Early Fatigue Improvement With Guselkumab Associates With Longer Term Disease Control in Patients With Active Psoriatic Arthritis Reporting Substantial Fatigue: Post Hoc Analyses of a Sub-Population of a Phase 3, Randomized, Controlled Trial of Guselkumab in Biologic-Naïve Patients

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Background

- Psoriatic arthritis (PsA) is a chronic inflammatory disease with diverse manifestations often leading to substantial impairments in health-related quality of life, including moderate-to-severe fatigue occurring in up to half of patients (pts) with PsA[1]
- In the Phase 3 DISCOVER-2 study, the fully human IL-23p19-subunit inhibitor guselkumab (GUS) demonstrated efficacy in reducing the signs and symptoms of PsA across disease domains compared with placebo (PBO)[2]
- GUS has also demonstrated clinically meaningful and sustained fatigue improvements through 1 year (y), with GUS exhibiting a substantial direct effect on fatigue as early as Week (W) 8, independent of its impact on other clinical outcomes[3,4]
- We previously showed that early fatigue response in DISCOVER-2 predicted clinically meaningful and durable improvements, defined by ≥4-point improvement, in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score at 2y[5]

Objective

- **To further understand the relationship between early fatigue improvement and later achievement of measures of disease control at 1y, we performed a post hoc analysis utilizing a sub-population of DISCOVER-2 participants with active PsA and abnormal fatigue at baseline (BL)**

Methods

Phase 3 DISCOVER-2[a] (W0-W112)[6]

Randomized 1:1:1
(N=739 treated: 493 GUS + 246 PBO)

GUS 100 mg at W0, W4, then Q4W
GUS 100 mg at W0, W4, Q8W
PBO Q4W through W20; GUS 100 mg at W24, then Q4W

History of, or current, psoriasis
≥5 SJC and ≥5 TJC
CRP ≥0.6 mg/dL

Naïve to biologic agents and JAK inhibitors

[a]Data through W52 employed in these pooled analyses. CRP=C-reactive protein; GUS=Guselkumab; JAK=Janus kinase; PBO=Placebo; Q4W=Every 4 weeks; Q8W=Every 8 weeks; SJC=Swollen joint count; TJC=Tender joint count; W=Week.

Assessments and Statistical Methods

- FACIT-Fatigue instrument:
  - 13-item, pt reported, validated measure of fatigue and its impact on daily activities and function[7]
  - Score range: 0-52 (higher score = less fatigue)
  - Normative FACIT-Fatigue score: >43[8]
  - CMI: ≥4-point increase[9]
- GUS-randomized (Q4W+Q8W combined) bionaïve PsA pts with BL fatigue score below the normative level (i.e., more fatigue; score ≤43[8]) were assessed
- ROC analyses utilized Youden's index to determine optimal FACIT-Fatigue cutoffs at W8 (1st post-BL timepoint assessed) for predicting achievement of measures of disease control at 1y
  - The association of identified and established FACIT-Fatigue cutoffs (≥4-point improvement & score >43) with response at 1y was assessed via BL-adjusted logistic regression

BL=Baseline; CMI=Clinically meaningful improvement; FACIT=Functional Assessment of Chronic Illness Therapy; GUS=Guselkumab; PsA=Psoriatic arthritis; Pt=Patient; Q4W=Every 4 weeks; Q8W=Every 8 weeks; ROC=Receiver operating characteristic; W=Week; Y=Year.

Clinical Outcomes at 1y

Measure	Definition
ACR50/70	Improvement ≥50%/70%
DAPSA LDA	DAPSA ≤14
cDAPSA LDA	cDAPSA ≤13
PASDAS LDA	PASDAS ≤3.2
HAQ-DI response	Improvement ≥0.35[a]
Normalized HAQ-DI	HAQ-DI ≤0.5[b]
MDA[10]	5 of 7 criteria met[c]

[a]In pts with baseline HAQ-DI ≥0.35. [b]In pts with baseline HAQ-DI >0.5. [c]Achievement of MDA is defined as meeting 5 of 7 criteria: TJC ≤1; SJC ≤1; Psoriasis Area and Severity Index ≤1; pt pain VAS of ≤15; Pt Global Assessment (arthritis and psoriasis) VAS of ≤20; HAQ-DI score ≤0.5; and tender entheseal points ≤1; ACR50/70, ≥50%-70% improvement in ACR criteria. ACR=American College of Rheumatology; cDAPSA=Clinical Disease Activity in Psoriatic Arthritis; DAPSA=Disease Activity in Psoriatic Arthritis; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; MDA=Minimal disease activity; PASDAS=Psoriatic Arthritis Disease Activity Score; VAS=Visual analog scale.

