supplementary Table S2). Specifically, among guselkumab-treated biologic-naive participants, baseline levels of IL-17F were significantly higher in week 24 PASI 75 responders than in nonresponders (Figure 2). When assessed by the more stringent PASI 90 response, baseline IL-17F and BD-2 levels were significantly higher in biologic-naive week 24 responders than in nonresponders (Figure 3). Among guselkumab-treated TNFi-IR participants, baseline IL-22 and BD-2 levels were significantly higher in PASI 90 responders at week 24 (Figure 3) compared with nonresponders.

Utilizing IGA 0/1 response criteria, baseline IL-17A and BD-2 levels were significantly higher in guselkumab-treated TNFi-IR responders versus nonresponders (Figure 4). IGA 0/1 responders also had lower baseline IL-6 levels in the biologic-naive subgroup and lower TNFα levels in the TNFi-IR subgroup relative to IGA 0/1 nonresponders (Figure 4).

No associations were observed between baseline biomarker levels and ACR20 response at week 24 in the biologic-naive

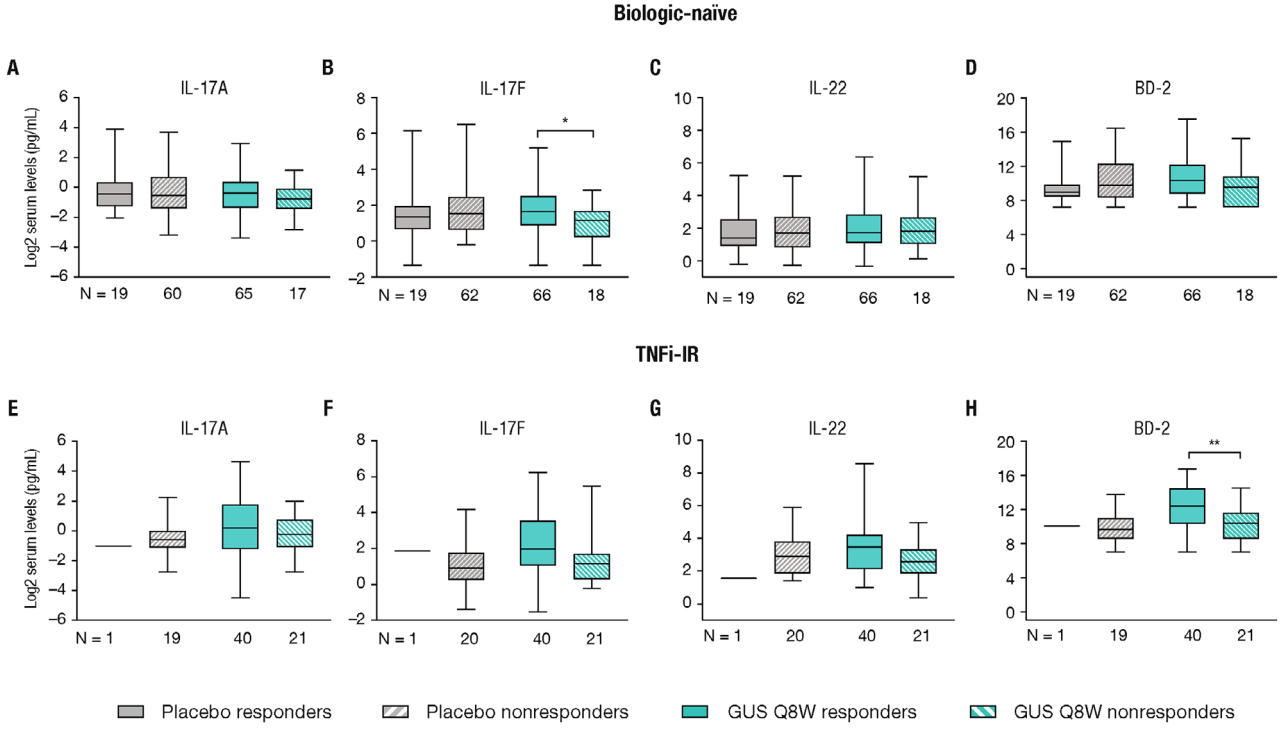

Figure 2. Baseline serum A) IL-17A, B) IL-17F, C) IL-22, and D) BD-2 levels among week 24 PASI 75 responders and E) IL-17A, F) IL-17F, G) IL-22, and H) BD-2 levels among week 24 PASI 75 nonresponders treated with either placebo or GUS Q8W in biologic-naive and TNFi-IR subgroups pooled across the DISCOVER-1, DISCOVER-2, and COSMOS clinical trials. *P* values indicate statistical (general linear model) significance versus nonresponders. *Nominal $P < 0.05$; **nominal $P < 0.01$. Lower whisker represents minimum, lower box boundary represents 25th percentile, horizontal line represents median, upper box boundary represents 75th percentile, upper whisker represents maximum. BD-2, beta defensin-2; GUS, guselkumab; IL, interleukin; PASI 75, ≥75% improvement from baseline in Psoriasis Area and Severity Index; Q8W, every 8 weeks; TNFi-IR, tumor necrosis factor inhibitor–inadequate response.

