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Guselkumab Provides Durable Improvement Across Psoriatic Arthritis Disease Domains: Post Hoc Analysis of a Phase 3, Randomized, Double-Blind, Placebo Controlled Study

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1 **Title:**

2 Guselkumab Provides Durable Improvement Across Psoriatic Arthritis Disease Domains: Post Hoc
3 Analysis of a Phase 3, Randomized, Double-Blind, Placebo Controlled Study
4

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31 **ABSTRACT**

32 **Objective:** Evaluate long-term guselkumab effectiveness across Group for Research and Assessment of
33 Psoriasis and Psoriatic Arthritis (GRAPPA)-recognized domains/related conditions of psoriatic arthritis
34 (PsA).

35 **Methods:** Post hoc analyses utilized data from DISCOVER-2 (NCT03158285) biologic/Janus-kinase
36 inhibitor-naïve participants with active PsA (≥ 5 swollen/ ≥ 5 tender joints, C-reactive protein ≥ 0.6 mg/dL),
37 randomized (1:1:1) to guselkumab every 4 or 8 weeks (Q4W/Q8W) or placebo with crossover to
38 guselkumab. Outcomes aligned with key GRAPPA-recognized domains of overall disease activity,
39 peripheral arthritis, axial disease, enthesitis/dactylitis, and skin psoriasis (nail psoriasis not assessed).
40 PsA-related conditions (inflammatory bowel disease [IBD]/uveitis) were assessed via adverse events.

41 Least squares mean changes from baseline through W100 in continuous outcomes employed repeated
42 measures mixed-effects models adjusting for baseline scores. Binary measure response rates were
43 determined with nonresponder imputation for missing data.

44 **Results:** 442/493 (90%) of guselkumab-randomized patients completed treatment through W100.
45 Following early reductions in disease activity with guselkumab, durable improvements were observed
46 across key PsA domains (swollen/tender joints, psoriasis, spinal pain, enthesitis/dactylitis) through
47 W100. Response rates of therapeutically relevant targets generally increased through W100 with
48 Q4W/Q8W: Disease Activity Index for PsA low disease activity (LDA) 62%/59%, enthesitis
49 61%/70%/dactylitis 72%/83% resolution, Psoriasis Area and Severity Index 100 59%/53%, Psoriatic
50 Arthritis Disease Activity Score LDA 51%/49%, and minimal disease activity 38%/40%. Through W112, no
51 cases of IBD developed among guselkumab-randomized patients and 1 case of uveitis was reported.

52 **Conclusion:** In biologic-naïve patients with active PsA, guselkumab provided early and durable
53 improvements in key GRAPPA-recognized domains through 2 years, with substantial proportions
54 achieving important treatment targets.

55 Q&A BOX

56 • What is already known on this topic

57 • Guidelines from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
58 (GRAPPA)-recommend that PsA therapy achieves lowest possible levels of disease activity
59 across six domains and two related conditions.

60 • Guselkumab, a fully human monoclonal interleukin-23p19-subunit inhibitor, has previously
61 been shown to significantly improve signs and symptoms of psoriatic arthritis (PsA) by Week
62 24, with improvements sustained or further increased through Week 52.

63 • What this study adds

64 • Treatment with guselkumab every 4 or 8 weeks provided early and durable improvements in
65 all assessed GRAPPA-recognized PsA domains through 2 years of treatment, resulting in
66 considerable proportions achieving low levels of joint disease activity, enthesitis/dactylitis
67 resolution, complete skin clearance, and low/minimal levels of overall disease activity.

68 • Through Week 100 among guselkumab-randomized patients, no exacerbation or new onset
69 of inflammatory bowel disease occurred, and a single occurrence of uveitis (iridocyclitis) was
70 reported.

71 • How this study might affect research, practice, or policy

72 • Given the multidomain nature of PsA, as well as the comprehensive and durable
73 effectiveness and favorable safety profile of guselkumab shown in the current analysis,
74 guselkumab represents an important treatment option to address key GRAPPA-recognized
75 therapeutic goals for patients with PsA.

76 **INTRODUCTION**

77 Psoriatic arthritis (PsA) is a clinically heterogeneous, progressive, chronic inflammatory disease involving
78 the skin and musculoskeletal systems with potential to irreversibly damage joints and impair health-
79 related quality of life (HRQoL) [1-3]. PsA affects approximately 30% of individuals with psoriasis [4] and
80 has an estimated worldwide prevalence between 0.3 and 1% [5].

81 The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recognizes six
82 disease domains (peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail
83 disease), two related conditions (inflammatory bowel disease [IBD] and uveitis) [6], and several
84 comorbidities (e.g., obesity, metabolic syndrome, diabetes mellitus) of PsA, all of which impact patients'
85 HRQoL [7]. Current international guidelines for PsA put forward optimizing functional status, improving
86 HRQoL, preventing structural damage, and minimizing complications both from untreated active disease
87 and from therapy as key therapeutic goals [6, 8, 9]. Furthermore, the GRAPPA guidelines specifically
88 highlight achieving the lowest possible level of disease activity across all disease domains affected in an
89 individual patient [6].

90 Guselkumab, a fully human monoclonal antibody that is an interleukin (IL)-23p19-subunit inhibitor, is
91 approved to treat adults with moderate-to-severe plaque psoriasis, as well as those with active PsA. In
92 two separate Phase 3 randomized trials (DISCOVER-1 and DISCOVER-2) in PsA, participants treated with
93 guselkumab, either every 4 (Q4W) or 8 weeks (Q8W), were reported to have significantly higher rates of
94 response or mean improvements in joint signs and symptoms, enthesitis and dactylitis, skin disease,
95 physical function, and HRQoL at Week 24 compared with the placebo group [10, 11]. In pooled analyses
96 of these studies, guselkumab provided robust and sustained benefits through 1 year of treatment as
97 measured by composite disease activity indices (including Disease Activity Index for Psoriatic Arthritis
98 [DAPSA], Psoriatic Arthritis Disease Activity Score [PASDAS], and minimal disease activity [MDA]), which
99 incorporate multiple domains recognized by GRAPPA [12]. In the DISCOVER-2 study of biologic-naïve
100 patients with highly active PsA, improvements with guselkumab treatment were found to be durable
101 through 2 years of follow up across multiple disease domains [13].

