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Manuscript

Title Guselkumab Provides Sustained Domain-Specific and Comprehensive Efficacy Using Composite Indices in Patients With Active Psoriatic Arthritis

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44 **Running head** Guselkumab Improves PsA-Specific Composite Indices

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52 **ABSTRACT**

53 **Objectives:** Evaluate the efficacy of guselkumab for the treatment of active psoriatic arthritis
54 (PsA) utilizing composite indices.

55 **Methods:** Data were pooled from the Phase 3 DISCOVER-1 (N=381) and DISCOVER-2
56 (N=739) studies. In both studies, patients were randomized 1:1:1 to subcutaneous guselkumab
57 100 mg every 4 weeks (Q4W); guselkumab 100 mg at Week 0, Week 4, then Q8W; or placebo
58 Q4W with crossover to guselkumab 100 mg Q4W at Week 24. Composite indices used to
59 assess efficacy through Week 52 included Disease Activity Index for Psoriatic Arthritis
60 (DAPSA), Psoriatic Arthritis Disease Activity Score (PASDAS), minimal disease activity (MDA),
61 and very low disease activity (VLDA). Through Week 24, treatment failure rules were applied.
62 Through Week 52, non-responder imputation was used for missing data.

63 **Results:** Greater proportions of guselkumab- than placebo-treated patients achieved DAPSA
64 low disease activity (LDA) and remission, PASDAS LDA and VLDA, MDA, and VLDA at
65 Week 24 versus placebo (all unadjusted $p < 0.05$). At Week 52, in the guselkumab Q4W and
66 Q8W groups, respectively, response rates were as follows: DAPSA LDA, 54.2% and 52.5%;
67 DAPSA remission, 18.2% and 17.6%; PASDAS LDA, 45.3% and 41.9%; PASDAS VLDA,
68 16.9% and 19.5%; MDA, 35.9% and 30.7%; and VLDA, 13.1% and 14.4%. In the placebo-
69 crossover-to-guselkumab group, response rates for all composite indices increased after
70 patients switched to guselkumab, from Week 24 through Week 52.

71 **Conclusion:** Treatment with guselkumab provided robust and sustained benefits across
72 multiple PsA domains through 1 year, indicating that guselkumab is an effective therapy for the
73 diverse manifestations of PsA.

74 **Trial registration:** NCT03162796; NCT03158285

75 **Key words:** guselkumab, psoriatic arthritis, composite indices, remission, skin clearance, joint
76 disease

77

78 **KEY MESSAGES**

79 • Composite indices combine physician-assessed and patient-reported measures to
80 comprehensively evaluate outcomes across psoriatic arthritis domains.

81 • Assessments of guselkumab efficacy using composite indices showed significant,
82 sustained achievement of low disease activity/remission.

83 • These results suggest that guselkumab is an effective treatment for diverse
84 manifestations of psoriatic arthritis.

85

86

87 **INTRODUCTION**

88 Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by several distinct
89 clinical manifestations, including peripheral arthritis, axial disease, dactylitis, enthesitis, skin
90 disease, and nail disease [1,2]. The initial presentation and disease course of PsA is remarkably
91 heterogeneous, making diagnosis and treatment challenging. Most patients develop a range of
92 both musculoskeletal and extra-articular disease manifestations, which respond differently to
93 available therapies [2,3].

94
95 As a result of the multifaceted, systemic nature of PsA development and progression, treatment
96 guidelines evolved to recommend a “treat-to-target” approach, with the goal of achieving
97 remission or low disease activity (LDA) across all domains of disease [2,4,5]. The need to define
98 thresholds for achievement of remission and LDA resulted in the development of several
99 multidimensional indices [6,7], including the Disease Activity in Psoriatic Arthritis (DAPSA) [8],
100 the Psoriatic Arthritis Disease Activity Score (PASDAS) [9,10], and minimal disease activity
101 (MDA)/very low disease activity (VLDA) criteria [11,12]. These composite indices combine
102 various physician-assessed and patient-reported outcome measures applicable to both PsA
103 clinical trials and real-world clinical practice to comprehensively evaluate outcomes across PsA
104 domains [6,7,13–16].

