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1   **Title:** The Effect of Guselkumab on Work Productivity in Biologic-Naïve Patients With Active

2   Psoriatic Arthritis Through Week 52 of the Phase 3, Randomized, Placebo-Controlled

3   DISCOVER-2 Trial

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ABSTRACT

Introduction: The DISCOVER-2 phase 3 trial evaluated guselkumab effect on impaired work productivity and nonwork activity in biologic-naïve patients with psoriatic arthritis (PsA).

Methods: Adults with active PsA were randomized (1:1:1) to guselkumab 100 mg every 4 weeks (Q4W); at weeks 0, 4, then every 8 weeks (Q8W); or placebo (with crossover to guselkumab Q4W at week 24). Least squares mean change from baseline in Work Productivity and Activity Impairment Questionnaire for PsA (WPAI-PsA) domains and employment were assessed by treatment group. Multivariate analysis of weeks 0 through 24 data assessed independent associations between PsA clinical features and WPAI-PsA domains.

Results: In total, 738 patients were evaluated (guselkumab Q4W N=245; guselkumab Q8W N=248; placebo N=245). At week 24, improvements (reduced impairment) in presenteeism (Q4W -20.1%, Q8W -19.6%, placebo -10.5%), work productivity (Q4W -20.1%, Q8W -19.2%, placebo -10.6%), and nonwork activity (Q4W -20.5%, Q8W -21.2%, placebo -9.9%) were greater in guselkumab-treated versus placebo-treated patients. At week 52, following placebo crossover at week 24, improvements were similar among groups. Baseline absenteeism was minimal and did not change in any group. By week 52, 23.1% to 25.9% of guselkumab-treated patients who were unemployed at baseline were employed. All WPAI-PsA domains were positively associated with C-reactive protein level, fatigue, and pain. All domains except absenteeism were positively associated with enthesitis and Psoriasis Area and Severity Index score. Age was negatively associated with presenteeism and work productivity loss, female sex and tender joint count were positively associated with nonwork activity impairment, and dactylitis was positively associated with presenteeism.

60 **Conclusion:** Both guselkumab regimens reduced work productivity loss and nonwork activity

61 impairment in patients with active PsA. Association of work productivity loss and nonwork

62 activity impairment with PsA joint and skin features suggests that improvement in both features

63 is beneficial to optimize improved work productivity loss and nonwork activity impairment.

64 **Trial registration:** Clinicaltrials.gov identifier, NCT03158285

65 **Keywords**

66 Guselkumab, Psoriatic Arthritis, Work Productivity

67

68 **Key Summary Points**

69 *Why carry out this study?*

70 • Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with peripheral

71 arthritis, psoriasis, enthesitis, dactylitis, axial inflammation, and fatigue that can result in

72 disability, work productivity loss, and economic consequences.

73 • Guselkumab is an interleukin-23 p19-subunit inhibitor approved for use in patients with

74 active PsA that has been shown to significantly improve signs and symptoms of joint and

75 skin disease, physical function, and overall quality of life through 2 years in patients with

76 active PsA.

77 • The objectives of these analyses were to assess the effects of guselkumab 100 mg every 4

78 or 8 weeks on the domains of the Work Productivity and Activity Impairment

79 Questionnaire for PsA (WPAI-PsA) and employment through 1 year in biologic-naïve

80 patients with PsA in the phase 3 DISCOVER-2 trial, to estimate the impact of changes in

81   work productivity on PsA-related costs, and to assess the independent association

82   between PsA patient characteristics and clinical features and the WPAI-PsA domains

83   *What was learned from the study?*

84   • Both guselkumab regimens reduced impairment in presenteeism, work productivity, and

85   nonwork daily activity in patients with active PsA

86   • Reductions in work productivity loss in guselkumab-treated patients were estimated to

87   result in substantial yearly indirect work productivity-related cost savings

88   • Work productivity loss was positively associated with C-reactive protein level, fatigue,

89   patient-reported pain, skin involvement, and enthesitis, and nonwork activity impairment

90   was positively associated with female sex, C-reactive protein level, fatigue, patient-

91   reported pain, skin involvement, tender joint count, and enthesitis

92   • These results suggest that improvement in multiple clinical features of PsA is beneficial

93   for optimal reduction in work productivity loss and nonwork daily activity impairment

94   associated with PsA

95

INTRODUCTION

The multiple clinical features of psoriatic arthritis (PsA), a chronic inflammatory disease associated with peripheral arthritis, psoriasis, enthesitis, dactylitis, axial inflammation, and fatigue, can result in significant physical, psychological, social, and functional impairment [1, 2]. This impairment, in turn, is associated with disability, work productivity loss, and economic consequences [1, 2]. It has been estimated that 22% to 23% of patients with PsA are unemployed due to PsA, and 16% to 39% experience work productivity loss due to PsA [2]. The direct and indirect costs of unemployment and work productivity loss that have been shown to be associated with disease activity and physical function [3] are a significant burden for individuals with PsA, their employers, and society as a whole [4, 5]. Thus, work productivity loss, which is defined as a combination of missed work time (absenteeism) and reduced effectiveness at work (presenteeism) [2], and impaired ability to perform regular activities outside of work are important outcomes to monitor and address in patients with PsA. Indeed, participation, which includes employment as well as family roles and social and leisure activities, is an outcome measure that is recommended for inclusion in PsA trials by Outcome Measures in Rheumatology (OMERACT) [6, 7].

Guselkumab, a high-affinity interleukin-23 p19-subunit inhibitor, is the first IL-23 inhibitor approved for use in adults with active PsA [8, 9]. In the pivotal phase 3 DISCOVER-1 and DISCOVER-2 trials, subcutaneous guselkumab 100 mg every 4 or 8 weeks improved signs and symptoms of joint and skin disease, physical function, and overall quality of life through 2 years in patients with active PsA despite standard treatment [10-14]. Imaging assessments from the larger DISCOVER-2 trial demonstrated that subcutaneous guselkumab 100 mg every 4 weeks

118 also significantly inhibited the progression of structural damage at 24 weeks and through 2 years

119 [11, 13, 14].

120 Herein, we report the effects of guselkumab therapy on work productivity, nonwork activity, and

121 employment through 1 year in the DISCOVER-2 trial and the estimated impact of changes in

122 work productivity on PsA-related costs. We also report the results of a post hoc analysis of

123 pooled DISCOVER-2 data through week 24 that assessed the independent associations between

124 PsA patient characteristics and clinical features and work productivity and nonwork activity.

125 **METHODS**

126 **Patients and Trial Design**

127 DISCOVER-2 (NCT03158285) was a phase 3, randomized, double-blind, placebo-controlled

128 3-arm trial. Trial design details have been previously reported [11, 13]. A total of 739 patients

129 aged ≥18 years who met the classification criteria for PsA [15] and had ≥5 swollen and ≥5 tender

130 joints and C-reactive protein (CRP) ≥0.6 mg/dL despite standard nonbiologic treatment were

131 randomized and treated in DISCOVER-2 [11]. Patients were randomized in a 1:1:1 ratio to

132 receive subcutaneous guselkumab 100 mg every 4 weeks (Q4W); guselkumab 100 mg at weeks

133 0, 4, and then every 8 weeks (Q8W); or placebo. Randomization was stratified by most recent

134 high-sensitivity serum CRP value before randomization (<2.0 mg/dL versus ≥2.0 mg/dL) and by

135 baseline nonbiologic disease-modifying antirheumatic drug (DMARD) use (yes versus no). At

136 week 24, patients randomized to placebo crossed over to receive subcutaneous guselkumab 100

137 mg Q4W. Patients were naïve to biologic agents and Janus kinase inhibitors but could continue

138 baseline use of stable doses of selected nonbiologic therapies.

139   This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical

140   Practice guidelines. All patients provided written informed consent, and the protocols were

141   approved by local institutional review boards or ethics committees (Sterling Institutional Review

142   Board approval number for United States sites is 5910C).

143   **Outcome Assessments**

144   At baseline, week 16, week 24, and week 52, patient productivity was assessed using the Work

145   Productivity and Activity Impairment Questionnaire for PsA (WPAI-PsA), a validated

146   instrument that evaluates the impact of PsA on patients' ability to work (among patients working

147   at baseline) and perform daily nonwork activities (among all patients) during the previous 7 days

148   [16-18]. Four scores are derived from the questionnaire: percentage of work time missed

149   (absenteeism), percentage of reduced productivity while at work (presenteeism), an overall work

150   productivity impairment score that combines absenteeism and presenteeism, and percentage of

151   impairment in activities performed outside of work. Greater scores indicate greater impairment

152   due to PsA (0% no impairment, 100% complete impairment). Employment status was also

153   evaluated at baseline and throughout the trial. Data collected through week 52 are reported

154   herein.