102 Informed by the GRAPPA treatment goal of achieving the lowest possible level of disease activity in all
103 affected disease domains, in the context of minimal side effects, and knowledge that residual disease
104 burdens patients and impairs function [14], the objective of the present post hoc analysis was to
105 evaluate the long-term (Week 100) effectiveness of guselkumab across GRAPPA-identified PsA domains
106 and related conditions assessed in DISCOVER-2. These included peripheral arthritis, axial symptoms,
107 enthesitis, dactylitis, and skin disease, as well as the incidence of new onset or exacerbation of IBD and
108 uveitis.

109

110 **METHODS**

111 Full details of the study design and eligibility criteria for DISCOVER-2 (NCT03158285) have been reported
112 [11]. Briefly, this was a randomized, double-blind, placebo-controlled, Phase 3 trial of guselkumab in
113 adults with active PsA, conducted between July 2017 and November 2020. The trial was carried out at
114 118 sites across 13 countries in Europe, Asia, and the USA. The DISCOVER-2 study conformed with the
115 Declaration of Helsinki and Good Clinical Practice guidelines and obtained all necessary ethics approvals.

116 Eligible patients had active PsA (swollen joint count [SJC] ≥ 5 , tender joint count [TJC] ≥ 5 , and C-reactive
117 protein [CRP] level ≥ 0.6 mg/dL) and an inadequate response to, or intolerance of, standard non-biologic
118 treatment. Patients could not have previously received biologics or Janus-kinase inhibitors. Study
119 participants were randomized (1:1:1) to receive subcutaneous injections of guselkumab 100 mg Q4W;
120 guselkumab 100 mg at Week 0, Week 4, then Q8W; or placebo with crossover to guselkumab 100 mg
121 Q4W at Week 24 through Week 100.

122 **Outcome Measures**

123 Efficacy assessments selected for the current post hoc analysis aligned with GRAPPA-identified domains,
124 i.e., peripheral arthritis (66-joint SJC, 68-joint TJC), axial symptoms (patient-reported spinal pain; Bath
125 Ankylosing Spondylitis Disease Activity Index Question 2 [15]), enthesitis (Leeds Enthesitis Index [LEI]
126 [16]), dactylitis (Dactylitis Severity Score [DSS] [17]), and skin psoriasis (Psoriasis Area and Severity Index
127 [PASI] [18], Investigator's Global Assessment of psoriasis [IGA] [19], Patient's Assessment of Skin Disease
128 on a Visual Analog Scale [Skin VAS]). As longitudinal nail disease assessments were not performed in
129 DISCOVER-2, nail psoriasis was not considered in the present analysis.

130 Composite scores were also assessed as measures of joint and overall disease activity. Peripheral
131 disease activity was assessed with DAPSA [20], calculated via the addition of SJC, TJC, patient
132 assessment of arthritis disease activity on a VAS, patient assessment of joint pain on a VAS, and CRP
133 level, as well as clinical DAPSA (cDAPSA) [21], a simplified version of DAPSA that omits CRP. PASDAS [22]
134 is a multi-domain measure of overall disease activity that combines SJC, TJC, tender dactylitis count, LEI,
135 serum CRP concentration, physician global assessment of disease activity, patient global assessment of
136 disease activity, and Short Form (SF)-36 physical component summary (PCS) score. MDA [23] is defined
137 as meeting ≥ 5 of the following 7 criteria: TJC ≤ 1 , SJC ≤ 1 , PASI ≤ 1 , patient pain VAS ≤ 15 , patient global
138 assessment of disease activity on a VAS ≤ 20 mm, Health Assessment Questionnaire-Disability Index
139 (HAQ-DI) score ≤ 0.5 , and ≤ 1 tender enthesal points.

140 Continuous outcomes evaluated were changes from baseline through Week 100 in SJC, TJC, spinal pain
141 (in patients with axial symptoms and imaging-confirmed sacroiliitis [24, 25]), LEI (in patients with
142 baseline enthesitis), DSS (in patients with baseline dactylitis), Skin VAS and PASI (in patients with
143 $\geq 3\%$ body surface area [BSA] and IGA score ≥ 2 at baseline).

144 Achievement of therapeutic endpoints was assessed with DAPSA low disease activity (LDA; score ≤ 14) or
145 remission (≤ 4); cDAPSA LDA (≤ 13) or remission (≤ 4); resolution of enthesitis (LEI=0) in patients with
146 enthesitis at baseline; resolution of dactylitis (DSS=0) in patients with dactylitis at baseline; PASDAS LDA
147 (≤ 3.2) or remission (≤ 1.9); and MDA. Skin assessments, evaluated among patients with $\geq 3\%$ BSA and IGA
148 score ≥ 2 at baseline, included Skin VAS ≤ 15 mm (among those with baseline Skin VAS > 15 mm), PASI
149 improvement $\geq 90\%$ or 100% (PASI90/100), and IGA=0 or 1 with ≥ 2 grade improvement from baseline.
150 Certain results presented herein, including the proportions of patients achieving MDA at Week 24, and
151 enthesitis and dactylitis resolution, PASI90, PASI100, and IGA 0/1 response at Weeks 24, 52, and 100

152 have been previously reported [11, 13]; they are shown in this paper to provide context surrounding the
153 patterns of group-level effectiveness through Week 100.

154 Adverse events (AEs) were assessed through Week 112 of DISCOVER-2. The occurrence of IBD (defined
155 by Medical Dictionary for Regulatory Activities [MedDRA] System Organ Class preferred terms [PTs] of
156 Crohn's disease, ulcerative colitis, or IBD) and uveitis (defined by MedDRA PTs of uveitis, iridocyclitis, or
157 iritis), or their exacerbation in patients with IBD or uveitis at baseline, was determined following blinded
158 review of the reported AEs.