105
106 Guselkumab is a fully human monoclonal antibody that selectively and specifically binds and
107 inhibits the p19 subunit of interleukin (IL)-23. Guselkumab is approved for the treatment of
108 adults with moderate to severe plaque psoriasis and active PsA [17]. The safety and efficacy of
109 guselkumab 100 mg administered every 4 weeks (Q4W) or every 8 weeks (Q8W) were
110 evaluated in the DISCOVER-1 and DISCOVER-2 randomized, placebo-controlled, Phase 3
111 studies in patients with active PsA. In these studies, guselkumab Q4W and Q8W significantly
112 improved signs and symptoms of PsA, including psoriasis-related skin symptoms, enthesitis,

113 dactylitis, physical function, and health-related quality of life, compared with placebo at Week 24
114 [18,19], with sustained improvements through 1 year [20,21]. In the current analyses, data were
115 pooled from the DISCOVER-1 and DISCOVER-2 Phase 3 studies to assess guselkumab
116 efficacy through 1 year utilizing various composite indices of PsA disease activity.

117

118 **METHODS**

119 **Patients and study designs**

120 DISCOVER-1 (NCT03162796) [18] and DISCOVER-2 (NCT03158285) [19] were similarly
121 designed, randomized, placebo-controlled studies of guselkumab in patients with active PsA,
122 diagnosed according to Classification Criteria for Psoriatic Arthritis (CASPAR) [22], who had an
123 inadequate response or intolerance to nonbiologic disease-modifying anti-rheumatic drugs
124 (DMARDs), apremilast, and/or nonsteroidal anti-inflammatory drugs (NSAIDs). In DISCOVER-1,
125 active PsA was defined as ≥ 3 tender and ≥ 3 swollen joints and serum C-reactive protein (CRP)
126 concentration ≥ 0.3 mg/dL. In DISCOVER-2, the definition of active PsA was more stringent,
127 requiring ≥ 5 tender and ≥ 5 swollen joints and serum CRP concentration ≥ 0.6 mg/dL. In
128 DISCOVER-1, prior treatment with 1 or 2 tumour necrosis factor- α inhibitors (TNFi) was
129 permitted but was limited to approximately 30% of the study population [18], while all patients in
130 DISCOVER-2 were biologic-naïve [19].

131

132 In both studies, patients were randomized in a 1:1:1 ratio to receive subcutaneous guselkumab
133 100 mg Q4W; guselkumab 100 mg at Week 0, Week 4, then Q8W; or placebo Q4W with
134 crossover to guselkumab 100 mg Q4W at Week 24. Patients could continue stable baseline use
135 of selected nonbiologic DMARDs, including methotrexate ≤ 25 mg/week, sulfasalazine ≤ 3 g/day,
136 hydroxychloroquine ≤ 400 mg/day, or leflunomide ≤ 20 mg/day; oral corticosteroids (≤ 10 mg/day
137 of prednisone or equivalent); and NSAIDs or other analgesics. At Week 16, patients with $< 5\%$
138 improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) were

139 eligible for early escape and had the option to initiate or increase their dose of one selected
140 nonbiologic DMARD, oral corticosteroids, NSAIDs, or other analgesics.

141

142 DISCOVER-1 and DISCOVER-2 were conducted in accordance with the principles of the
143 Declaration of Helsinki and Good Clinical Practice. The study protocols were approved by
144 governing ethics bodies. All participants provided written informed consent.

145

146 **Assessments**

147 The proportions of patients achieving DAPSA LDA, DAPSA remission, PASDAS LDA, PASDAS
148 VLDA, MDA, and VLDA by visit were prespecified efficacy assessments in the DISCOVER-1
149 and DISCOVER-2 studies. The proportions of patients achieving clinical DAPSA (cDAPSA) LDA
150 and remission were calculated post hoc for both studies. For the current analyses, data for
151 these outcomes were pooled across the 2 studies and are also presented separately for each
152 study.

153

154 DAPSA scores are calculated as the sum of TJC (range, 0-68), SJC (range, 0-66), patient pain
155 assessment (0-10 cm visual analogue scale [VAS]), patient global assessment (PtGA) of
156 arthritis activity (0-10 cm VAS), and CRP (mg/dL) [3,8]. cDAPSA is a modification of the DAPSA
157 that excludes CRP [23]. Higher DAPSA and cDAPSA scores represent more severe disease
158 activity. DAPSA LDA and remission are defined as scores of ≤ 14 and ≤ 4 , respectively, and
159 cDAPSA LDA and remission are defined as scores of ≤ 13 and ≤ 4 , respectively [23]. Based on
160 the measurement schedule for the individual assessments included, DAPSA and cDAPSA
161 scores were determined at Weeks 4, 8, 12, 16, 20, 24, 28, 36, 44, and 52.