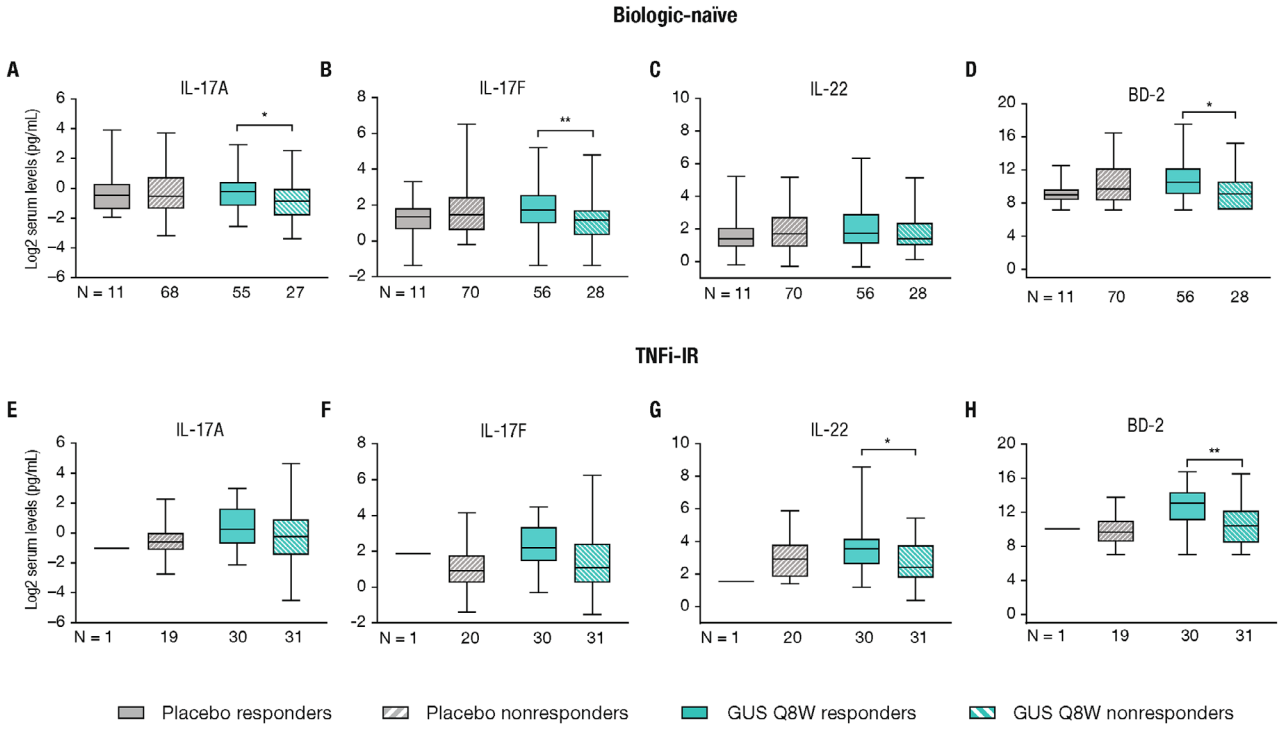

Figure 3. Baseline serum A) IL-17A, B) IL-17F, C) IL-22, and D) BD-2 levels among week 24 PASI 90 responders and E) IL-17A, F) IL-17F, G) IL-22, and H) BD-2 levels among week 24 PASI 90 nonresponders treated with either placebo or GUS Q8W in biologic-naive and TNFi-IR subgroups pooled across the DISCOVER-1, DISCOVER-2, and COSMOS clinical trials. *P* values indicate statistical (general linear model) significance versus nonresponders. *Nominal $P < 0.05$; **nominal $P < 0.01$. Lower whisker represents minimum, lower box boundary represents 25th percentile, horizontal line represents median, upper box boundary represents 75th percentile, upper whisker represents maximum. BD-2, beta defensin-2; GUS, guselkumab; IL, interleukin; PASI 90, ≥90% improvement from baseline in Psoriasis Area and Severity Index; Q8W, every 8 weeks; TNFi-IR, tumor necrosis factor inhibitor–inadequate response.

subgroup. Among TNFi-IR participants receiving guselkumab, week 24 ACR20 responders had numerically higher baseline IL-22 and BD-2 levels than nonresponders (Figure 5).

DISCUSSION

Results of these analyses using pooled data across the DISCOVER-1, DISCOVER-2, and COSMOS studies provide further understanding of biomarker profiles in both biologic-naive and TNFi-IR patients with active PsA and their associations with clinical response to guselkumab treatment. Significantly lower baseline TNFα levels were seen in the biologic-naive subgroup compared with the TNFi-IR subgroup. Considering that TNFi-experienced participants of the DISCOVER-1 and COSMOS trials completed a required TNFi washout period to minimize influence of prior TNFi treatment on study results, these post hoc findings suggest that continued dysregulation