159 **Statistical Methods**

160 Analyses were limited to patients randomized to guselkumab. Least squares mean (LSM) changes from
161 baseline to available visits between Week 8 and Week 100 in SJC, TJC, spinal pain, LEI, DSS, and Skin VAS
162 were analyzed by repeated measures generalized linear mixed-effects models adjusting for respective
163 baseline score, time, guselkumab dosing regimen, and the interaction of time with guselkumab regimen.
164 Although SJC and TJC were first assessed at Week 4, Week 8 was used as the first timepoint of
165 assessment to standardize timeframes across outcome measures, except for PASI, which was first
166 evaluated at Week 16. Radar plots, reported logarithmically due to scale differences in the outcomes
167 assessed, were used to describe changes in SJC, TJC, spinal pain, LEI, DSS, and Skin VAS at each time
168 point for each guselkumab regimen. Achievement of therapeutic endpoints was summarized by
169 descriptive statistics using nonresponder imputation (NRI) for missing data applied at rates
170 approximating study discontinuations (<10%). Composite scores with missing component data were
171 imputed as non-response. The incidence/exacerbation of IBD and uveitis was summarized descriptively.
172 All analyses were performed using the Statistical Analysis System (SAS) statistical software package,
173 version 9.4 (SAS Institute Inc., Cary, NC, USA).

174 RESULTS

175 Patient Disposition and Baseline Characteristics

176 Among the 493 patients who were randomized to guselkumab in DISCOVER-2, 245 and 248 received
177 guselkumab 100 mg Q4W and Q8W, respectively. The additional 246 patients randomized to placebo
178 were not included in these post hoc analyses assessing long-term effectiveness. Baseline demographic
179 and PsA disease characteristics were generally similar across the treatment groups [11].

180 **Table 1** summarizes the baseline characteristics of patients randomized to and treated with guselkumab.
181 Mean PASDAS, DAPSA, and cDAPSA scores were consistent with highly active PsA. Approximately one-
182 third of patients were identified by the investigator as having axial symptoms and had imaging-
183 confirmed sacroiliitis, nearly half had dactylitis, two-thirds had enthesitis, and three-quarters had BSA
184 $\geq 3\%$ and IGA ≥ 2 . Approximately 60% and 20% of patients reported concomitant use of methotrexate
185 and corticosteroids, respectively, at baseline (**Table 1**).

186 Among patients randomized to guselkumab, 93% completed study treatment at Week 52, and 90% did
187 so through Week 100. Patients were analyzed by intention to treat, and those who discontinued were
188 imputed as nonresponders.

189 Overall Patterns of Improvement

190 Substantial mean improvements were observed as early as Week 8 for each endpoint assessed (**Figure**
191 **1**). A significant decrease in mean PASI score was observed with both guselkumab regimens at Week 16
192 ($p < 0.0001$), the first timepoint assessed, which was subsequently maintained through Week 100. In all
193 other PsA domains assessed, specifically SJC, TJC, spinal pain, LEI, DSS, and Skin VAS, mean
194 improvements among patients treated with either guselkumab Q4W or Q8W were continuously
195 enhanced through Week 100 (**Figure 1**; **Supplemental Figure 1**).

196 Similarly, therapeutic endpoint response rates increased over time in all key PsA domains and were
197 generally maintained or continued to increase between Week 52 and Week 100 of guselkumab
198 treatment, regardless of dosing regimen (**Table 2**). Adding to the considerable improvements between
199 baseline and the first analysis timepoint, notable increases in endpoint response rates between
200 consecutive visits were also observed later in the follow-up period. For most endpoints assessed, in one
201 or both guselkumab regimens, the between-timepoint increase in response rate was highest or second
202 highest for the period between Week 24 and Week 52 (**Table 2**).

203 Arthritis Improvement

204 For both guselkumab regimens, significant reductions in SJC and TJC were observed by Week 8 (all
205 $p < 0.0001$), the first analysis timepoint, and improvements at the group level continued through Week
206 100 (**Figure 1**; **Supplemental Figure 1**). In patients receiving guselkumab Q4W, the LSM changes from
207 baseline to Week 24 and Week 100, respectively, were -8.4 and -10.4 for SJC and -11.2 and -15.5 for TJC.
208 The same pattern was seen in Q8W-randomized patients at Week 24 and Week 100, with LSM changes
209 of -8.4 and -10.3 for SJC and -10.9 and -15.5 for TJC, respectively (**Figure 1**). These improvements
210 represent 69%-88% reductions in the mean joint scores by Week 100.

211 Skin Psoriasis Improvement

212 For both skin assessments (Skin VAS and PASI), a significant improvement was seen in patients with $\geq 3\%$
213 BSA and IGA score ≥ 2 at baseline at the first timepoint of assessment (Weeks 8 and 16, respectively;

214 both $p < 0.0001$; **Figure 1**). With both guselkumab regimens, mean improvements in Skin VAS continued
215 through Week 100 and the significant mean decreases in PASI scores recorded as of the first assessment
216 timepoint were maintained through Week 100 (**Figure 1**; **Supplemental Figure 1**).

217 Among Q4W-randomized patients, the respective LSM changes from baseline to Week 24 and Week 100
218 were -39.0 and -46.1 for Skin VAS and -12.1 and -12.7 for PASI. Similarly, in Q8W-randomized patients,
219 changes averaged -39.8 and -47.2 for Skin VAS and -12.0 and -12.4 for PASI at these timepoints (**Figure**
220 **1**). Overall, these results indicate a 72%-96% improvement in symptoms of skin psoriasis by Week 100.
221 Achievement of PASI90 response by patients receiving guselkumab Q4W and Q8W (54% and 55% at
222 Week 16, 77% and 74% at Week 52, respectively) and IGA score of 0 or 1 and a ≥ 2 grade improvement
223 (66% and 62% at Week 16, 80% and 74% at Week 52, respectively) showed consistent durability of
224 response across guselkumab dosing regimens and was maintained through Week 100 (**Table 2**).
225 Between Week 16 and Week 100, the proportion of patients achieving skin clearance (PASI100)
226 increased by 25% and 26% with guselkumab Q4W and Q8W, respectively (**Table 2**).

227 Among patients with Skin VAS > 15 mm, IGA ≥ 2 , and BSA $\geq 3\%$ at baseline, achievement of Skin VAS ≤ 15
228 mm was seen in 14% and 22% of patients receiving Q4W and Q8, respectively, by Week 8; by Week 100,
229 53% and 56% of patients receiving each regimen achieved minimal skin involvement, respectively (**Table**
230 **2**).