155   Clinical features assessed in DISCOVER-2 included evaluation of joints for tenderness (n=68;

156   tender joint count [TJC]) and swelling (n=66, excluding hips; swollen joint count [SJC]), the

157   presence of enthesitis (using the Leeds enthesitis index, 0-6 scale), and the presence and severity

158   of dactylitis by independent assessors [11, 19-21]. Dactylitis severity for each digit was scored as

159   0 or none, 1 for mild, 2 for moderate, or 3 for severe dactylitis (total score: 0-60) [11]. Skin

160   disease severity and extent was evaluated using the Investigator's Global Assessment of psoriasis

161   (IGA; 0 [clear] to 4 [severe]) [22] and the Psoriasis Area and Severity Index (PASI; 0 [none] to

162   72 [severe]) [23] at weeks 0, 16, 24, and 52. Serum CRP level was evaluated as a marker of

163   inflammation [24]. Patients reported their pain level using a visual analog scale (VAS; 0 [no

164   pain] to 10 [worst possible pain] cm), their physical function using the Health Assessment

165   Questionnaire Disability Index (HAQ-DI; 0 [best] to 3 [worst]) [25], and their health-related

166   quality of life (HRQoL) using the Short Form 36 health survey (SF-36) [26] physical component

167   summary (PCS) and mental component summary (MCS) (0 [worst] to 100 [best]), EuroQol-5

168   dimension-5 level (EQ-5D-5L) Index (0 [death] to 1 [perfect health]), and EuroQol visual analog

169   scale (EQ-VAS; 0 [worst] to 100 [best]) [27]. Fatigue over the previous 7 days was evaluated

170   using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; 0 [severe] to 52

171   [none]) [28]. Clinical efficacy and HAQ-DI assessments were conducted at week 0, then Q4W

172   up to week 28, and then Q8W up to week 52. Skin assessments were conducted at weeks 0, 16,

173   24, and 52. HRQoL assessments were conducted at weeks 0, 8, 16, 24, and 52.

174   **Statistical Analyses**

175   *Change From Baseline in WPAI-PsA*

176   A summary of the change from baseline in WPAI-PsA scores was prespecified, and least squares

177   (LS) mean changes from baseline in WPAI-PsA domains were determined using an analysis of

178   covariance model with baseline WPAI-PsA score, prior use of nonbiologic DMARDs (yes/no),

179   and baseline CRP level (<2.0/≥2.0 mg/dL) as explanatory factors. A missing WPAI-PsA score,

180   including domain scores, at any visit was imputed using the predicted value from an imputation

181   model using the full conditional specification regression method. LS means and 95% confidence

182   intervals were calculated as the average of all multiple imputation datasets at week 24 and week

183   52. Treatment differences between the guselkumab 100 mg Q4W (hereafter referred to as

184   guselkumab Q4W) and guselkumab 100 mg Q8W (hereafter referred to as guselkumab Q8W)

185   groups and the placebo group at weeks 16 and 24 were estimated by the difference in the LS

186   means. Changes in absenteeism, presenteeism, and overall work productivity impairment were

187   assessed in patients employed at baseline who had postbaseline values. Changes in nonwork

188   activity impairment were assessed in all patients who had postbaseline values. All patients were

189   eligible for analysis; there was no minimal impairment required for analysis of the LS mean

190   change in WPAI-PsA domains.

191   The proportion of patients who achieved the minimum clinically important difference (MCID) in

192   work productivity (15% improvement) [16] was evaluated among patients with ≥15% work

193   productivity impairment at baseline. The proportion of patients who achieved the MCID for

194   nonwork activity (20% improvement) [16] was evaluated among patients with ≥20% impairment

195   at baseline.

196   *Changes From Baseline in Employment*

197   Changes in employment status over the trial period were assessed post hoc by analyzing shifts in

198   patient-reported employment status by treatment group from baseline through week 52. All

199   patients were included in these analyses and were grouped by employment status (employed or

200   unemployed) at baseline.

201   *Association of Work Productivity and Nonwork Activity Impairment With Patient Variables and*

202   *PsA Clinical Features*

203   In post hoc analyses, observed baseline data pooled across treatment groups were used to

204   calculate the Spearman correlation coefficient between WPAI-PsA domains and key variables,

205   including EQ-5D-5L Index, EQ-VAS, patient-reported pain, FACIT-F, HAQ-DI, PASI, IGA,

206   SF-36 PCS and MCS, TJC, SJC, CRP level, age, and body mass index (BMI).

207 Associations between selected variables and WPAI-PsA domains were also assessed using linear

208 regression mixed models with random intercept. Observed data from week 0 through week 24

209 for all patients across all treatment groups who had postbaseline measurements were pooled to

210 attain sufficient statistical power for analysis and were analyzed in a cross-sectional manner.

211 Univariate linear regression was executed to identify independent variables, chosen based on the

212 core outcome measures recommended by OMERACT [7], that were associated with WPAI-PsA

213 domains. Independent variables assessed were EQ-5D-5L Index, EQ-VAS, patient-reported pain,

214 FACIT-F, HAQ-DI, PASI, IGA, SF-36 PCS and MCS, TJC, SJC, dactylitis, enthesitis, CRP

215 level, age, sex, and BMI. Multivariate mixed model for repeated measures (MMRM) regression

216 models evaluated variables with associations with WPAI-PsA domains that reached $p<0.10$ in

217 univariate analysis, taking collinearity between variables into account. Variables with $p<0.05$ in

218 the multivariate models were considered to be significantly associated with WPAI-PsA domains.

219 A sensitivity analysis that did not include patient-reported pain as a covariate was also conducted

220 to control for collinearity between arthritis (TJC and SJC) and pain.

221 *Cost Analyses*

222 Potential yearly indirect cost savings from improved overall work productivity were estimated by

223 multiplying the Organisation for Economic Co-operation and Development (OECD)-reported

224 average wages for 2020 for Europe (including France, Germany, Italy, Spain, and the United

225 Kingdom), the United States, and Japan [29] by the percentage change from baseline in WPAI-

226 PsA overall work productivity impairment at weeks 24 and 52 for each treatment group. Note

227 that all values are presented in United States dollars.

228 The significance level of all statistical tests reported were based on $\alpha=0.05$ (2-tailed). Statistical

229 analyses were performed using SAS, version 9.4, and R-studio version 1.3.1056.

230   **RESULTS**

231   **Patients**

232   Among the 739 patients randomized and treated in this trial, 738 had evaluable WPAI-PsA data

233   at baseline, and 733 had evaluable WPAI-PsA (nonwork activity) postbaseline data (guselkumab

234   Q4W N=242, guselkumab Q8W N=246, and placebo N=245) (**Supplementary Material Figure**

235   **S1a**). Of the 738 total patients, 475 (64.4%) were actively employed at baseline (guselkumab

236   Q4W N=153, guselkumab Q8W N=151, and placebo N=171) (**Supplementary Material Figure**

237   **S1b**). A postbaseline missing value was imputed for 0.6% (5/738) of total patients and 5%

238   (20/440) of employed patients with baseline and postbaseline WPAI-PsA values, including

239   domain scores.

240   Overall, patients had a mean age of 45.7 years; majority (98.0%) were White, and more than half

241   (52.5%) were male (**Table 1**). Baseline characteristics represented a patient population with

242   moderate to severe disease activity (mean [standard deviation (SD)] SJC, 12.3 [7.2]; TJC, 21.3

243   [12.9]; patient pain score, 6.3 [1.9]; and median CRP, 1.2 mg/dL) and moderately impaired

244   HRQoL (mean [SD] EQ-5D-5L Index score, 0.6 [0.1] and EQ-VAS score, 44.6 [19.7]). This

245   patient population also had clinically significant impairment in most of the WPAI-PsA domains

246   at baseline; overall mean (SD) percentage of presenteeism was 48.3% (24.7), work productivity

247   impairment was 51.4% (25.9), and percentage of daily nonwork activity impairment was 55.5%

248   (22.8). The percentage of absenteeism due to PsA was relatively low in this population (mean

249   [SD] 11.2% [22.7]) and was unbalanced among treatment groups (guselkumab Q4W 8.4 [17.4],

250   guselkumab Q8W 10.5 [21.0], and placebo 14.5 [27.5]). In addition, 61.3% of employed patients

251   had 0% work time missed due to PsA, but only approximately 6% of patients had 0%

252 impairment in presenteeism (6.4%) and overall work productivity (6.1%), and only 2.2% of

253 patients had 0% nonwork activity impairment.