of TNFα may be related to inadequate response to therapies targeting TNFα. These findings align with observations in patients with rheumatoid arthritis,[30] in whom elevated TNFα levels are postulated to be an adaptive response to TNFi therapy that leads to inadequate response.[31] Among participants treated with guselkumab in the present study, TNFα expression was also significantly lower among TNFi-IR week 24 IGA 0/1 responders compared with nonresponders, but no apparent difference was observed between PASI 75/90 responders and nonresponders. In previous biomarker analyses from the DISCOVER and COSMOS studies, no associations between TNFα levels and clinical response were found.[32,33] Further investigation into the role of TNFα expression in achieving treatment response in PsA may be warranted.

Serum levels of the proinflammatory cytokine IL-22, which is known to be upregulated by IL-23 and involved in the pathogenesis of psoriatic disease,[14,17] were also significantly lower at baseline in the biologic-naive subgroup than in the TNFi-IR subgroup. In PsA, activated synovial T cells produce higher levels of IL-22 than activated peripheral blood T cells, and IL-22 is a potent mitogenic agent for fibroblast-like synoviocytes.[17,34,35] Results of the present analysis suggest that this cytokine may be involved in perpetuating PsA disease activity, particularly in a TNFi-IR population. Greater dysregulation of the IL-23/Th17 pathway in patients with TNFi-IR PsA is consistent with previous research in which long-term in vivo blockade of TNFα enhanced production of Th17 cytokines in a murine model of psoriasis.[36]

Across patients comprising the biologic-naive and TNFi-IR patient subgroups, guselkumab significantly reduced IL-22 levels