231 **Spinal Pain Improvement**

232 Among patients with axial symptoms in the guselkumab Q4W (33%) and Q8W (27%) groups, significant
233 improvement in spinal pain was recorded as of Week 8 (first timepoint assessed; $p < 0.0001$). Between
234 subsequent follow-up visits through Week 100, mean improvements were either maintained or further
235 enhanced (**Figure 1 & Supplemental Figure 1**). The respective LSM changes in spinal pain from baseline
236 to Week 24 and Week 100 were -2.3 and -3.0 among patients treated with guselkumab Q4W and -2.6
237 and -3.3 for those receiving the Q8W regimen, representing 46%-50% improvement by Week 100
238 (**Figure 1**).

239 **Enthesitis and Dactylitis Improvement**

240 Among patients with baseline enthesitis (Q4W: 69%; Q8W: 64%) and those with baseline dactylitis
241 (Q4W: 49%; Q8W: 45%), significant improvements in both enthesitis and dactylitis were recorded as of
242 the first follow-up assessment at Week 8 (both $p < 0.0001$), regardless of guselkumab regimen. Mean
243 improvements were either maintained or further increased between subsequent follow-up visits
244 through Week 100 (**Figure 1**; **Supplemental Figure 1**).

245 In affected patients randomized to the Q4W regimen, the respective LSM changes from baseline to
246 Week 24 and Week 100 were -1.6 and -2.1 for LEI and -6.5 and -7.5 for DSS. Consistent improvements
247 were seen in Q8W-randomized patients, with respective LSM changes from baseline to Week 24 and
248 Week 100 of -1.7 and -2.2 for LEI and -6.2 and -7.9 for DSS (**Figure 1**).

249 Among patients with enthesitis as baseline, the proportions of patients achieving enthesitis resolution
250 (LEI=0) increased continuously through Week 100 in both guselkumab groups, whereby response rates
251 were 27% and 32% at Week 8, 56% and 62% at Week 52, and 61% and 70% at Week 100 for guselkumab
252 Q4W and Q8W, respectively (**Table 2**).

253 Proportions of patients achieving dactylitis resolution (DSS=0), among those with baseline dactylitis,
254 increased through Week 52 and were then maintained or continued to improve through Week 100

255 (32%, 74%, and 72% at Week 8, 52, and 100 with guselkumab Q4W and 31%, 77%, and 83% with
256 guselkumab Q8W; **Table 2**).

257 **Composite Responses**

258 Despite mean composite scores indicative of high disease activity at baseline, NRI response rates for
259 DAPSA LDA/remission, cDAPSA LDA/remission, PASDAS LDA/remission, and MDA increased continuously
260 through Week 100, regardless of guselkumab regimen (**Table 2**). More precisely, among patients in the
261 Q4W group, respective Week 8, Week 24, Week 52, and Week 100 response rates for DAPSA
262 LDA/remission were 18%/2%, 36%/9%, 51%/16%, and 62%/21%; for PASDAS LDA/remission were
263 10%/2%, 24%/9%, 43%/15% and 51%/21%, and MDA were 3%, 19%, 34%, and 38%. A similar pattern of
264 achievement was seen with the Q8W dosing regimen, with response rates at Week 8, Week 24, Week
265 52, and Week 100 of 17%/1%, 39%/9%, 52%/19%, and 59%/24% for DAPSA LDA/remission; 11%/1%,
266 31%/9%, 43%/21%, and 49%/23% for PASDAS LDA/remission; and 4%, 25%, 31%, and 40% for MDA,
267 respectively. Results for cDAPSA were comparable to those obtained for DAPSA for both guselkumab
268 regimens (**Table 2**).

269 **PsA-related Conditions**

270 Among guselkumab-randomized patients, 1 patient had a history of IBD and 4 had a history of uveitis;
271 none of these patients experienced an AE of exacerbation of these conditions through Week 100.
272 Furthermore, through Week 100, no guselkumab-randomized patient developed IBD. One case of
273 uveitis was reported (Q8W group; Week 70) that resolved following treatment with steroid and
274 nonsteroid anti-inflammatory drugs with no changes to guselkumab dosing.

275 DISCUSSION

276 Previous analyses of the Phase 3 DISCOVER-1 and DISCOVER-2 studies have demonstrated that,
277 compared with placebo, treatment with guselkumab was associated with significantly greater
278 improvements in signs and symptoms of PsA by Week 24 [10, 11] and that these improvements were
279 sustained through Week 52 [26, 27] and, in DISCOVER-2, Week 100 [13]. In the current post hoc analysis
280 of DISCOVER-2 data, both guselkumab regimens provided both early significant improvements and
281 continuously increasing response rates through Week 100 in key GRAPPA-identified domains. The robust
282 improvements in skin disease seen in these PsA patients were highly durable over time. Importantly,
283 early significant improvements in peripheral arthritis, dactylitis, enthesitis, and axial symptoms were
284 also enhanced and durable over time. Following the considerable improvements between baseline and
285 the first analysis timepoint (Week 8, except for PASI [Week 16]), both joint and skin response rates were
286 further increased at 1 year. Furthermore, the substantial increases in overall disease response rates
287 (PASDAS LDA and MDA) as well as achievement of remission targets (cDAPSA/DAPSA and PASDAS)
288 generally found at 1 year were sustained through 2 years.

289 Regardless of guselkumab dosing regimen, considerable proportions of patients achieved disease
290 control across domains at Week 100. Specifically, approximately 60% of guselkumab-randomized
291 patients reached low levels of joint disease activity as defined by either DAPSA or cDAPSA; 61%-83%
292 achieved enthesitis or dactylitis resolution; 53%-76% achieved almost clear or clear skin as indicated by
293 PASI90, PASI100, or IGA scores of 0 or 1 and a ≥ 2 grade improvement from baseline; approximately 50%
294 achieved PASDAS LDA; and 38%-40% achieved MDA. In patients with axial symptoms and imaging-
295 confirmed sacroiliitis, spinal pain was diminished by nearly 50% on average. Overall, findings were in
296 agreement with previous guselkumab trials in psoriasis patients demonstrating substantial and durable
297 improvement in skin disease [28] and with a network meta-analysis of data from randomized controlled
298 trials [29] of patients with PsA that found guselkumab provides comparable joint disease efficacy and
299 superior skin disease efficacy relative to other advanced PsA treatments.