162

163 PASDAS scores are calculated based on a formula that includes physician global opinion of
164 skin and joints (0-100 mm VAS), patient global opinion of skin and joints (0-100 mm VAS), 36-

165 item Short Form Health Survey physical component summary score (range, 0-100), SJC (0-66),
166 TJC (0-68), Leeds Enthesitis Index (LEI) score (range, 0-6) [24], tender dactylitis count (range,
167 0-20), and CRP (mg/L). Total PASDAS scores range from 0 to 10, with higher scores
168 representing more severe disease activity [9,10,12]. PASDAS LDA is defined as a score of ≤ 3.2 ,
169 and PASDAS VLDA is defined as a score of ≤ 1.9 [12]. Based on the measurement schedule for
170 the individual assessments included, PASDAS scores were calculated at Weeks 8, 16, 24, and
171 52.

172
173 Patients are considered to meet MDA or VLDA criteria, respectively, if they achieve 5 (MDA) or
174 7 (VLDA) of the following 7 outcomes: TJC ≤ 1 , SJC ≤ 1 , LEI ≤ 1 , Psoriasis Area and Severity
175 Index (PASI) score ≤ 1 , patient pain VAS ≤ 15 mm (range, 0-100), PtGA of the maximum
176 component of either psoriasis activity or PsA activity VAS ≤ 20 mm (range, 0-100), and Health
177 Assessment Questionnaire-Disability Index (HAQ-DI) score ≤ 0.5 (range, 0-3) [3,11,12]. MDA
178 and VLDA results were determined at Weeks 16, 24, and 52.

179
180 In DISCOVER-2, single radiographs of the hands (posteroanterior) and feet (anteroposterior)
181 were obtained at Weeks 0, 24, and 52 (or at discontinuation if between Weeks 24 and 52;
182 Reading Session 2) and scored by blinded central primary readers using the modified van der
183 Heijde-Sharp score for PsA [25]. Mean changes in PsA-modified van der Heijde-Sharp score
184 from Week 0 to Week 52 were compared for patients who did and did not achieve PASDAS
185 LDA, DAPSA LDA, and MDA responses at Week 24 (all using observed data).

186 187 **Statistical analyses**

188 Through Week 24, data were imputed as non-response for patients meeting treatment failure
189 criteria (i.e., discontinued study treatment, terminated study participation, initiated or increased
190 their dose of nonbiologic DMARDs or oral corticosteroids, or initiated any protocol-prohibited

191 PsA treatments) and for patients with missing data (non-responder imputation). After Week 24,
192 patients with missing data were considered to be non-responders (non-responder imputation),
193 and treatment failure rules were not applied.

194
195 Comparisons between the guselkumab groups and the placebo group through Week 24 were
196 performed using a Cochran-Mantel-Haenszel test stratified by randomization stratification
197 factors (baseline use of nonbiologic DMARDs [yes/no] and prior exposure to TNFi [yes/no] in
198 DISCOVER-1, and baseline use of nonbiologic DMARDs [yes/no] and most recent CRP value
199 prior to randomization [<2.0 or ≥ 2.0 mg/dL] in DISCOVER-2). P-values were not adjusted for
200 multiplicity. No treatment comparison was performed after Week 24.

201

202 **RESULTS**

203 **Patient disposition and baseline characteristics**

204 In these pooled analyses, 1120 patients were randomized and treated in the DISCOVER-1
205 (guselkumab Q4W, n=128; guselkumab Q8W, n=127; placebo, n=126) and DISCOVER-2
206 (guselkumab Q4W, n=245; guselkumab Q8W, n=248; placebo, n=246) studies. A total of
207 118 patients in DISCOVER-1 (10.5% of the pooled population) had prior exposure to 1 or
208 2 TNFi. In this pooled population, 351 (94%) patients randomized to guselkumab Q4W,
209 350 (93%) patients randomized to guselkumab Q8W, and 335 (90%) patients randomized to
210 placebo who crossed over to guselkumab at Week 24 received study treatment through 1 year.

211

212 At baseline, pooled patient demographic and PsA disease characteristics were comparable
213 across randomized treatment groups (Table 1). On average, patients had PsA for more than
214 5 years, with active skin disease (mean PASI score of 8.8-10.4), joint inflammation (mean SJC
215 of 11.4-11.5, mean TJC of 19.9-21.0), and impaired physical function (mean HAQ-DI score of
216 1.2-1.3). More than 60% of patients presented with enthesitis, and more than 40% of patients

217 presented with dactylitis. Mean DAPSA (45.9-46.9), PASDAS (6.4-6.5), patient assessment of
218 pain (6.1-6.2), and PtGA of disease activity (6.3-6.5) scores, and mean CRP concentrations
219 (1.6-1.9 mg/dL) were consistent with highly active PsA.