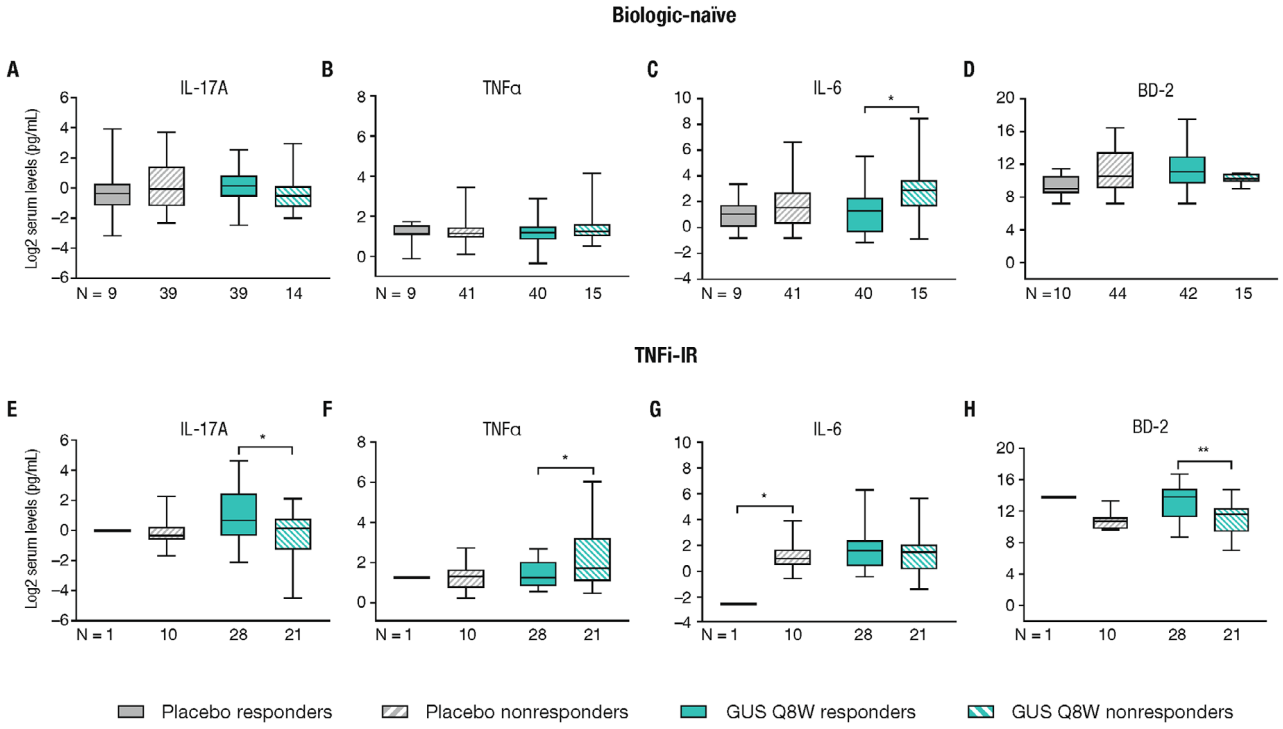

Figure 4. Baseline serum A) IL-17A, B) TNFα, C) IL-6, and D) BD-2 levels among week 24 IGA 0/1 responders and E) IL-17A, F) TNFα, G) IL-6 and H) BD-2 levels among week 24 IGA 0/1 nonresponders treated with either placebo or GUS Q8W in biologic-naive and TNFi-IR subgroups pooled across the DISCOVER-1, DISCOVER-2, and COSMOS clinical trials. *P* values indicate statistical (general linear model) significance versus nonresponders. *Nominal $P < 0.05$. Lower whisker represents minimum, lower box boundary represents 25th percentile, horizontal line represents median, upper box boundary represents 75th percentile, upper whisker represents maximum. BD-2, beta defensin-2; GUS, guselkumab; IGA 0/1, Investigator's Global Assessment score of 0 (clear) or 1 (minimal) with ≥2-point improvement from baseline (among patients with an IGA score ≥2 and ≥3% body surface area affected at baseline); IL, interleukin; Q8W, every 8 weeks; TNFα, tumor necrosis factor alpha; TNFi-IR, tumor necrosis factor inhibitor–inadequate response.