Change From Baseline in WPAI-PsA

255 Greater mean reductions from baseline in presenteeism, work productivity loss, and nonwork

256 activity were observed in guselkumab-treated versus placebo-treated patients at weeks 16 and 24

257 (**Figure 1**). At week 24, among patients who were employed at baseline, in the guselkumab

258 Q4W, guselkumab Q8W, and placebo groups, LS mean reductions in presenteeism were -20.1%,

259 -19.6%, and -10.5%, respectively, and LS mean reductions in work productivity loss

260 were -20.1%, -19.2%, and -10.6%, respectively (**Figure 1b-c**). Among all patients (employed

261 and not employed), LS mean reduction in nonwork activity impairment at week 24 was -20.5%

262 in the guselkumab Q4W group, -21.2% in the guselkumab Q8W group, and -9.9% in the placebo

263 group (**Figure 1d**). LS mean reductions in presenteeism (guselkumab Q4W -22.4%, guselkumab

264 Q8W -25.7%), work productivity loss (guselkumab Q4W -22.6%, guselkumab Q8W -25.9%),

265 and nonwork activity impairment (guselkumab Q4W -25.7%, guselkumab Q8W -25.4%)

266 continued through 1 year in both guselkumab treatment groups. In addition, by 1 year, LS mean

267 reductions from baseline in presenteeism, work productivity loss, and nonwork activity

268 impairment in the placebo→guselkumab Q4W group (-18.5%, -17.6%, and -22.3%, respectively)

269 were similar to those observed in patients who received a full year of guselkumab treatment. LS

270 mean reductions in absenteeism remained stable in all groups through week 52, ranging

271 from -3.0% to -5.0% across treatment groups at all time points (**Figure 1a**).

272 Among patients with ≥15% work productivity impairment at baseline (394 [89.5%] of 440), the

273 proportions of patients who achieved the MCID for improvement in work productivity were

274 numerically greater in the guselkumab treatment groups than in the placebo group at weeks 16

13

275   and 24 (**Figure 2a**). At week 52, the proportions of patients who achieved the MCID for work

276   productivity impairment were relatively similar between the guselkumab treatment groups

277   (66.4% in the guselkumab Q4W group and 76.4% in the guselkumab Q8W group) and the

278   placebo→guselkumab Q4W group (62.9%).

279   Similarly, among patients with nonwork activity impairment ≥20% at baseline (701 [95.0%] of

280   738), the proportions of patients who achieved the MCID for improvement in nonwork activity

281   were significantly (p≤0.002) greater in the guselkumab treatment groups than in the placebo

282   group at weeks 16 and 24 (**Figure 2b**). At week 52, the proportions of patients who achieved the

283   MCID for improvement in nonwork activity were similar between the guselkumab treatment

284   groups (66.1% in the guselkumab Q4W group, 69.2% in the guselkumab Q8W group) and the

285   placebo→guselkumab Q4W group (65.6%).

286   **Change From Baseline in Employment**

287   In a post hoc analysis evaluating change in work status among the 35.6% (263/738) of patients

288   who were unemployed at baseline, the increase in the proportion of patients reporting active

289   employment at week 16 was 13.0% and 12.4% in the guselkumab Q4W and Q8W groups,

290   respectively, compared with 8.1% in the placebo group (**Figure 3a**). At week 52, active

291   employment increased to 25.9% in the guselkumab Q4W group (12.9% difference versus week

292   16; p<0.05) and to 23.1% in the guselkumab Q8W group (10.7% difference versus week 16;

293   p≥0.05). After crossover to guselkumab, active employment among patients in the placebo group

294   increased to 17.1% at week 52 (9.0% difference versus week 16; p≥0.05). Among the 64.4%

295   (475/738) of patients who were employed at baseline, active employment was relatively stable

296   through 1 year (**Figure 3b**).

14

Association of Work Productivity Loss and Nonwork Activity Impairment With Patient Variables and PsA Clinical Features

A total of 738 patients were included in the Spearman, univariate, and multivariate post hoc analyses. At baseline, work productivity loss and nonwork activity impairment scores were moderately to strongly correlated (ie, Spearman correlation coefficient ≥0.4) with multiple clinical features and patient-reported outcomes, including scores for patient-reported pain and measures of physical function, fatigue, and HRQoL (**Figure 4**). In the multivariate analysis, after controlling for all other variables, higher CRP level, greater fatigue (lower FACIT-F score), and greater patient-reported pain (higher score) were associated with greater impairment in all WPAI-PsA domains (**Table 2**). In addition, the presence of enthesitis and a higher (worse) PASI score were associated with greater presenteeism, work productivity loss, and nonwork activity impairment; younger age was associated with greater presenteeism and work productivity loss; female sex and a higher TJC were associated with greater nonwork activity impairment; and the presence of dactylitis was associated with greater presenteeism. Results of the sensitivity analysis that did not include patient-reported pain as a covariate were similar to those presented above, except that dactylitis presence was no longer associated with greater presenteeism, a higher SJC became associated with greater nonwork activity impairment, and a higher TJC became associated with greater presenteeism and work productivity loss in addition to greater nonwork activity impairment (**Supplementary Material Table S1**).

Cost Analyses

Cost analyses suggest that annualized monetized employment-related productivity gains associated with guselkumab treatment of PsA could result in significant indirect and employer-related economic benefits. In all countries evaluated, potential yearly cost savings from improved

320   overall work productivity at week 24 were similar between the 2 guselkumab treatment groups

321   and nearly 2 times greater in guselkumab-treated versus placebo-treated patients (**Figure 5a-c**).

322   At week 52, after placebo crossover to guselkumab Q4W, potential yearly cost savings were

323   generally similar among all treatment groups. In Europe, the United States, and Japan, estimated

324   annual cost savings at week 52 were $10453, $15648, and $8858, respectively, in the

325   guselkumab Q4W group; $11817, $17938, and $10014, respectively, in the Q8W group; and

326    $8181, $12241, and $6933, respectively, in the placebo→guselkumab Q4W group (**Figure 5a-c**).

327   **DISCUSSION**

328   The data presented here demonstrate that, consistent with prior research in this population [1, 2,

329   30], biologic-naïve patients with active PsA had substantial impairment in most WPAI-PsA

330   domains at baseline. Reduction in impairment in these domains was observed 16 weeks after

331   initiation of guselkumab, which was the earliest timepoint assessed. At week 24, improvement in

332   presenteeism, work productivity loss, and daily nonwork activity impairment was significantly

333   greater in guselkumab-treated versus placebo-treated patients. Improvement in presenteeism,

334   work productivity loss, and nonwork activity impairment was maintained at week 52 in

335   guselkumab-treated patients and was similar between guselkumab-treated and

336   placebo→guselkumab Q4W patients at this time point. At week 52, among patients with

337   impairment at baseline, improvement in work productivity and nonwork activity was clinically

338   meaningful in up to 76.4% and 69.2% of patients, respectively, in the guselkumab groups and in

339   62.9% and 65.6% of patients, respectively, in the placebo→guselkumab Q4W group. These

340   results are consistent with those from randomized controlled trials of other biologics in similar

341   populations of patients with PsA [2, 31-36].

16

342 Substantial improvements in the percentage of absenteeism due to PsA were not observed in any

343 of the treatment groups at any time point. This is likely because the percentage of work time

344 missed due to PsA was limited at baseline, which is consistent with what has been previously

345 reported [16, 32, 33]. Absenteeism may be relatively low in patients with PsA compared with

346 presenteeism or impairment in daily activities due to the personal economic consequences of

347 missing work.

348 Although absenteeism remained unchanged throughout the trial, among the 35.6% of patients

349 who were unemployed at baseline, the proportion of patients who shifted to active employment

350 was greater in guselkumab-treated patients versus placebo-treated patients at all time points.

351 There was also a substantial increase in the proportion of patients who reported active

352 employment in the placebo→guselkumab Q4W group from week 16 to week 52, after patients

353 randomized to placebo had been receiving guselkumab treatment for 28 weeks. Among patients

354 who were employed at baseline, the proportion of patients reporting active employment

355 remained relatively stable in all treatment groups.