300 Although nail disease, an important GRAPPA-identified domain, was not assessed in DISCOVER-2, a post
301 hoc analysis of pooled data from the VOYAGE-1 and -2 studies of patients with moderate-to-severe
302 psoriasis found that, among patients with fingernail psoriasis, guselkumab-treated patients achieved
303 clearance of or minimal fingernail psoriasis in significantly higher proportions by Week 16 than those
304 receiving placebo [30]. Furthermore, a subgroup analysis of VOYAGE-1 and -2 patients with self-reported
305 PsA also found that, compared with placebo, a significantly greater proportion of guselkumab-treated
306 patients saw improvements in nail, scalp, and palmoplantar psoriasis by Week 16 [31].

307 In addition to achieving the lowest possible level of disease activity in all disease domains affected, the
308 GRAPPA, American College of Rheumatology (ACR)/National Psoriasis Foundation and European Alliance
309 of Associations for Rheumatology (EULAR) treatment guidelines promote optimizing functional status,
310 improving HRQoL, preventing structural damage, and minimizing complications both from untreated
311 active disease and from therapy [6, 8, 9, 32]. Analyses of the DISCOVER-1 and -2 studies through Week
312 24 found that both guselkumab dosing regimens were associated with significant improvements versus
313 placebo in physical function and HRQoL, as measured by the HAQ-DI and SF-36 PCS scores, respectively,
314 as well as numerical improvements in SF-36 mental component summary (MCS) score [10, 11].
315 Importantly, these improvements by Week 24 were sustained or continued through Week 52 [26, 27]
316 and, in DISCOVER-2, through Week 100 [13]. Furthermore, in DISCOVER-2, which included imaging
317 assessments, patients treated with guselkumab demonstrated less radiographic progression relative to
318 placebo at Week 24, with this effect reaching statistical significance in the Q4W group [11]. Regardless
319 of guselkumab dosing regimen, low rates of radiographic progression were maintained through
320 Week 100 in this same study [13].

321 The high retention rate (90%) of guselkumab-randomized patients that was observed in this trial
322 through Week 100 further supports a durable positive risk-benefit profile. Specific to PsA-related
323 conditions, this analysis found no exacerbations or new cases of IBD during the 2-year period of
324 guselkumab treatment and one case of uveitis (iridocyclitis) through Week 100, with comparable
325 incidence in the placebo group through Week 24 [13]. The absence of IBD occurrence and the very low
326 incidence of uveitis are in line with long-term guselkumab safety data previously reported and through
327 up to 2 years in the largest cohort of PsA patients assessed to date [33], through up to 5 years among
328 patients with moderate-to-severe psoriasis [34, 35], and through up to 5 years among a large population
329 of patients with psoriatic disease from 11 Phase 2/3 studies [36].

330 The durable effectiveness of guselkumab in such a broad range of PsA domains is likely associated with
331 the central role of IL-23 in the pathophysiology of psoriasis and inhibition of Th17 clonal expansion
332 through IL-23p19-subunit blockade [37]. Biomarker studies in patients with active PsA have shown that
333 guselkumab treatment leads to reductions in circulating protein levels of acute phase and Th17 effector
334 cytokines through Week 24 [38], as well as serum collagen levels (including C1M), through Week 52 [39].
335 These pharmacodynamic effects were sustained, or in some cases, enhanced through Week 100 [40]
336 and associated with enduring clinical improvements in PsA disease activity through Week 100 [40, 41].
337 Preliminary in vitro studies have demonstrated that guselkumab, as a fully human IgG1 monoclonal
338 antibody with a native Fc region, has high affinity for binding of the IL-23 p19 subunit, high potency for
339 inhibiting IL-23 signaling, and dose-dependent Fc-mediated binding to the Fcγ receptor I found on
340 primary human inflammatory monocytes, also known as CD64. CD64-bound guselkumab was further
341 shown to simultaneously capture IL-23 endogenously secreted from the same cells [42]. Although the
342 clinical implications of guselkumab Fcγ receptor binding to CD64 are not yet clear, it is possible that the
343 durable and substantial multi-domain effectiveness of guselkumab may be related to its unique
344 molecular attributes. Given that CD64⁺ IL-23-producing myeloid cells are increased within inflamed
345 tissue of patients with psoriatic disease [43] and joint disease activity positively correlates with
346 frequency of peripheral CD64⁺ monocytes [44], these findings may suggest a mechanistic benefit. Thus,
347 the dual-acting capability of guselkumab may neutralize inflammation at its cellular source by potentially
348 block IL-23 activity and binding CD64 and may contribute to differences in therapeutic profiles across
349 antibodies inhibiting IL-23 [45].

350 As with all data derived from clinical trials, findings may not be generalizable to all patients seen in
351 routine care and incentives for investigators and patients may have influenced patient retention.
352 Furthermore, the analysis may not have been powered to detect rare safety signals, with additional
353 larger studies required to accurately quantify the incidence of IBD and uveitis during guselkumab
354 treatment. However, a safety analysis involving ~4,400 patients with psoriatic disease found the rates of
355 uveitis were similar in guselkumab- and placebo-treated patients, with no cases of Crohn's disease or
356 ulcerative colitis reported in guselkumab-treated patients through 5 years [36]. The absence of data
357 collection on nail psoriasis in DISCOVER-2 is an additional limitation of this study assessing key GRAPPA-
358 identified domains. Additionally, identification of patients with axial involvement in this study was
359 limited by the use of locally-read imaging that was restricted to evaluation of sacroiliitis and did not
360 objectively assess spinal inflammation. The present study did not examine the influence of baseline
361 patient characteristics on guselkumab efficacy; however, a previous analysis of a broad population of
362 patients with active PsA in the DISCOVER-1 and 2 studies demonstrated robust and durable guselkumab
363 efficacy across evaluated disease domains irrespective of baseline demographics, disease characteristics,
364 and PsA medication use [46]. Specifically, higher response rates were observed with guselkumab than
365 placebo in joint and skin disease, fatigue, functional status, and composite measures of PsA disease
366 activity at Week 24 across patient subgroups stratified by patient sex and baseline body mass index,

367 swollen and tender joint counts, CRP levels, PsA duration, and use of conventional synthetic disease-
368 modifying antirheumatic drugs (csDMARD) or methotrexate. As well, response rates within each
369 baseline subgroup were sustained or increased through 1 year [46]. Direct subgroup comparisons,
370 including males vs. females and patients on monotherapy vs. combination therapy with methotrexate,
371 have not been previously conducted, and are an important area of future investigation. Although the
372 current analysis included only biologic-naïve patients with active PsA, the effectiveness of guselkumab
373 has also been shown in tumor necrosis factor inhibitor experienced patients, including a real-world PsA
374 population characterized by longstanding, treatment-resistant, active disease at baseline [47-49].
375 Furthermore, the long-term effectiveness of guselkumab in routine care is being examined in the
376 ongoing prospective observational PsABIOnD study conducted in 20 countries worldwide [50]. Strengths
377 of the current analyses include the conservative NRI approach that assigns non-response for all missing
378 data and was employed at low rates (<10%) reflecting those of study discontinuation; the randomized
379 controlled design of DISCOVER-2; and the focus on guselkumab effectiveness across important disease
380 domains, which aligns with GRAPPA recommendations for PsA treatment and is relevant to clinical
381 practice.