as early as week 4, with lower levels maintained from week 4 to week 24. These data suggest IL-23 inhibition with guselkumab may reduce IL-22 in both biologic-naive and TNFi-IR PsA patients to levels seen in healthy controls. This is consistent with clinical findings that guselkumab is efficacious in both biologic-naive and TNFi-IR patient populations.[23,24,26,37,38] Previous research found that baseline IL-22 levels were significantly lower in patients with PsA who achieved Disease Activity in Psoriatic Arthritis (DAPSA) remission after 1 year of therapy with an IL-17 inhibitor than in those who did not, although IL-22 levels were not associated with response to TNFi.[39] This previous work also showed that TNFα levels, but not IL-17A or IL-23 levels, were significantly higher at the initiation of bDMARD therapy in a group of patients characterized by high levels of IL-22 relative to patients with low levels of IL-22. These findings suggest that unrestrained expression of TNFα and IL-22 may contribute to insufficient response to TNFi therapy in some patients. As such, achieving reduction in IL-22 levels could explain, in part, guselkumab efficacy in the TNFi-IR population. This hypothesis is further supported by the finding in the present study that baseline levels of IL-22 trended higher ($P = 0.07$) in guselkumab-treated ACR20 responders versus nonresponders in the TNFi-IR subgroup, but not the biologic-naive, subgroup. Previous post hoc analyses of the DISCOVER and COSMOS studies assessing the relationship between ACR20 response and baseline IL-22 levels are inconclusive[32,33]; further understanding of this relationship is needed.

Guselkumab also exhibited significant pharmacodynamic effects on IL-17A and IL-17F, elevated levels of which have been observed in patients with psoriatic disease.[14,18,40,41] Results presented herein using data from the pooled DISCOVER-1, DISCOVER-2, and COSMOS data set are corroborated by previous analyses of the pooled DISCOVER-1 and DISCOVER-2 studies (combined biologic-naive and TNFi-experienced) and COSMOS (IR or intolerance to TNFi).[32,33] Taken together with findings reported herein for IL-22, specifically blocking the IL-23p19 subunit with guselkumab may inhibit IL-17 and IL-22 in an IL-23–dependent manner.

Serum concentrations of BD-2, an antimicrobial peptide biomarker of skin pathology in psoriasis, have been shown to positively correlate with skin disease activity.[19,20] As such, the lower baseline serum BD-2 levels seen in biologic-naive than in TNFi-IR participants may align with the lower mean baseline PASI score and percent psoriatic BSA in the biologic-naive versus TNFi-IR subgroups. Significant pharmacodynamic effects of guselkumab on BD-2 levels, combined with significant associations between higher baseline BD-2 levels and achievement of skin responses