356 The observed increase in employment among guselkumab-treated patients who were

357 unemployed at baseline demonstrates a potential indirect societal and economic benefit of

358 guselkumab treatment in patients with active PsA. In addition, the reductions in work

359 productivity loss observed in guselkumab-treated patients with PsA were estimated to result in

360 significant indirect and employer-related economic benefits based on cost analyses using 2020

361 mean yearly wages (all occupations) for Europe, the United States, and Japan.

362 To identify the impact that PsA clinical features may have on work productivity loss and

363 nonwork daily activity impairment, we used DISCOVER-2 data to explore the association

364 between WPAI-PsA scores and PsA clinical features and patient demographics. In this

17

365   population of patients with active PsA, we found that both work productivity loss and nonwork

366   activity impairment were associated with higher CRP levels and greater fatigue, pain, skin

367   involvement, and enthesitis. Greater nonwork activity impairment was also associated with

368   female sex and higher TJC. These results are similar to those previously reported in a systematic

369   review of studies in patients with PsA, where unemployment and work productivity loss were

370   found to be associated with longer disease duration, worse physical function, high TJC and/or

371   SJC, low educational level, female sex, erosive disease, and manual work [2]. Younger age was

372   associated with greater presenteeism and work productivity loss; however, the mean (SD) age in

373   this trial was relatively low, 45.7 (11.7) years, and elderly patients are more likely to be retired

374   and not included in the assessment of these domains because they were not employed at baseline.

375   The multivariate MMRM regression models used in these analyses did not evaluate the

376   association between improvement in PsA clinical features and improvement in WPAI-PsA

377   domains or guselkumab treatment effect. To enhance the statistical power of the analyses, cross-

378   sectional, observed data from all time points were pooled across all treatment groups, allowing

379   for a more robust analysis. Future studies may include a mediation analysis to identify

380   relationships between treatment impact on PsA clinical features and treatment impact on WPAI-

381   PsA domains.

382   These data are limited because change from baseline in WPAI-PsA domains was not assessed

383   until week 16 in DISCOVER-2, so it is not known how early a treatment effect could be

384   observed. In previously published analyses from DISCOVER-2, clinically significant

385   improvements in FACIT-F [37, 38] were observed in guselkumab-treated patients as early as

386   week 8, suggesting that improvement in work productivity loss may also have occurred earlier

387   than week 16. In addition, for the analyses of changes in WPAI-PsA domains, we did not require

388   that patients have any minimal amount of impairment at baseline, and as previously noted,

389   61.3% of patients had 0% work time missed due to PsA. This was unlikely to affect the mean

390   improvement in overall work productivity and nonwork activity, however, because only 6.1%

391   and 2.2% of patients, respectively, had 0% impairment in these domains. Furthermore, the

392   overall population in these analyses had a mean of 12.3 swollen and 21.3 tender joints and

393   substantial systemic inflammation (median serum CRP 1.2 mg/dL) at baseline, potentially

394   limiting the generalization of the results of these analyses to patients with less active disease.

395   Selection bias should also be considered when evaluating the generalizability of these results, in

396   that the type of work a patient performs or the number of hours they are required to work can

397   affect their decision to participate in a clinical trial. It is also unknown whether patients who

398   were not working at baseline were not working because of their disease or due to other factors. It

399   is conceivable that there are additional factors contributing to absence of new employment.

400   **CONCLUSIONS**

401   We observed that in biologic-naïve patients with active PsA, treatment with guselkumab, the first

402   IL-23 inhibitor approved for the treatment of adults with PsA, resulted in clinically meaningful

403   improvement in work productivity loss and daily nonwork activity impairment, with

404   improvement observed at week 16 and sustained at week 52. The observed improvements in

405   work productivity loss were estimated to result in substantial yearly indirect work productivity-

406   related cost savings. Multivariate analyses demonstrated that multiple PsA clinical features,

407   including fatigue, physical disability, and skin and joint symptoms, were positively associated

408   with the WPAI-PsA domains, suggesting that improvement in multiple clinical manifestations of

409   PsA are beneficial for the optimization of improvement in work productivity loss and nonwork

410   daily activity impairment.

419   **Authorship**

420   All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria

421   for authorship for this article, take responsibility for the integrity of the work as a whole, and

422   have given their approval for this version to be published.

423   **Author Contributions**

424   Trial conception and design were performed by Jeffrey R. Curtis, Iain B. McInnes, Proton

425   Rahman, Prasheen Agarwal, Alexa P. Kollmeier, Elizabeth C. Hsia, Bei Zhou, Chenglong Han,

426   May Shawi, and Philip J. Mease; data collection and analysis were performed by Feifei Yang,

427   Steve Peterson, and Prasheen Agarwal. All authors critically revised previous drafts of the

428   manuscript content and read and approved the final manuscript.

429   **Disclosures**

430   **Jeffrey R. Curtis** received grant/research support from AbbVie, Amgen, Bristol Myers

431   Squibb, Corrona, Eli Lilly, Janssen, Myriad, Pfizer, Regeneron, Roche, and UCB and

460   **Compliance With Ethics Guidelines**

461   DISCOVER-2 (NCT03158285) conformed with the Declaration of Helsinki and Good Clinical

462   Practice guidelines, and the protocols were approved by local governing ethical bodies at each

463   site (Sterling Institutional Review Board approval number for United States sites is 5910C). All

464   patients provided written informed consent.

465   **Data Availability**

466   The datasets generated and/or analyzed during the current study are available upon reasonable

467   request. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is

468   available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests

469   for access to the trial data can be submitted through Yale Open Data Access (YODA) Project site

470   at http://yoda.yale.edu.

471   **Prior Presentations of Data**

472   Curtis JR, McInnes IB, Rahman P, et al. Clinical characteristics and outcomes associate with

473   work productivity in bio-naïve patients with active psoriatic arthritis through week 24 of

474   DISCOVER-2 study (POS0200). Presented at European Alliance of Associations for

475   Rheumatology (EULAR) 2021, June 2-5, 2021.

476   Curtis JR, McInnes IB, Rahman P, et al. Guselkumab provides sustained improvements in work

477   productivity and non-work activity in patients with psoriatic arthritis: results through 1 year of a

478   phase 3 trial (P0S1026). Presented at European Alliance of Associations for Rheumatology

479   (EULAR) 2021, June 2-5, 2021.

480   Curtis JR, McInnes IB, Rahman P, et al. Guselkumab provides sustained improvements in work

481   productivity and non-work activity in patients with psoriatic arthritis: results through 1 year of a

482   phase 3 trial. Presented at 23rd Asia-Pacific League of Associations for Rheumatology (APLAR)

483   Congress 2021, August 28-31, 2021.

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591

593	**Table 1. Baseline demographics and disease characteristics**

	Guselkumab		Placebo	All
	Q4W N=245	Q8W N=248	N=246	N=739
Age (years)	45.9 (11.5)	44.9 (11.9)	46.3 (11.7)	45.7 (11.7)
Sex				
Male, n (%)	142 (58.0)	129 (52.0)	117 (47.6)	388 (52.5)
Female, n (%)	103 (42.0)	119 (48.0)	129 (52.4)	351 (47.5)
White, n (%)	242 (98.8)	240 (96.8)	242 (98.4)	724 (98.0)
BMI (kg/m^2)	29.1 (5.9)	28.7 (6.3)	29.0 (6.4)	28.9 (6.2)
PsA disease duration (years)	5.5 (5.9)	5.1 (5.5)	5.8 (5.6)	5.5 (5.7)
SJC (0-66)	12.9 (7.8)	11.7 (6.8)	12.3 (6.9)	12.3 (7.2)
TJC (0-68)	22.4 (13.5)	19.8 (11.9)	21.6 (13.1)	21.3 (12.9)
Patient pain VAS (0-10 cm)	6.2 (2.0)	6.3 (2.0)	6.3 (1.8)	6.3 (1.9)
HAQ-DI (0-3)	1.2 (0.6)	1.3 (0.6)	1.3 (0.6)	1.3 (0.6)
CRP level (mg/dL), median	1.2	1.3	1.2	1.2
Enthesitis, n (%)[a]	170 (69.4)	158 (63.7)	178 (72.7)	506 (68.6)
Dactylitis, n (%)[a]	121 (49.4)	111 (44.8)	99 (40.4)	331 (44.9)
PASI (0-72)[a]	10.8 (11.7)	9.7 (11.7)	9.3 (9.8)	9.9 (11.1)
IGA total score ≥2, n (%)[a]	201 (82.0)	195 (78.6)	209 (85.3)	605 (82.0)
EQ-5D-5L Index (0-1)[a]	0.6 (0.1)	0.6 (0.2)	0.6 (0.1)	0.6 (0.1)
EQ-VAS (0-100)[a]	46.9 (20.1)	44.5 (19.8)	42.5 (19.2)	44.6 (19.7)
FACIT-F (0-52)[a]	30.8 (9.6)	29.3 (9.9)	29.1 (9.5)	29.7 (9.7)
SF-36 PCS[a]	33.3 (7.1)	32.6 (7.9)	32.4 (7.0)	32.8 (7.3)
SF-36 MCS[a]	48.4 (11.0)	47.4 (10.8)	47.2 (12.0)	47.7 (11.3)
Employed, n (%)[a]	153 (62.4)	151 (60.9)	171 (69.8)	475 (64.4)
Unemployed, n (%)[a]	92 (37.6)	97 (39.1)	74 (30.2)	263 (35.6)
WPAI-PsA (%)[a]				
n	153	151	171	475
Work time missed (absenteeism)[b]	8.4 (17.4)	10.5 (21.0)	14.5 (27.5)	11.2 (22.7)
No time missed, n (%)	96 (62.8)	92 (60.9)	103 (60.2)	291 (61.3)
n	146	140	154	440
Impairment while working (presenteeism)[b]	46.9 (23.5)	48.8 (24.4)	49.3 (26.2)	48.3 (24.7)
No impairment, n (%)	8 (5.5)	9 (6.4)	11 (7.1)	28 (6.4)
n	146	140	154	440
Overall work productivity impairment (absenteeism+presenteeism)[b]	49.7 (25.0)	51.5 (25.4)	52.9 (27.2)	51.4 (25.9)
≥15% impairment, n (%)	130 (89.0)	126 (90.0)	138 (89.6)	394 (89.5)
No impairment, n (%)	8 (5.5)	9 (6.4)	10 (6.5)	27 (6.1)