220

221 **Placebo-controlled period through Week 24**

222 At Week 24, greater proportions of guselkumab- than placebo-treated patients achieved low
223 levels of disease activity when assessed with DAPSA LDA (≤ 14), cDAPSA LDA (≤ 13), PASDAS
224 LDA (≤ 3.2), and MDA (5 of 7 components) composite indices (Figure 1). Separation from
225 placebo was observed in the guselkumab groups as early as Week 8 for achievement of
226 DAPSA LDA, cDAPSA LDA, and PASDAS LDA and at Week 16 (earliest timepoint assessed)
227 for MDA.

228

229 At Week 24, greater proportions of guselkumab- than placebo-treated patients achieved near or
230 complete remission when assessed with DAPSA (≤ 4) and cDAPSA (≤ 4) remission, PASDAS
231 VLDA (≤ 1.9), and VLDA (7 of 7 components) composite indices (Figure 2). Guselkumab-treated
232 patients separated from the placebo group as early as Week 12 for DAPSA and cDAPSA
233 remission, at Week 16 for PASDAS VLDA, and at Week 24 for VLDA.

234

235 In the pooled results, no notable differences in response rates were observed between the
236 guselkumab Q4W and Q8W dosing regimens. Response trends were generally consistent in the
237 individual DISCOVER-1 (biologic-naïve and TNFi-experienced patients) and DISCOVER-2
238 (biologic-naïve patients) studies (Supplementary Figures 1 and 2). However, response rates
239 were higher in DISCOVER-1 than in DISCOVER-2 at Week 24 for both guselkumab dosing
240 regimens (Q4W and Q8W) for DAPSA LDA, cDAPSA LDA, and PASDAS LDA, and for the
241 guselkumab Q4W regimen for DAPSA remission, cDAPSA remission, PASDAS VLDA, and
242 VLDA.

243

244 **Active treatment period after Week 24 through Week 52**

245 Among the guselkumab-randomized patients, response rates increased post-Week 24 through
246 Week 52, with indications of the potential for higher response rates beyond Week 52 (i.e., no
247 plateau was reached by Week 52 for PASDAS LDA/VLDA or MDA/VLDA). At Week 52, 54%
248 (Q4W) and 52% (Q8W) of guselkumab-randomized patients achieved DAPSA LDA; 55% (Q4W)
249 and 53% (Q8W) achieved cDAPSA LDA; 45% (Q4W) and 42% (Q8W) achieved PASDAS LDA,
250 and 36% (Q4W) and 31% (Q8W) achieved MDA (Figure 1). For placebo-randomized patients
251 who crossed over to guselkumab Q4W at Week 24, response rates for DAPSA LDA, cDAPSA
252 LDA, PASDAS LDA, and MDA at Week 52 approached those achieved by guselkumab-
253 randomized patients.

254

255 For the more stringent remission-related endpoints at Week 52, 18% (Q4W and Q8W) achieved
256 DAPSA remission; 21% (Q4W and Q8W) achieved cDAPSA remission; 17% (Q4W) and 20%
257 (Q8W) achieved PASDAS VLDA, and 13% (Q4W) and 14% (Q8W) achieved VLDA (Figure 2).
258 Notably, VLDA was more difficult to attain than DAPSA remission and PASDAS remission when
259 assessing longer-term treatment effect via these composite indices. In patients who crossed
260 over from placebo to guselkumab Q4W at Week 24, substantial increases in composite
261 response rates were seen by Week 52.

262

263 Across all composite indices, no notable differences in response rates were observed between
264 the guselkumab Q4W and Q8W dosing regimens. Results were generally consistent in the
265 individual DISCOVER-1 and DISCOVER-2 studies (Supplementary Figures 1 and 2).
266 Differences in response rates between DISCOVER-1 and DISCOVER-2 were smaller at
267 Week 52 than at Week 24, but DISCOVER-1 response rates remained notably higher in

268 patients randomized to guselkumab Q4W for DAPSA and cDAPSA LDA and remission,
269 PASDAS LDA, and MDA (Supplementary Figures 1 and 2).