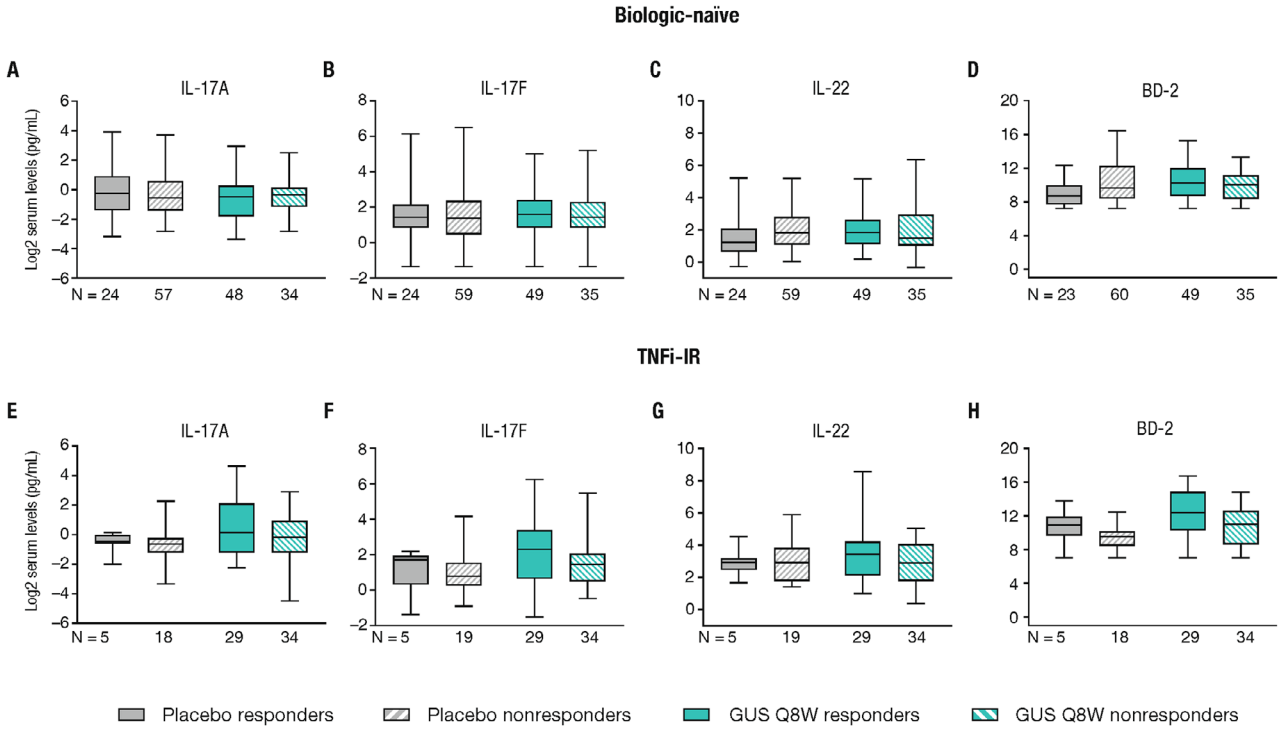

Figure 5. Baseline serum A) IL-17A, B) IL-17F, C) IL-22, and D) BD-2 levels among week 24 ACR20 responders and E) IL-17A, F) IL-17F, G) IL-22, and H) BD-2 levels among week 24 ACR20 nonresponders treated with placebo or GUS Q8W in biologic-naive and TNFi-IR subgroups pooled across the DISCOVER-1, DISCOVER-2, and COSMOS clinical trials. Lower whisker represents minimum, lower box boundary represents 25th percentile, horizontal line represents median, upper box boundary represents 75th percentile, upper whisker represents maximum. ACR20, ≥20% improvement from baseline in American College of Rheumatology response criteria; BD-2, beta defensin-2; GUS, guselkumab; IL, interleukin; Q8W, every 8 weeks; TNFi-IR, tumor necrosis factor inhibitor–inadequate response.

observed in both biologic-naive and TNFi-IR subgroups, support guselkumab as an efficacious treatment option for improving skin disease in patients with PsA. This is further supported by the significant associations observed between higher baseline IL-22 and IL-17A levels and achievement of skin responses in participants who have TNFi-IR. These findings also suggest a potential role for BD-2, IL-22, and IL-17A as predictors of skin disease improvement in patients who have TNFi-IR. High baseline BD-2 levels were associated with achieving ACR20/50/70 responses after IL-17A inhibition by secukinumab, particularly in patients who had TNFi-IR,[42] suggesting that BD-2 levels may be useful in identifying PsA patients with an IL-17-driven disease endotype who may be less likely to achieve response with TNFi. Such biomarkers predictive of PsA clinical response are valuable in guiding treatment choices for individual patients, although existing biomarker data are limited. Continued investigation of these biomarkers and their role in PsA pathogenesis is needed.