382 **CONCLUSION**

383 In the DISCOVER-2 study of biologic-naïve patients with highly active PsA, both guselkumab regimens
384 (Q4W and Q8W) provided early, durable, and continuous improvements in key GRAPPA-recommended
385 domains of PsA through up to 2 years of treatment, resulting in considerable proportions achieving low
386 levels of joint disease activity, enthesitis/dactylitis resolution, complete skin clearance, and low/minimal
387 levels of overall disease activity. No exacerbations or new onset of IBD were reported, with a single
388 occurrence of uveitis observed through Week 100 in guselkumab-treated patients, aligning with the
389 established safety profile of guselkumab.

390

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399 and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead,
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418 Johnson, and own stocks in Johnson & Johnson.

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436

437 **Data Availability Statement**

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

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598

	Guselkumab 100 mg	
	Q4W (N=245)	Q8W (N=248)
Demographics		
Age, years	45.9 (11.5)	44.9 (11.9)
Male	142 (58%)	129 (52%)
Body weight, kg	85.8 (19.5)	83.0 (19.3)
PsA Characteristics		
PsA disease duration, years	5.5 (5.9)	5.1 (5.5)
CRP, mg/dL	1.2 (0.6-2.3)	1.3 (0.7-2.5)
SJC (0-66)	12.9 (7.8)	11.7 (6.8)
TJC (0-68)	22.4 (13.5)	19.8 (11.9)
Patients with axial symptoms ^a	82 (33%)	68 (27%)
Spinal pain (0-10) ^b	6.5 (2.2)	6.6 (2.2)
Patients with enthesitis	170 (69%)	158 (64%)
LEI (0-6) ^c	3.0 (1.7)	2.6 (1.5)
Patients with dactylitis	121 (49%)	111 (45%)
DSS (0-60) ^d	8.6 (9.6)	8.0 (9.6)
BSA, %	18.2 (20.0)	17.0 (21.0)
Skin VAS (0-100 mm)	60.9 (22.6)	59.2 (25.3)
PASI (0-72)	10.8 (11.7)	9.7 (11.7)
Patients with BSA ≥3% and IGA score ≥2	184 (75.1%)	176 (71.0%)
Skin VAS (0-100 mm) ^e	64.4 (20.3)	65.3 (21.9)
PASI (0-72) ^e	13.8 (12.0)	12.9 (12.5)
DAPSA ^f	49.7 (21.1)	46.3 (19.4)
cDAPSA ^g	47.9 (20.9)	44.3 (18.8)
PASDAS ^h	6.6 (1.09)	6.6 (1.09)
HAQ-DI (0-3)	1.2 (0.6)	1.3 (0.6)
Concomitant medications		
Methotrexate	146 (60%)	141 (57%)
Oral corticosteroids	46 (19%)	50 (20%)

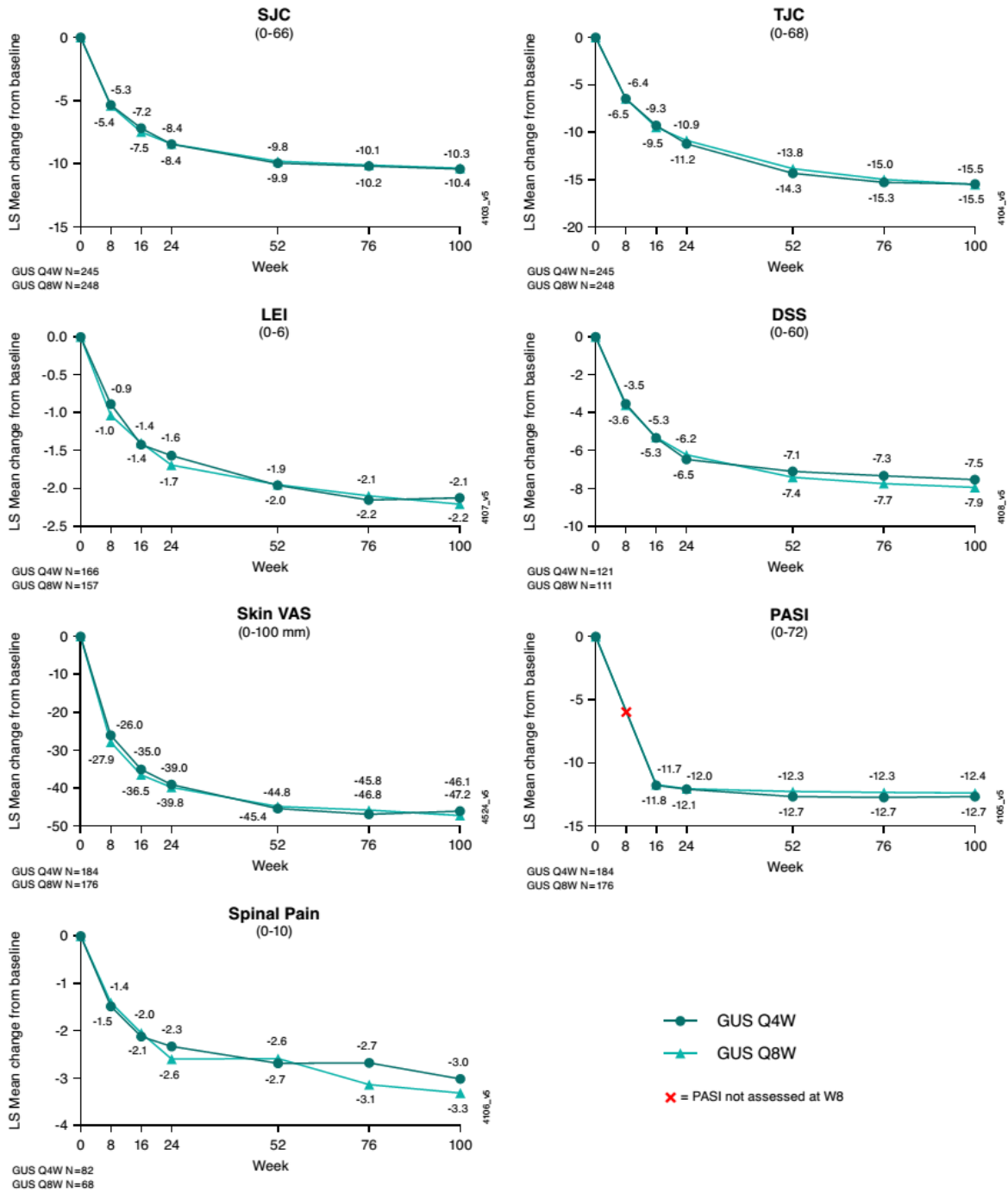
Data are n (%), mean (SD), or median (IQR). ^aPatients were identified by the investigator as having axial symptoms and had imaging-confirmed sacroiliitis. ^bAmong patients with axial symptoms and available spinal pain score at baseline (Q4W group n=79 and Q8W n=62). ^cAmong patients with enthesitis and available LEI score at baseline (Q4W group n=166 and Q8W n=157). ^dAmong patients with dactylitis and available DSS at baseline (Q4W group n=121 and Q8W n=111). ^eAmong patients with BSA ≥3% & IGA score ≥2 at baseline (Q4W group n=184 and Q8W n=176). ^fDAPSA disease activity states include remission (≤4), low disease activity (>4 and ≤14), moderate disease activity (>14 and ≤28), and high