n	245	248	245	738
Daily nonwork activity impairment	54.4 (22.0)	56.2 (23.5)	56.0 (23.0)	55.5 (22.8)
≥20% impairment, n (%)	236 (96.3)	234 (94.4)	231 (94.3)	701 (95.0)
No impairment, n (%)	3 (1.2)	7 (2.8)	6 (2.5)	16 (2.2)

594 All data are mean (standard deviation) unless noted otherwise.

595 [a]Placebo N=245, All N=738

596 [b]Limited to patients who were employed at baseline.

597 BMI, body mass index; CRP, C-reactive protein; EQ-5D-5L, EuroQol-5 dimension-5 level; EQ-
598 VAS, EuroQol visual analog scale; FACIT-F, Functional Assessment of Chronic Illness
599 Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; IGA,
600 Investigator's Global Assessment of psoriasis; MCS, mental component summary; PASI,
601 Psoriasis Area and Severity Index; PCS, physical component summary; PsA, psoriatic arthritis;
602 Q4W, every 4 weeks; Q8W, every 8 weeks; SF-36, Short Form 36 health survey; SJC, swollen
603 joint count; TJC, tender joint count; VAS, visual analog scale; WPAI-PsA, Work Productivity
604 and Activity Impairment Questionnaire for Psoriatic Arthritis

605

Table 2. Final multivariate regression mixed models of association of patient variables with WPAI-PsA domains

Parameter	Absenteeism		Presenteeism		Work Productivity Loss		Nonwork Activity Impairment	
	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value
Age	-0.05	0.416	**-0.27**	**<0.001**	**-0.28**	**<0.001**	-0.06	0.170
Female sex	0.91	0.458	-1.54	0.221	-1.74	0.200	**2.38**	**0.016**
CRP level (mg/dL)	**0.73**	**0.041**	**0.97**	**0.006**	**1.01**	**0.007**	**0.89**	**<0.001**
FACIT-F score (0-52)	**-0.31**	**<0.001**	**-0.67**	**<0.001**	**-0.73**	**<0.001**	**-0.75**	**<0.001**
Patient pain VAS (0-10 cm)	**1.03**	**<0.001**	**4.15**	**<0.001**	**4.25**	**<0.001**	**4.02**	**<0.001**
PASI score (0-72)	0.06	0.356	**0.16**	**0.020**	**0.14**	**0.047**	**0.15**	**0.003**
SJC (0-66)	0.08	0.475	-0.05	0.608	-0.05	0.663	0.03	0.750
TJC (0-68)	-0.10	0.129	0.11	0.086	0.09	0.191	**0.10**	**0.036**
Dactylitis (Yes/No)	-1.10	0.392	**2.47**	**0.050[a]**	2.58	0.051	0.54	0.572
Enthesitis (Yes/No)	1.52	0.203	**2.38**	**0.042**	**2.99**	**0.015**	**2.40**	**0.006**

Values in bold are statistically significant at p<0.050. Mixed-effects models for repeated measures analysis was conducted using cross-sectional data from week 0 through week 24 combined and pooled across treatment groups (N=738). Variables were included in the final multivariate model based on association with all WPAI-PsA domains (p<0.10) in univariate analyses and evaluation of collinearity between variables.

[a]p=0.0498

CRP, C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; PASI, Psoriasis Area and Severity Index; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; WPAI-PsA, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis

Figure 1. LS mean change from baseline through week 52 in WPAI-PsA absenteeism (a), presenteeism (b), work productivity loss (c), and nonwork activity impairment (d).