The pharmacodynamic effects described herein are consistent with the mechanism of action of guselkumab and the role of IL-23 in regulating the production of IL-23/Th17 effector cytokines. Additionally, reductions in IL-17A, IL-17F, IL-22, and BD-2 levels at week 4 (the earliest postbaseline assessment) support the early clinical improvements observed in the individual phase 3 trials.[23,24,26] Sustained decreases in IL-23/Th17 effector cytokines and acute phase proteins through week 24 in this pooled analysis are also consistent with durable clinical response rates previously reported in each study.[37,38,43]

As mentioned, several associations between IL-17A and IL-17F levels and skin responses, but not peripheral joint response (ACR20), were identified in the present analysis. Nonetheless, improvements in peripheral joint–related signs and symptoms with guselkumab were observed, suggesting that the other IL-23-driven mechanisms discussed previously (ie, IL-22 and BD-2 signaling) or other factors yet to be identified may be involved in joint pathology in PsA. Of note, as a fully human IgG1 monoclonal antibody with a native Fc region, guselkumab has demonstrated in vitro high affinity for binding the IL-23p19 subunit, high potency for inhibiting IL-23 signaling, and dose-dependent Fc-mediated binding to the Fcγ receptor I (also known as CD64) found on primary human inflammatory monocytes.[44] When bound to CD64, guselkumab was observed to simultaneously capture IL-23 being secreted from these same cells.[45] Based on prior observations of increased numbers of CD64+ IL-23–producing myeloid cells in inflamed tissue of patients with psoriatic disease,[46] and the positive correlation between joint disease activity and frequency of peripheral $CD64^{+}$ monocytes,[47] these molecular attributes may help explain improvements in joint disease with guselkumab treatment, although further study is needed.

This analysis was limited to participants with active PsA meeting criteria for phase 3 clinical trial inclusion and may not reflect the wider PsA population. Although inclusion criteria across the three trials were similar, differences apart from prior TNFi treatment included higher minimum SJC, TJC, and CRP levels at screening in DISCOVER-2 (≥5, ≥5, and ≥0.6 mg/dL, respectively) than in DISCOVER-1 (≥3, ≥3, and ≥0.3 mg/dL, respectively) or COSMOS (≥3, ≥3, and no minimum CRP level requirement, respectively). Most DISCOVER-1 and DISCOVER-2 participants were White (96%),[23,24] whereas participant race and ethnicity were not captured in the COSMOS study. Therefore, it cannot be ruled out that the immunologic and clinical differences observed between the biologic-naive and TNFi-IR subgroups are influenced by differences in race and/or ethnicity between the subgroups. Future studies are needed to evaluate the impact of race and ethnicity on immunologic differences between biologic-naive and TNFi-IR patients with PsA. Given the exploratory nature of these post hoc analyses, they were not adequately powered to estimate a treatment effect in multiple subgroups. Small sample sizes may also limit clinical interpretation. However, cytokine expression and clinical response findings of this pooled analysis are consistent with previously reported study findings demonstrating both efficacy of guselkumab in biologic-naive and TNFi-IR patients with active PsA and reduction of serum levels of effector cytokines associated with the IL-23/Th17 axis as early as week 4.[23,24,26,32,33,37]

Overall, guselkumab treatment exhibited generally comparable and significant pharmacodynamic effects on IL-23/Th17–associated cytokines across participants with PsA who are biologic-naive or have TNFi-IR. Baseline levels of IL-22 and BD-2 were significantly lower in biologic-naive than TNFi-IR participants. In both subgroups, levels of these cytokines at week 24 with guselkumab treatment reached or trended toward levels observed in healthy controls. The associations between elevated baseline levels of IL-22, IL-17A, and BD-2 and achievement of robust skin response at week 24 in TNFi-IR participants suggest that IL-23p19 subunit inhibition with guselkumab may play an important role in modulating aberrant IL-23/Th17 cell–mediated signaling in this difficult-to-treat population. Further clinical evaluation of guselkumab efficacy in TNFi-experienced patients is ongoing (NCT04936308 and NCT05669833).

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Siebert, Coates, Schett, Raychaudhuri, Chen, Gao, Kollmeier, Xu, Rahman, Mease, Deodhar.

Acquisition of data. Chen, Gao, Seridi, Kollmeier, Xu.

Analysis and interpretation of data. Siebert, Coates, Schett, Raychaudhuri, Chen, Gao, Seridi, Chakravarty, Shawi, Lavie, Sharaf, Zimmermann, Kollmeier, Xu, Rahman, Mease, Deodhar.

ROLE OF THE STUDY SPONSOR

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