270

271 **Maintenance of response**

272 As shown in Figure 3, among guselkumab-treated patients who achieved low levels of disease
273 activity at Week 24, nearly all maintained responses at Week 52 (PASDAS LDA: 88% Q4W and
274 91% Q8W; DAPSA LDA: 85% Q4W and 89% Q8W; MDA: 76% Q4W and 80% Q8W). Similarly,
275 among guselkumab-treated patients who achieved remission/VLDA at Week 24, the majority
276 maintained response at Week 52 (PASDAS VLDA: 82% Q4W and 90% Q8W; VLDA: 71% Q4W
277 and 94% Q8W; DAPSA remission: 68% Q4W and 74% Q8W).

278

279 **Association of radiographic progression at 1 year with composite efficacy responses at** 280 **Week 24**

281 In DISCOVER-2, patients who achieved PASDAS LDA, DAPSA LDA, and MDA at Week 24 had
282 smaller mean changes in total PsA-modified van der Heijde-Sharp scores from Week 0 to
283 Week 52 compared with patients who did not achieve these responses (Figure 4).

284

285 **Assessment of residual disease based on components of MDA and VLDA**

286 At Week 52, among guselkumab-randomized patients, a majority achieved ≤ 1 tender enthesal
287 point (Q4W, 79%; Q8W, 77%), PASI score ≤ 1 (Q4W, 79%; Q8W, 73%), and SJC ≤ 1 (Q4W,
288 66%; Q8W, 61%) (Supplementary Figure 3). However, most patients continued to show signs of
289 potential residual disease activity, as evidenced by lower rates achieving normalized physical
290 function (HAQ-DI ≤ 0.5 ; Q4W, 44%; Q8W, 39%), PtGA ≤ 20 (Q4W, 39%; Q8W, 38%), TJC ≤ 1
291 (Q4W, 30%; Q8W, 33%), and pain ≤ 15 (Q4W, 32%; Q8W, 31%) (Figure 5).

292

293 **DISCUSSION**

294 Results of these pooled post hoc analyses from DISCOVER-1 and DISCOVER-2 showed that
295 patients with active PsA who received guselkumab Q4W or Q8W achieved consistent and
296 robust responses over placebo based on achievement of numerous composite measures of
297 disease activity. Separation of guselkumab from placebo was observed as early as Week 8 for
298 DAPSA LDA and PASDAS LDA. Among guselkumab-randomized patients, response rates for
299 all composite indices continued to increase from baseline through Week 52. Furthermore, the
300 majority of guselkumab-randomized patients who achieved responses at Week 24 had
301 maintained or increased levels of response at Week 52, and in many cases slopes of the
302 response curves suggest the potential for further improvement over time. Placebo-randomized
303 patients who crossed over to guselkumab Q4W at Week 24 showed steady improvements in all
304 composite indices, with response rates approaching those observed for guselkumab-
305 randomized patients at Week 52.

306
307 Response trends were generally consistent when results from DISCOVER-1 and DISCOVER-2
308 were considered separately. However, across most composite indices, Week 24 response rates
309 were higher in DISCOVER-1 than in DISCOVER-2, despite the fact that approximately 30% of
310 patients in DISCOVER-1 had prior exposure to TNFi, and these TNFi-experienced patients had
311 numerically lower MDA response rates compared with TNFi-naïve patients at Week 24 (17%-
312 26% vs 32%-34%) [20]. The observed differences between studies may be related to
313 differences in eligibility criteria requiring patients in DISCOVER-2 to have more severe disease
314 (SJC and TJC ≥ 5 , and CRP ≥ 0.6 mg/dL) at baseline than in DISCOVER-1 (SJC and TJC ≥ 3 ,
315 and CRP ≥ 0.3 mg/dL).

316
317 In DISCOVER-2, composite measure responses at Week 24 were associated with reduced
318 long-term radiographic progression based on smaller mean changes in total PsA-modified van

319 der Heijde-Sharp scores at Week 52. This finding suggests that early treatment with
320 guselkumab may reduce the risk for permanent joint damage.

321
322 Pooled results showed that by Week 52, approximately one-third of all guselkumab-treated
323 patients achieved the widely accepted treatment target of MDA. Evaluation of the proportions of
324 patients achieving the individual MDA components showed particularly high and consistent
325 response rates for objective measures, including resolution of enthesitis, swollen joints, and skin
326 disease. Through Week 52, pain and TJC >1 – which would be expected to heavily influence
327 the patient-reported outcomes of physical function (HAQ-DI) and PtGA – appeared to be the
328 symptoms limiting achievement of MDA for many patients. However, the trajectory of responses
329 for achievement of TJC ≤1, pain ≤15, and PtGA ≤20 suggest a possibility of increased response
330 rates with continued treatment with guselkumab.