disease activity (>28) [21]. ^gcDAPSA disease activity states include remission (≤ 4), low disease activity (>4 and ≤ 13), moderate disease activity (>14 and ≤ 27), moderate (score >3.2 to <5.4), and high disease activity (>27) [21]. ^hPASDAS disease activity states include very low (≤ 1.9), low (>1.9 to ≤ 3.2), and high disease activity (≥ 5.4) [17, 22].

BSA=body surface area; CRP=C-reactive protein; cDAPSA=clinical Disease Activity Index for Psoriatic Arthritis; DAPSA=Disease Activity Index for Psoriatic Arthritis; DSS=dactylitis severity score; HAQ-DI=health assessment questionnaire-disability index; IGA=Investigator's Global Assessment of psoriasis; IQR=interquartile range; LEI=Leeds enthesitis index; PASDAS=Psoriatic Arthritis Disease Activity Score (0-10); PASI=Psoriasis Area and Severity Index; PsA=psoriatic arthritis; Q4W=every 4 weeks; Q8W=every 8 weeks; SD=standard deviation; SJC=swollen joint count (0-66); TJC=tender joint count (0-68); VAS=Visual Analog Scale

602

603 **Figure 1 Least squares mean changes from baseline over time in continuous outcomes assessing key**
 604 **PsA domains among guselkumab-randomized patients**



605 All changes from baseline were significant at the 0.05 level. X=PASI not assessed at Week 8. N represents
 606 patients with available score at baseline. DSS=Dactylitis Severity Score; GUS=guselkumab; LEI=Leeds
 607 Enthesitis Index; LS Mean=least squares mean; PASI=Psoriasis Area and Severity Index; PsA=psoriatic
 608 arthritis; Q4W= every 4 weeks; Q8W=every 8 weeks; SJC=swollen joint count; TJC=tender joint count;
 609 VAS=Visual Analog Scale; LEI was analyzed among patients with enthesitis and available LEI score at
 611 baseline. DSS was analyzed among patients with dactylitis and available DSS at baseline. Skin VAS and
 612 PASI were analyzed among patients with body surface area $\geq 3\%$ and Investigator's Global Assessment of

613 *psoriasis score ≥ 2 at baseline. Spinal pain was analyzed among patients with axial symptoms and*
614 *imaging-confirmed sacroiliitis.*