Key Takeaways

- **In a subpopulation of DISCOVER-2 pts with active PsA and abnormal fatigue levels at BL:**
  - **On average, pts reported clinically significant fatigue[11] at BL**
  - **Among GUS-randomized pts, achievement of FACIT-Fatigue endpoints at the first timepoint assessed (W8) was associated with significantly greater likelihood of achieving disease control at 1y across disease domains, including:**
    - **Low levels of joint disease activity (ACR50/70, DAPSA LDA)**
    - **Improved/normalized physical function (HAQ-DI)**
    - **Low levels of overall disease activity (MDA, PASDAS LDA)**
- **Of note, regardless of the FACIT-Fatigue endpoint assessed, nonresponse at W8 did not preclude achievement of disease control with 1y of GUS**
- **These results underscore the importance of early improvement in pt-reported outcomes, such as fatigue, on the trajectory of long-term pt outcomes, including achieving stringent thresholds of response**

Results

Among the >90% of DISCOVER-2 bionaïve PsA pts with BL FACIT-Fatigue score ≤43, the mean (SD) score of 28.3 (8.7) indicated clinically significant fatigue[11] at BL

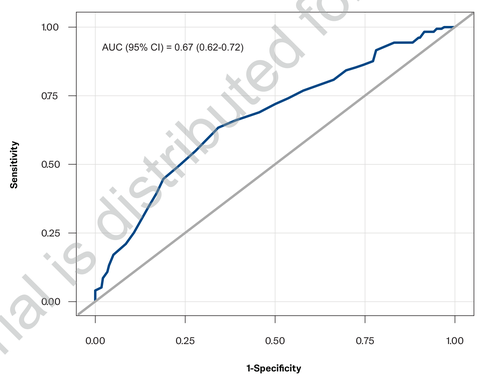
BL characteristics by FACIT-Fatigue levels	FACIT-Fatigue ≤43 (N=681)	FACIT-Fatigue >43 (N=57)
Age, years	45.6 (11.7)	46.3 (11.4)
Male, n (%)	350 (51.4)	38 (66.7)
White, n (%)	669 (98.2)	54 (94.7)
Body Mass Index, kg/m^2	29.0 (6.3)	28.4 (4.7)
PsA duration, years	5.5 (5.8)	4.6 (4.8)
CRP, mg/dL	2.0 (2.4)	1.7 (2.8)
SJC [0-66]	12.4 (7.2)	11.2 (7.1)
TJC [0-68]	21.8 (13.0)	15.2 (10.2)
Leeds Enthesitis Index [1-6]*	2.0 (1.9)	1.4 (1.6)
Physicians Global Assessment [VAS 0-100 mm]	66.7 (15.2)	58.8 (16.8)
DAPSA	49.1 (19.9)	37.7 (18.4)
cDAPSA [0-154]	47.1 (19.6)	36.0 (18.2)
PASDAS [0-10]	6.7 (1.0)	5.8 (1.1)
% Body Surface Area [0-100]	17.7 (20.6)	14.6 (17.6)
Psoriasis Area and Severity Index [0-72]	10.0 (11.1)	9.2 (11.1)
Pt Pain [VAS 0-100 mm]	63.7 (18.2)	47.0 (22.6)
Pt Global Assessment [VAS 0-100 mm]	68.8 (18.7)	54.3 (21.8)
FACIT-Fatigue [0-52]	28.3 (8.7)	46.6 (2.1)
HAQ-DI [0-3]	1.3 (0.6)	0.7 (0.6)
csDMARDs, n (%)	473 (69.5)	38 (66.7)
Methotrexate, n (%)	411 (60.4)	31 (54.4)

*Data are mean (SD) unless otherwise specified. *Assessed in pts with score >0 at BL. BL=Baseline; cDAPSA=Clinical Disease Activity in Psoriatic Arthritis; CRP=C-reactive protein; csDMARDs=Conventional synthetic disease-modifying anti-rheumatic drugs; DAPSA=Disease Activity in Psoriatic Arthritis; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; PASDAS=Psoriatic Arthritis Disease Activity Score; PsA=Psoriatic arthritis; Pt=Patient; SD=Standard deviation; SJC=Swollen joint count; TJC=Tender joint count; VAS=Visual analog scale.*

Among optimal FACIT-Fatigue cutoffs at W8 for predicting 1y disease control with GUS, a FACIT-Fatigue cutoff ≥37 was selected for further analyses

- A FACIT-Fatigue cutoff ≥37 was the lowest score (most fatigue) with a significantly higher probability of achievement with GUS vs PBO (32% vs 24%; p=0.0445)
- Optimal FACIT-Fatigue cutoff scores for outcome prediction were ≥36 (ACR20, ACR50, DAPSA LDA, HAQ-DI ≤0.5, PASDAS LDA, cDAPSA LDA), ≥37 (ACR70), ≥40 (MDA), and ≥41 (HAQ-DI response)