331
332 Our findings that disease activity based on TJC, pain, and PtGA measurements often limit the
333 achievement of composite outcomes are generally consistent with published studies identifying
334 pain, PtGA, skin disease, and tender joints as the most common unmet criteria in patients failing
335 to achieve MDA/VLDA treatment targets [16,26,27]. However, in contrast to other studies
336 [3,16,26], achievement of the skin disease criterion was not a limiting factor in attaining
337 MDA/VLDA for most patients in DISCOVER-1 and DISCOVER-2. This finding is likely related to
338 better efficacy of guselkumab (an IL-23 inhibitor) for the treatment of psoriasis compared with
339 biologic DMARDs with different mechanisms of action (i.e., TNF, IL-17, or IL-12/23 inhibition)
340 [28–33]. Specifically, in the DISCOVER studies, approximately 70% of guselkumab-randomized
341 patients achieved PASI ≤1 at Week 24, and response rates increased to up to 79% by Week 52;
342 in the placebo to guselkumab Q4W crossover group, the PASI ≤1 response rate increased from
343 27% at Week 24 to 74% at Week 52. These results are particularly noteworthy since these

344 analyses used the more stringent of two MDA definitions of skin response (i.e., PASI score ≤ 1
345 instead of body surface area of psoriasis $\leq 3\%$) [3,11,12].

346
347 Similarly, for DAPSA, high pain and PtGA parameters often limit the achievement of remission,
348 even in patients without active joint inflammation [16,34]. For patients with established structural
349 damage to affected joints before initiating treatment with guselkumab, achieving low levels of
350 pain and satisfactory physical function and PtGA may not have been possible. Furthermore,
351 recent studies indicate that substantial proportions of patients with PsA experience persistent,
352 widespread pain despite effective control of inflammation with conventional or biologic DMARDs
353 [34–36]. In one model of chronic pain, peripheral neurologic hypersensitivity develops following
354 pathological changes in the central nervous system [35]. This altered pain perception in patients
355 with PsA may lead to overestimation of joint tenderness and inflammatory activity [35]. Thus,
356 achievement of low levels of pain may be especially difficult for some patients with PsA, and
357 adjustment of treatment targets may be warranted (e.g., based on disease duration, amount of
358 structural damage, or altered pain perception). Alternatively, centralized pain may develop in
359 association with prevalent comorbidities, such as obstructive sleep apnoea, anxiety and/or
360 depression, and deconditioned muscles and joints.

361
362 These analyses of the pooled DISCOVER-1 and DISCOVER-2 dataset provide a unique
363 opportunity to demonstrate consistent and robust response rates with guselkumab versus
364 placebo for several different composite measures, each with emphasis on different clinical
365 outcomes. The DAPSA, which focuses mainly on measures of peripheral articular disease, does
366 not include specific assessments of dactylitis, enthesitis, or skin disease, and requires
367 laboratory testing to measure CRP levels [3,22,37–40]. In contrast to the DAPSA, the PASDAS
368 and MDA assess multiple domains of articular and extra-articular disease activity [37,38];
369 therefore, these measures are more likely to be relevant as PsA treatment targets. In routine

370 clinical practice, MDA is used more often than the PASDAS because PASDAS scoring is
371 complicated and not intuitive, limiting its use in real-world settings [7,13]. Overall, increased use
372 of composite indices is important to promote recommended treat-to-target approaches, which
373 may reduce the undertreatment of PsA and improve patient outcomes [38].

374
375 As with all controlled clinical trials, patients enrolled in the DISCOVER-1 and DISCOVER-2
376 studies were required to meet predefined selection criteria based on previous treatment and
377 medical history. Additionally, while DAPSA LDA and remission, PASDAS LDA and VLDA, and
378 MDA were prespecified secondary efficacy endpoints of the individual DISCOVER-1 and
379 DISCOVER-2 studies, pooling the results across both studies was not prespecified and was
380 performed post hoc to increase the sample size. Therefore, results from the current analyses
381 may not be generalizable to all patients with PsA. However, consistent with results of these
382 analyses, in a recent small real-world observational study in 24 patients with early PsA and
383 severe skin disease, 75% (18/24) of patients achieved DAPSA LDA or remission after 6 months
384 of guselkumab treatment; 17 of these patients completed 1 year of treatment, and all achieved
385 DAPSA LDA (65% [11/17]) or remission (35% [6/17]) [41].