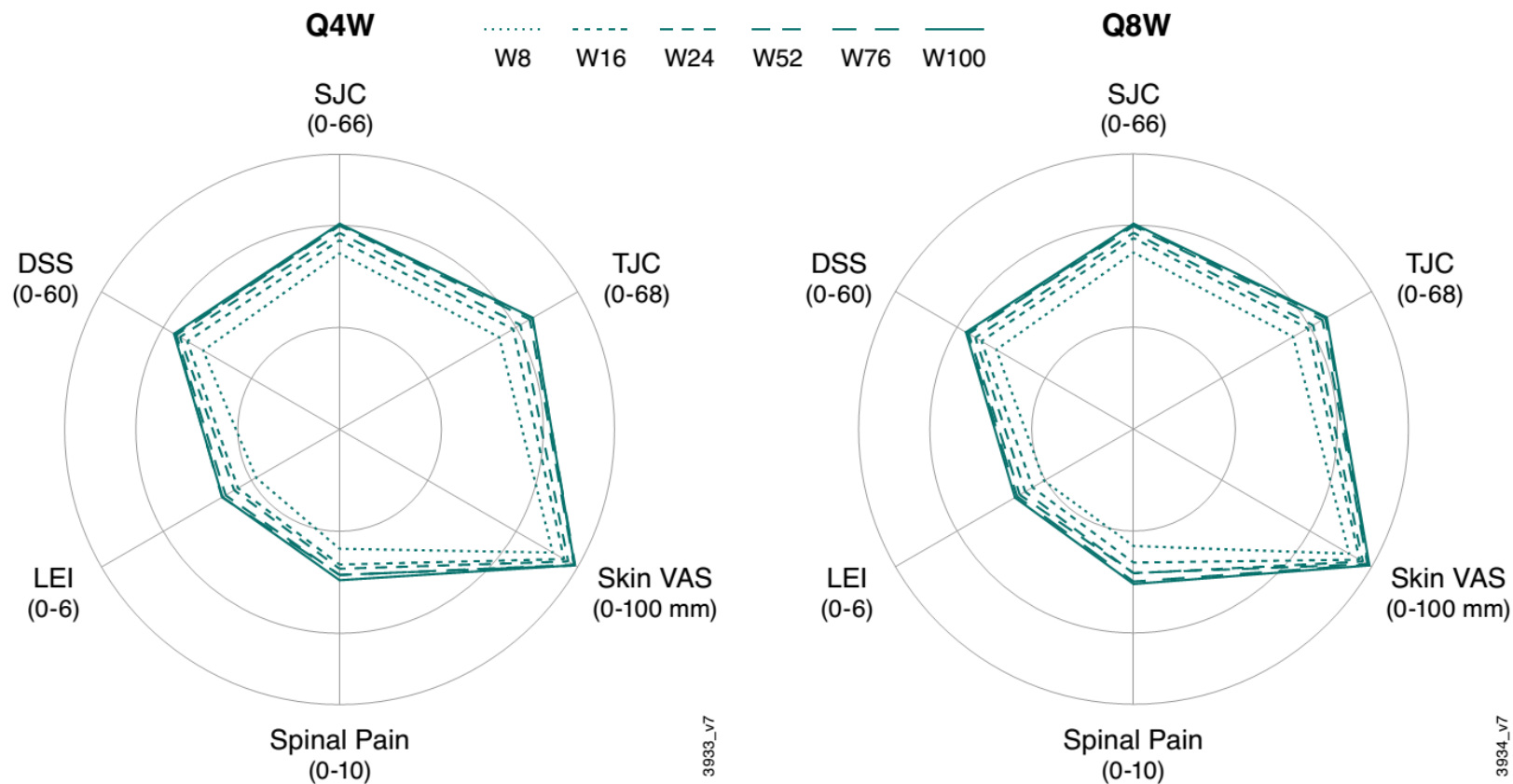
615 **Table 2 Achievement of therapeutic targets among guselkumab-randomized patients over time (NRI)**

Week	Guselkumab 100mg Q4W					Guselkumab 100mg Q8W				
	8	16	24	52	100	8	16	24	52	100
DAPSA										
LDA (≤14)	43 (18)	61 (25)	88 (36)	125 (51)	151 (62)	43 (17)	79 (32)	97 (39)	130 (52)	147 (59)
Remission (≤4)	5 (2)	12 (5)	21 (9)	39 (16)	52 (21)	3 (1)	15 (6)	23 (9)	46 (19)	60 (24)
cDAPSA										
LDA (≤13) ^a	41 (17)	58 (24)	89 (36)	125 (51)	150 (61)	44 (18)	75 (30)	95 (38)	131 (53)	147 (60)
Remission (≤4)	5 (2)	13 (5)	29 (12)	44 (18)	59 (24)	4 (2)	19 (8)	25 (10)	53 (21)	65 (26)
Enthesitis resolution^b	45 (27)	66 (40)	71 (43)	93 (56)	102 (61)	50 (32)	75 (48)	87 (55)	97 (62)	110 (70)
Dactylitis resolution^b	39 (32)	64 (53)	80 (66)	90 (74)	87 (72)	34 (31)	51 (46)	66 (59)	86 (77)	92 (83)
Skin										
PASI90 ^{c, d}	-	100 (54)	114 (62)	142 (77)	136 (74)	-	97 (55)	121 (69)	131 (74)	123 (70)
PASI100 ^{c, d}	-	62 (34)	83 (45)	106 (58)	109 (59)	-	48 (27)	80 (45)	93 (53)	94 (53)
IGA 0/1 response ^{c-e}	-	122 (66)	127 (69)	147 (80)	140 (76)	-	110 (62)	124 (70)	131 (74)	126 (72)
Skin VAS ≤15mm ^{d, f}	26 (14)	58 (32)	68 (37)	93 (51)	96 (53)	38 (22)	61 (36)	71 (42)	88 (52)	95 (56)
PASDAS										
LDA (≤3.2)	25 (10)	44 (18)	58 (24)	105 (43)	126 (51)	28 (11)	56 (23)	76 (31)	106 (43)	122 (49)
Remission (≤1.9)	4 (2)	11 (4)	22 (9)	36 (15)	51 (21)	2 (1)	16 (6)	23 (9)	52 (21)	58 (23)
MDA^a	8 (3)	33 (14)	47 (19)	83 (34)	93 (38)	9 (4)	42 (17)	63 (25)	77 (31)	100 (40)
Absolute change in response rate from previous visit										
± 1 to <5			+ 5 to <10		+ 10 to <15		+ 15 to <20		≥20	

616 Number (%) of guselkumab-randomized patients (N=493) achieving therapeutic endpoints over time (NRI) are shown. ^aExcludes patients who
617 achieved endpoint at baseline. ^bAmong patients with domain at baseline. ^cPASI and IGA not assessed at Week 8. ^dAmong patients with baseline
618 IGA ≥2 and BSA ≥3%. ^eIGA skin response=score of 0 or 1 and ≥2 grade improvement from baseline. ^fPatients with Skin VAS >15mm at baseline.
619 BSA=body surface area; cDAPSA=clinical Disease Activity Index for Psoriatic Arthritis; DAPSA=Disease Activity Index for Psoriatic Arthritis;
620 IGA=Investigator's Global Assessment of psoriasis; LDA=Low Disease Activity; MDA=Minimal Disease Activity; NRI=nonresponder imputation;

621 *PASDAS=Psoriatic Arthritis Disease Activity Score; PASI90/100= ≥90% improvement/100% improvement Psoriasis Area and Severity Index;*
622 *Q4W=every 4 weeks; Q8W=every 8 weeks; VAS=Visual Analog Scale.*

623 **Supplemental Figure 1 Improvement from baseline over time in continuous, key PsA domains in guselkumab-randomized patients**



624
 625 *Outer circles indicate greater improvement in outcome measures. Results are shown in logarithmic scale due to scale difference in the outcomes*
 626 *assessed. DSS=Dactylitis Severity Score; LEI=Leeds Enthesitis Index; PsA=psoriatic arthritis; Q4W=every 4 weeks; Q8W=every 8 weeks; SJC=swollen*
 627 *joint count; TJC=tender joint count; VAS=Visual Analog Scale; W=week.*