*p<0.05 vs placebo. Least squares (LS) mean changes from baseline were determined using an analysis of covariance model with baseline WPAI-PsA score, prior use of nonbiologic DMARDs (yes/no), and baseline CRP level (<2.0/≥2.0 mg/dL) as explanatory factors. GUS, guselkumab; LS, least squares; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; WPAI-PsA, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis
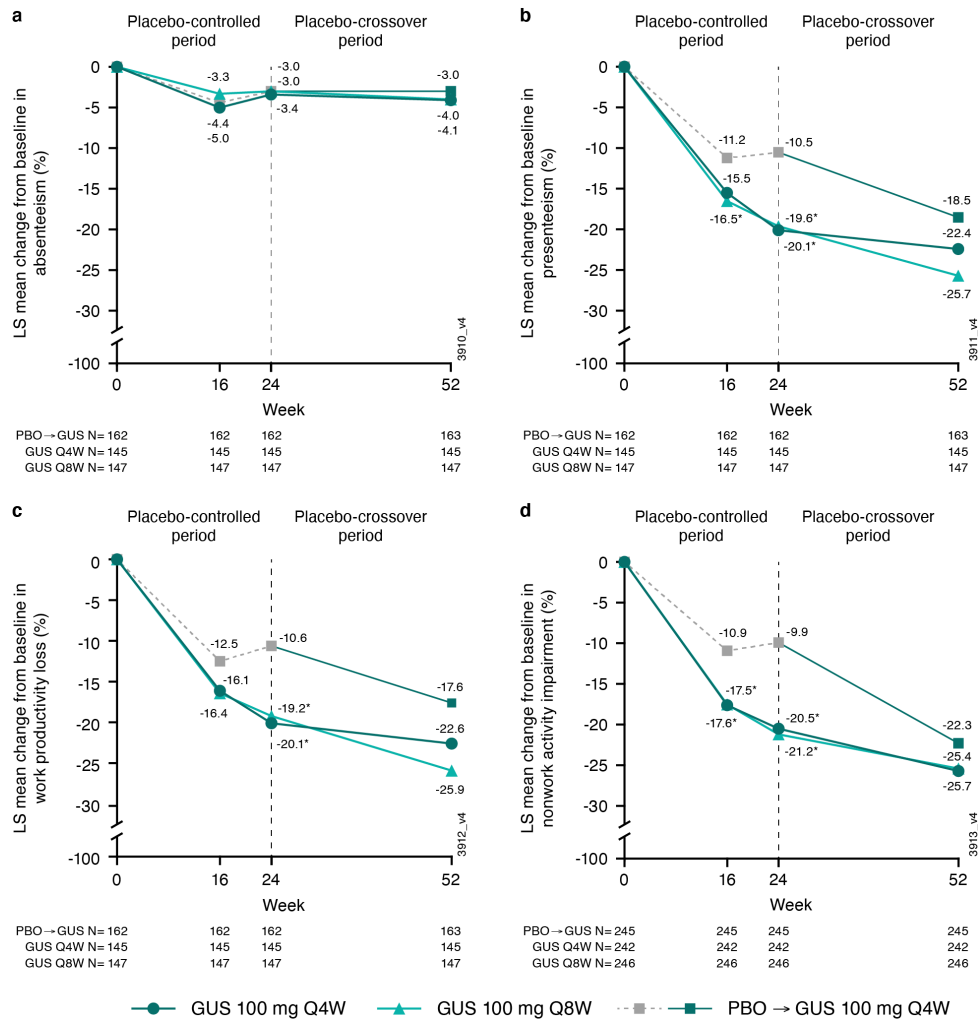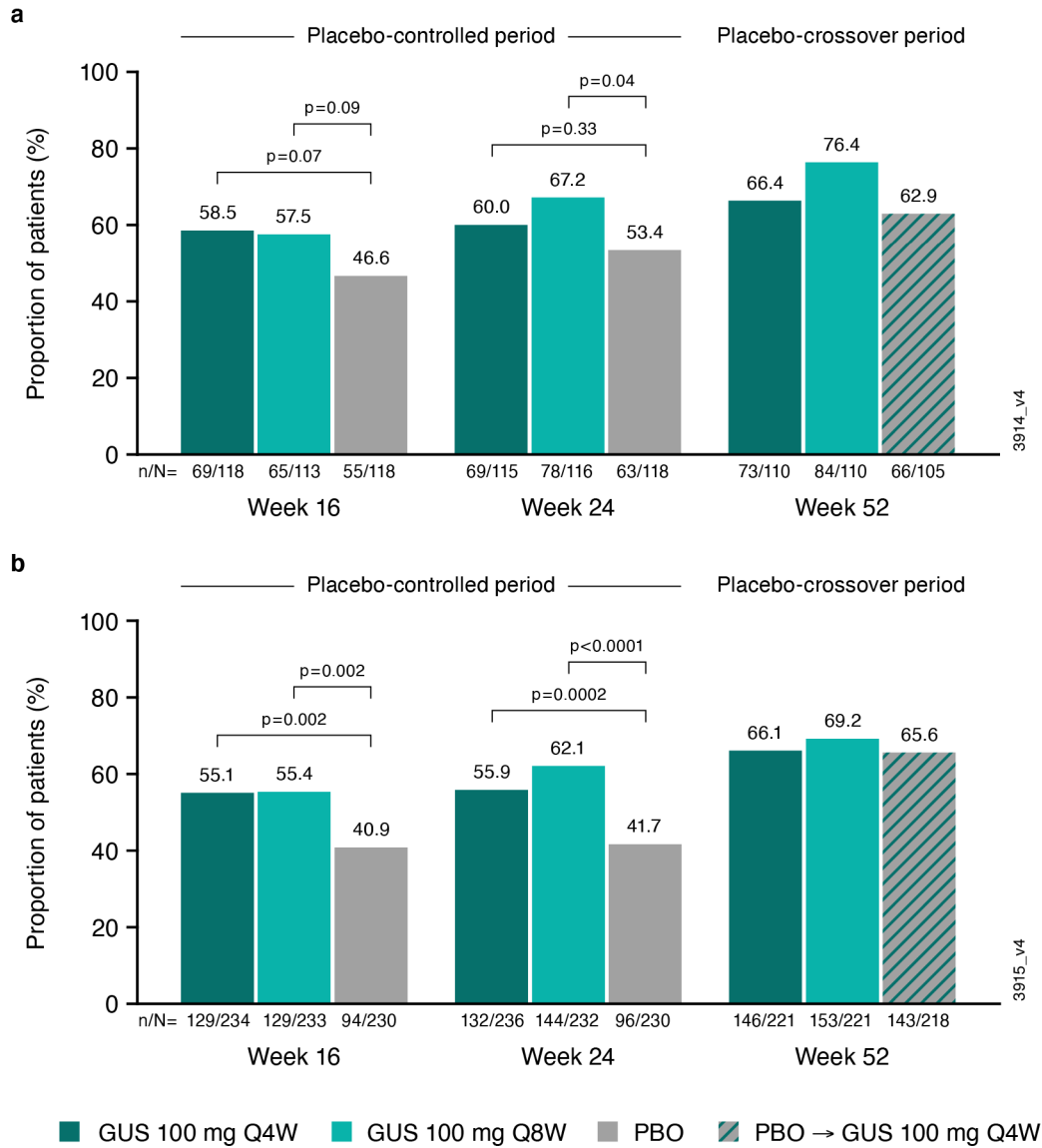
Figure 2. Proportions of patients who achieved improvements in WPAI-PsA work productivity loss ≥15% (a) or nonwork activity impairment ≥20% (b) through week 52.

For panel A, patients with a baseline work productivity impairment ≥15% were included in the analysis. For panel B, patients with a baseline nonwork activity impairment ≥20% were included in the analysis. P-values are versus placebo.