386
387 Comparison of the results from these analyses with other published studies is inherently limited.
388 To date, few clinical studies have reported composite index results, and among published
389 results, there are often differences in baseline disease and demographic characteristics, sample
390 sizes, analysis methods (i.e., observed vs imputed data), and the composite endpoints reported
391 [37,42-47]. However, results of analyses published to date suggest that composite indices can
392 provide more comprehensive assessments of the range of PsA disease manifestations than
393 conventional peripheral joint-based outcome measures (e.g., ACR20), and that treatment
394 targets such as MDA, DAPSA LDA/remission, and PASDAS LDA/VLDA are achievable for
395 many patients using currently available biologic or targeted synthetic therapies [37,42-47]. Thus,

396 composite indices may be useful in routine clinical practice and as key endpoints in future PsA
397 clinical trials.

398

399 Taken together, results of these analyses indicate that patients with active PsA who receive
400 treatment with guselkumab Q4W or Q8W can achieve robust and sustained low disease activity
401 or remission, based on various composite indices that measure responses across domains
402 including joint pain, swelling, stiffness, inflammation, and tenderness; and skin clearance. As
403 such, guselkumab is a novel therapy for PsA that can provide effective treatment of the diverse
404 manifestations of this disease.

405

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454

455 **Data availability statement**

456 The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is
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458 for access to the study data can be submitted through Yale Open Data Access (YODA)
459 Project site at <http://yoda.yale.edu>.

460

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FIGURE LEGENDS

Figure 1. Achievement of DAPSA LDA (A), cDAPSA LDA (B), PASDAS LDA (C), and MDA (D). Through Week 24, patients meeting treatment failure criteria or with missing data were considered non-responders. Treatment group comparisons through Week 24 were not adjusted for multiplicity of testing; all reported p-values are nominal. After Week 24 and through Week 52, patients with missing data were considered non-responders.

cDAPSA: clinical DAPSA (excludes C-reactive protein); DAPSA: Disease Activity in Psoriatic Arthritis; GUS: guselkumab; LDA: low disease activity; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PBO: placebo; Q4W: every 4 weeks; Q8W: every 8 weeks.

Figure 2. Achievement of DAPSA remission (A), cDAPSA remission (B), PASDAS VLDA (C), and VLDA (D). Through Week 24, patients meeting treatment failure criteria or with missing data were considered non-responders. Treatment group comparisons through Week 24 were not adjusted for multiplicity of testing; all reported p-values are nominal. After Week 24 and through Week 52, patients with missing data were considered non-responders.

cDAPSA: clinical DAPSA (excludes C-reactive protein); DAPSA: Disease Activity in Psoriatic Arthritis; GUS: guselkumab; PASDAS: Psoriatic Arthritis Disease Activity Score; PBO: placebo; Q4W: every 4 weeks; Q8W: every 8 weeks; VLDA: very low disease activity.

Figure 3. Maintenance of PASDAS LDA, DAPSA LDA, and MDA (A), and PASDAS VLDA, VLDA, and DAPSA remission (B) at Week 52 among guselkumab-randomized patients with response at Week 24. N represents the total number of patients with response at Week 24. Through Week 24, patients meeting treatment failure criteria or with missing data were considered non-responders. After Week 24 and through Week 52, patients with missing data were considered non-responders.

DAPSA: Disease Activity Index for Psoriatic Arthritis; GUS: guselkumab; LDA: low disease activity; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; Q4W: every 4 weeks; Q8W: every 8 weeks; VLDA: very low disease activity.

Figure 4. Mean changes in PsA-modified total vdH-S score in DISCOVER-2 patients based on Week 24 PASDAS LDA, DAPSA LDA, and MDA response status. Evaluable patients had an observed change from baseline to Week 52 in PsA-modified vdH-S score and observed PASDAS, DAPSA, or MDA status, respectively, at Week 24.

DAPSA: Disease Activity Index for Psoriatic Arthritis; LDA: low disease activity; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PsA: psoriatic arthritis; Q4W: every 4 weeks; Q8W: every 8 weeks; vdH-S: van der Heijde-Sharp.