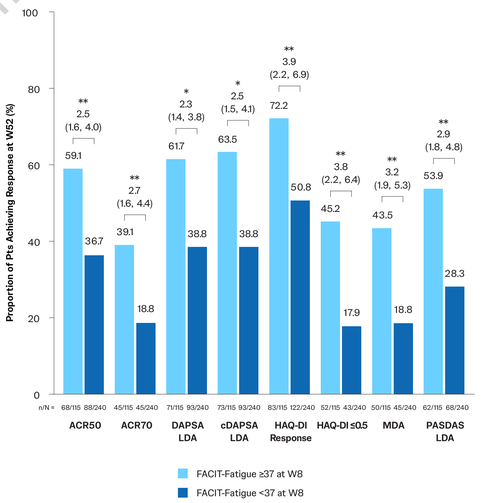
Representative ROC Analysis of Optimal FACIT-Fatigue Cutoff at W8 Associated With PASDAS LDA at W52



AUC=Area under the curve; CI=Confidence interval; FACIT=Functional Assessment of Chronic Illness Therapy; LDA=Low disease activity; PASDAS=Psoriatic Arthritis Disease Activity Score; ROC=Receiver operating characteristic; W=Week.

Among pts with BL FACIT-Fatigue <37, achievement of a FACIT-Fatigue score ≥37 at W8 of GUS was associated with significantly higher odds of achieving disease control at 1y

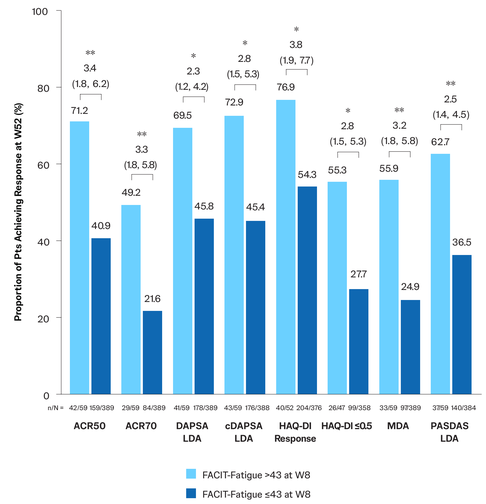
Clinical Response at W52 by Achievement of FACIT-Fatigue Score <37 or ≥37 at W8



**p≤0.05, **p≤0.0001. Data presented are % and OR (95% CI). ACR50=American College of Rheumatology ≥50% improvement; ACR70=American College of Rheumatology ≥70% improvement; cDAPSA=Clinical Disease Activity in Psoriatic Arthritis; CI=Confidence interval; DAPSA=Disease Activity in Psoriatic Arthritis; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; MDA=Minimal disease activity; OR=Odds ratio; PASDAS=Psoriatic Arthritis Disease Activity Score; Pts=Patients; W=Week.*

Among pts with abnormal levels of fatigue at BL, achievement of normative FACIT-Fatigue levels at W8 of GUS was associated with significantly higher likelihood of achieving disease control at 1y

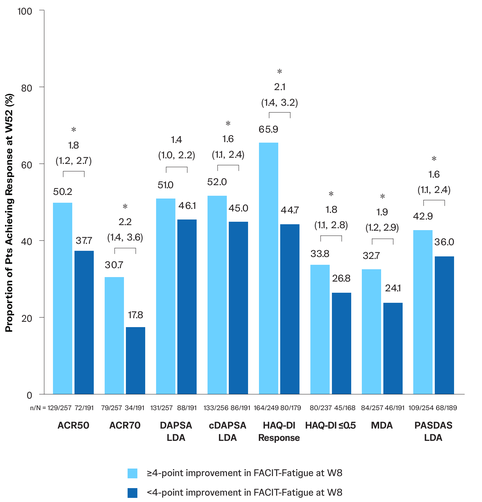
Clinical Response at W52 by Achievement of FACIT-Fatigue Score ≤43 or >43 at W8



**p≤0.05, **p≤0.0001. Data presented are % and OR (95% CI). ACR50=American College of Rheumatology ≥50% improvement; ACR70=American College of Rheumatology ≥70% improvement; cDAPSA=Clinical Disease Activity in Psoriatic Arthritis; CI=Confidence interval; DAPSA=Disease Activity in Psoriatic Arthritis; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; MDA=Minimal disease activity; OR=Odds ratio; PASDAS=Psoriatic Arthritis Disease Activity Score; Pts=Patients; W=Week.*

Among pts with abnormal levels of fatigue at BL, achievement of FACIT-Fatigue CMI at W8 of GUS was associated with significantly higher likelihood of achieving disease control at 1y

Clinical Response at W52 by Achievement of FACIT-Fatigue CMI (≥4-point improvement) at W8



**p≤0.05. Data presented are % and OR (95% CI). ACR50=American College of Rheumatology ≥50% improvement; ACR70=American College of Rheumatology ≥70% improvement; cDAPSA=Clinical Disease Activity in Psoriatic Arthritis; CI=Confidence interval; CMI=Clinically meaningful improvement; DAPSA=Disease Activity in Psoriatic Arthritis; HAQ-DI=Health Assessment Questionnaire-Disability Index; LDA=Low disease activity; MDA=Minimal disease activity; OR=Odds ratio; PASDAS=Psoriatic Arthritis Disease Activity Score; Pts=Patients; W=Week.*

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