GUS, guselkumab; Q4W, every 4 weeks; Q8W, every 8 weeks; WPAI-PsA, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis
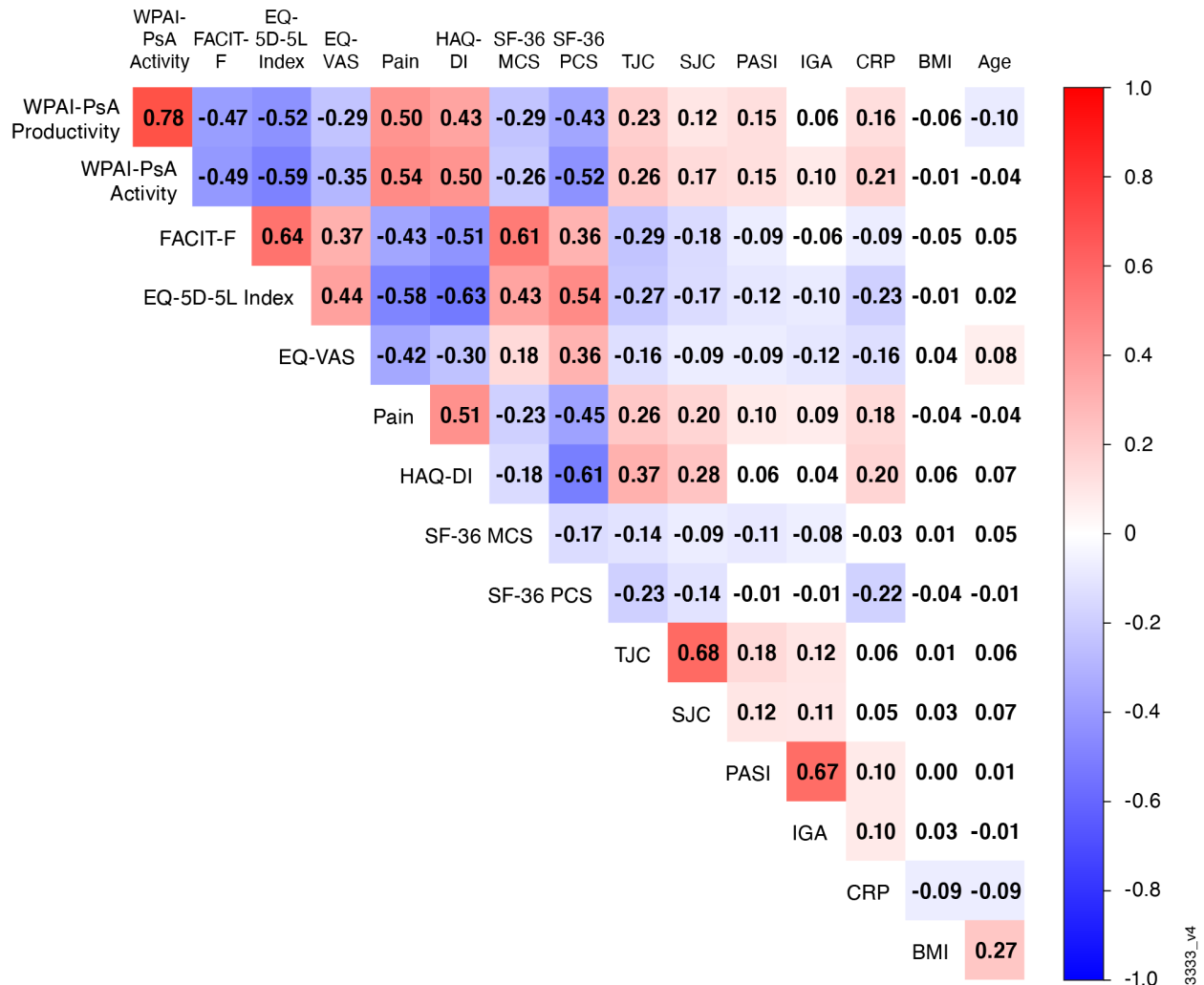
Figure 3. Employment shift analyses among patients who were unemployed (a) and employed (b) at baseline.
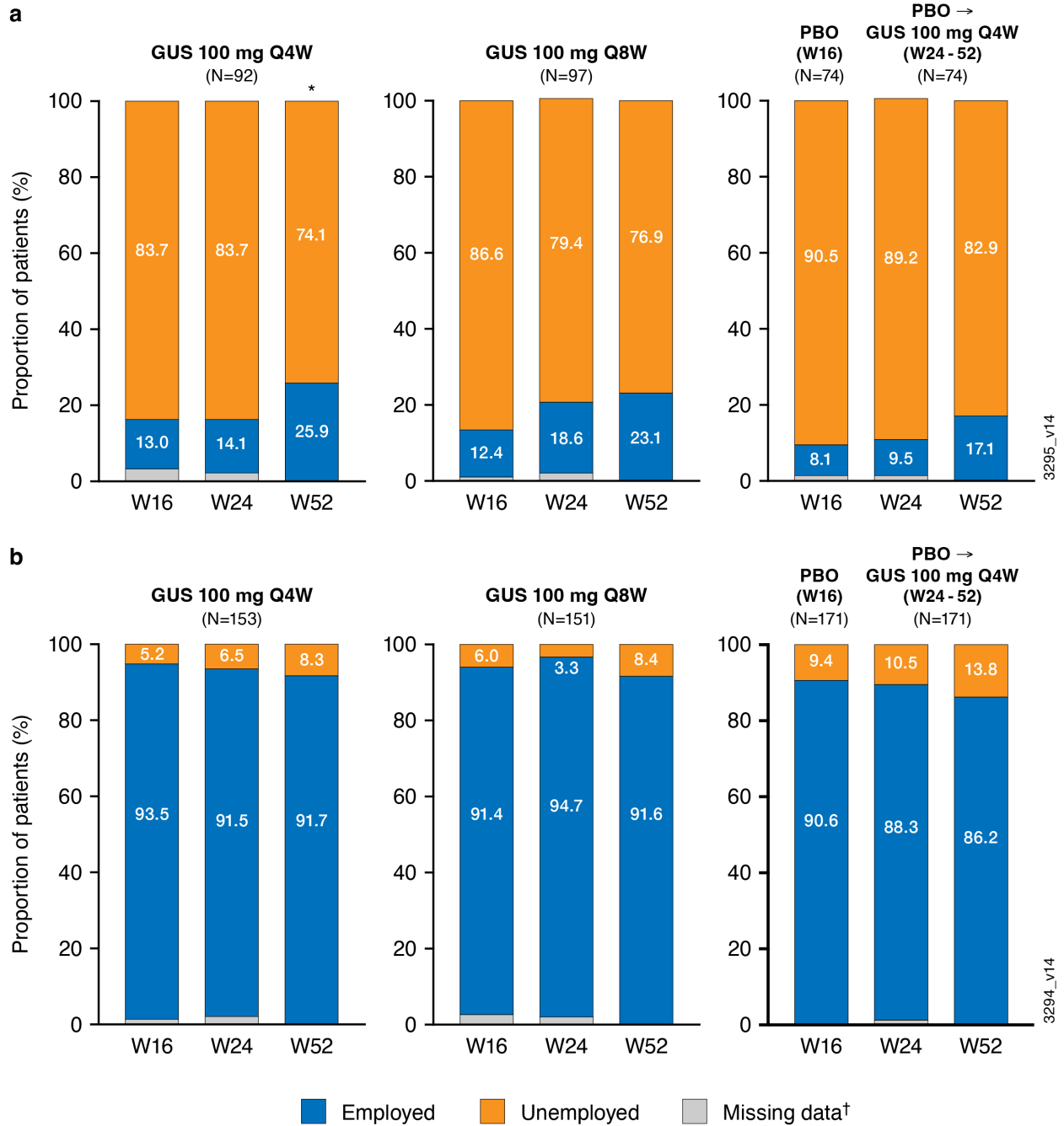
GUS, guselkumab; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; W, week

*p<0.05 versus W16; †Missing values were ≤3.3%.

**Figure 4. Spearman correlation analysis of associations at baseline.**

Analyses were based observed baseline data pooled across treatment groups (N=738).

BMI, body mass index; CRP, C-reactive protein; EQ-5D-5L, EuroQol-5 dimension-5 level; EQ-VAS, EuroQol visual analog scale; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire Disability Index; IGA, Investigator's Global Assessment of psoriasis; MCS, mental component summary; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; SF-36, Short Form 36

health survey; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale;

WPAI, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis

Figure 5. Estimated mean (SEM) indirect cost analysis of potential mean yearly savings due to reduced work productivity loss through week 52 in Europe (a), the United States (b), and Japan (c).

a

b

c
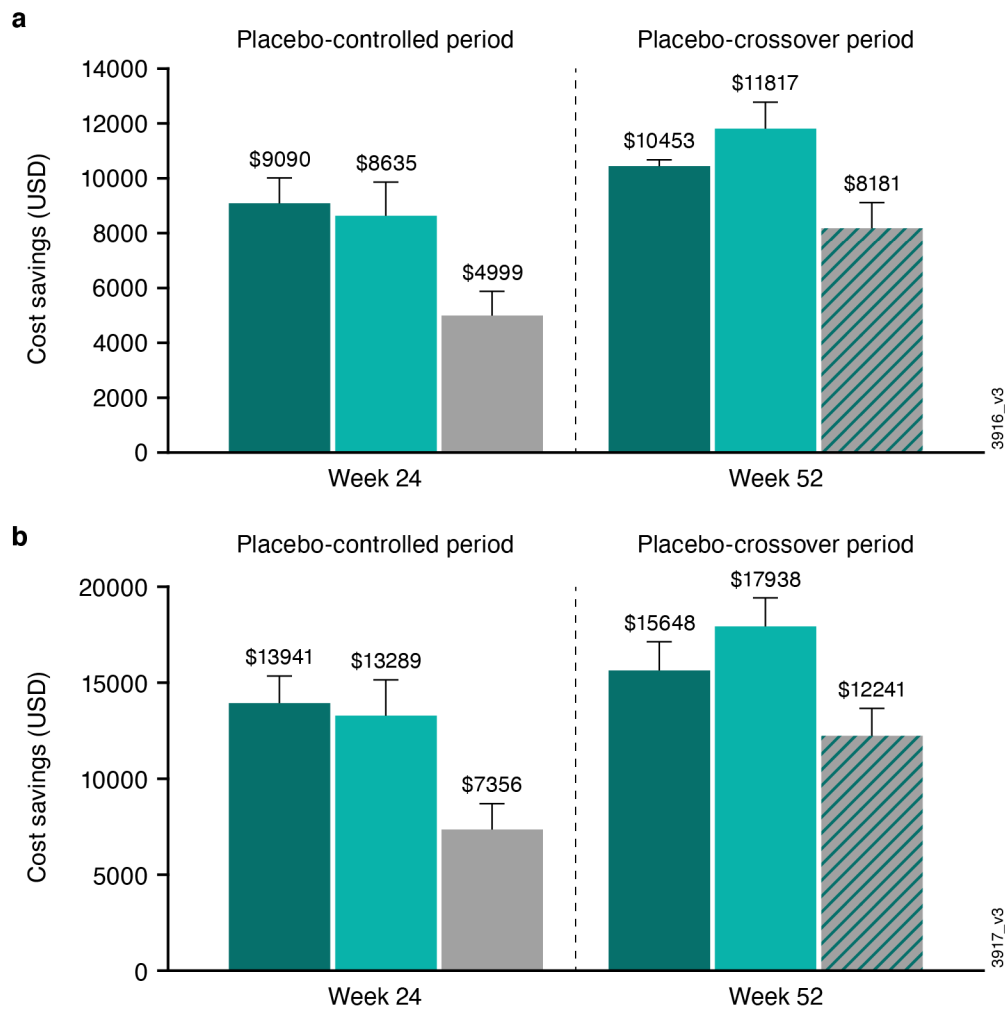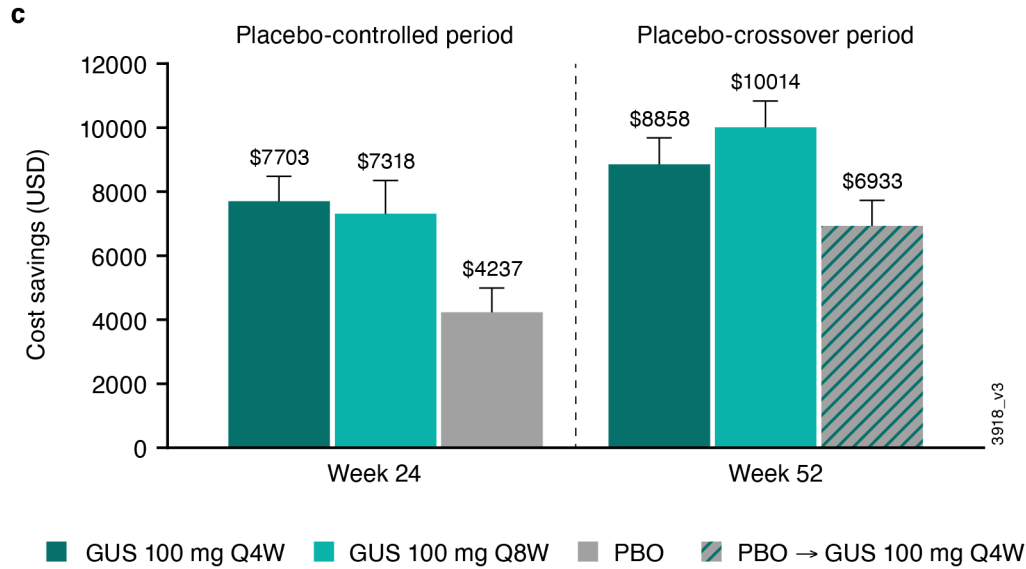
Europe includes France, Germany, Italy, Spain, and the United Kingdom. The average wage indicator for all countries is measured in USD constant prices using 2016 base year and Purchasing Power Parities for private consumption of the same year.