Figure 5. Achievement of ≤ 1 tender joint (A), patient assessment of pain VAS ≤ 15 (B), HAQ-DI score ≤ 0.5 (C), and PtGA ≤ 20 (D). Through Week 24, patients meeting treatment failure criteria or with missing data were considered non-responders. Treatment group comparisons through Week 24 were not adjusted for multiplicity of testing; all reported p-values are nominal. After Week 24 and through Week 52, patients with missing data were considered non-responders.

GUS: guselkumab; HAQ-DI: Health Assessment Questionnaire-Disability Index; PBO: placebo; PtGA: patient global assessment of disease activity (arthritis and psoriasis); Q4W: every 4 weeks; Q8W: every 8 weeks; VAS: visual analog scale.

TABLES

Table 1. Baseline characteristics for randomized and treated patients in DISCOVER-1 and DISCOVER-2

	DISCOVER-1 and DISCOVER-2		
	Guselkumab Q4W	Guselkumab Q8W	Placebo
Randomized and treated patients, N	373	375	372
Age (years)	46.5 (11.5)	46.2 (11.9)	47.2 (11.5)
Male, n (%)	208 (55.8)	197 (52.5)	178 (47.8)
BMI (kg/m ²)	29.4 (5.8)	29.1 (6.3)	29.2 (6.1)
PsA duration (years)	5.9 (6.1)	5.6 (5.7)	6.2 (6.4)
Swollen joint count (0-66)	11.4 (7.5)	11.4 (7.7)	11.5 (7.0)
Tender joint count (0-68)	20.8 (13.6)	19.9 (12.8)	21.0 (13.5)
Patients with enthesitis (LEI>0), n (%) ^a	243 (65.1)	230 (61.5)	255 (68.7)
LEI score (1-6)	3.0 (1.6)	2.7 (1.5)	2.8 (1.6)
Patients with dactylitis, n (%) ^a	159 (42.6)	160 (42.8)	154 (41.5)
Dactylitis score (1-60) ^b	8.8 (10.3)	8.1 (9.7)	7.7 (8.7)
Patient assessment of pain (VAS 0-10 cm)	6.1 (2.0)	6.2 (2.0)	6.1 (2.0)
Patient global assessment of disease activity (arthritis, VAS 0-10 cm)	6.3 (2.0)	6.5 (2.0)	6.4 (2.0)
Physician global assessment of disease activity (VAS 0-10 cm)	6.5 (1.6)	6.4 (1.6)	6.5 (1.6)
CRP (mg/dL)	1.6 (2.0)	1.9 (2.4)	1.9 (2.4)
PASI (0-72) ^c	10.4 (11.2)	9.2 (11.1)	8.8 (9.5)
HAQ-DI (0-3)	1.2 (0.6)	1.3 (0.6)	1.3 (0.6)
DAPSA score (remission ≤4; high disease activity >28)	46.2 (20.7)	45.9 (20.9)	46.9 (20.2)
cDAPSA score (remission ≤4; high disease activity >27)	44.6 (20.3)	44.1 (20.4)	45.0 (19.9)
PASDAS score ^d (low disease activity ≤3.2; high disease activity >5.4)	6.4 (1.1)	6.5 (1.1)	6.5 (1.0)
Patients receiving methotrexate, n (%)	218 (58.4)	209 (55.7)	227 (61.0)
Mean dose (mg/week)	15.6 (4.7)	15.8 (5.3)	15.4 (4.6)
Patients receiving oral corticosteroids, n (%)	62 (16.6)	68 (18.1)	69 (18.5)
Mean dose (mg/day)	6.9 (2.4)	6.6 (2.4)	7.4 (2.6)

Data are mean (SD) unless otherwise indicated.

^aGuselkumab Q4W, n = 373; guselkumab Q8W, n = 374; placebo, n = 371.

^bEach of 20 digits is scored from 0 (no dactylitis) to 3 (severe dactylitis), resulting in a total score range of 0-60; mean scores shown here are for patients with dactylitis (score ≥1) at baseline.

^cGuselkumab Q4W, n = 373; guselkumab Q8W, n = 375; placebo, n = 371.

^dGuselkumab Q4W, n = 369; guselkumab Q8W, n = 372; placebo, n = 367.

BMI: body mass index; cDAPSA: clinical DAPSA (excludes CRP); CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; HAQ-DI: Health Assessment Questionnaire-Disability Index; LEI: Leeds Enthesitis Index; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; Q4W: every 4 weeks; Q8W: every 8 weeks; SD: standard deviation; VAS: visual analog scale.