GUS, guselkumab; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; SEM, standard error of the mean; USD, United States dollars

SUPPLEMENTARY MATERIAL

Effect of Guselkumab on Work Productivity in Biologic-Naïve Patients With Active Psoriatic Arthritis Through Week 52 of the Phase 3, Randomized, Placebo-Controlled DISCOVER-2 Trial

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Supplementary Material Table S1. Final multivariate regression mixed models of association of patient variables with WPAI-PsA domains (sensitivity analysis excluding pain).
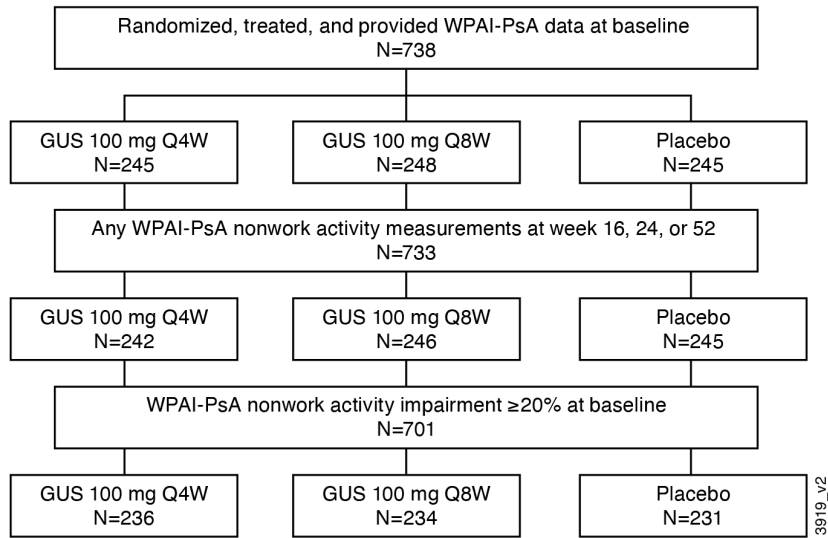
	Absenteeism		Presenteeism		Work Productivity Loss		Nonwork Activity Impairment	
	Estimate	P-value	Estimate	P-value	Estimate	P-value	Estimate	P-value
Age	-0.04	0.460	**-0.26**	**0.0001**	**-0.27**	**0.0001**	-0.05	0.302
Female	1.00	0.421	-1.22	0.388	-1.41	0.350	**2.99**	**0.008**
CRP level (mg/dL)	**0.92**	**0.010**	**1.73**	**<0.001**	**1.80**	**<0.001**	**1.34**	**<0.001**
FACIT-F (0-52)	**-0.42**	**<0.001**	**-1.11**	**<0.001**	**-1.19**	**<0.001**	**-1.15**	**<0.001**
PASI (0-72)	0.09	0.219	**0.25**	**0.001**	**0.24**	**0.003**	**0.26**	**<0.001**
SJC (0-66)	0.10	0.334	0.08	0.480	0.09	0.468	0.18	0.041
TJC (0-68)	-0.07	0.307	**0.24**	**0.001**	**0.23**	**0.002**	**0.21**	**0.0001**
Dactylitis (Yes/No)	-1.10	0.395	2.11	0.124	2.21	0.123	0.88	0.401
Enthesitis (Yes/No)	1.61	0.180	**2.74**	**0.031**	**3.39**	**0.010**	**3.07**	**0.001**

Values in bold are statistically significant at p<0.050. Mixed-effects models for repeated measures analysis of cross-sectional data from week 0 through week 24 combined and pooled across treatment groups (N=738). Variables were included in the final multivariate model based on association with all WPAI-PsA domains (p<0.10) in univariate analyses and evaluation of collinearity between variables.

CRP, C-reactive protein; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; SJC, swollen joint count; TJC, tender joint count; WPAI-PsA, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis
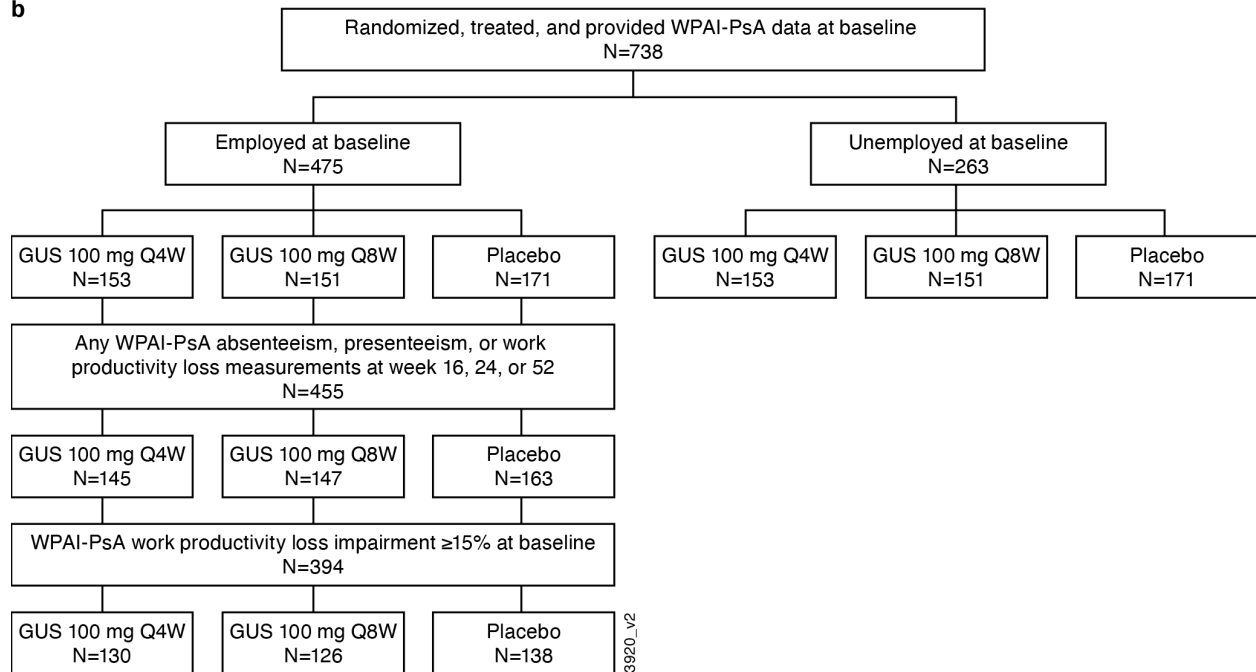
Supplementary Material Figure S1. Patient disposition for the overall population (a) and by baseline employment status (b).

a

b

GUS, guselkumab; Q4W, every 4 weeks; Q8W, every 8 weeks; WPAI-PsA, Work Productivity and Activity Impairment Questionnaire for Psoriatic Arthritis