Guselkumab Demonstrated an Independent Treatment Effect on Fatigue after Adjustment for Clinical Response (ACR 20) in Patients with Psoriatic Arthritis: Results from Phase-3 Trials DISCOVER 1 & 2

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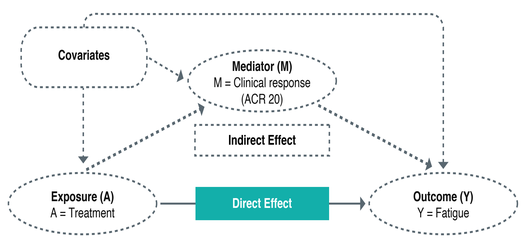
BACKGROUND

- DISCOVER 1 (NCT03796858) and DISCOVER 2 (NCT03158285) are phase-3, randomized, placebo-controlled trials of guselkumab (GUS, an antibody against the p19 subunit of IL-23) in moderate to severe psoriatic arthritis (PsA)[1,2]
  - o Both trials met their primary endpoints of a significantly greater proportion of patients achieving an American College of Rheumatology 20% Improvement (ACR 20) with GUS vs placebo (PBO) at 24 Weeks
  - o GUS-treated patients also achieved significantly greater improvements than PBO patients at Week 24 in the following measures:
    - – Psoriasis Area and Severity Index (PASI) 75 measure of psoriasis
    - – Health Assessment Questionnaire-Disability Index (HAQ-DI) assessment of physical function
    - – 36-Item Short Form Survey (SF-36) assessment of physical components of health-related quality of life
  - o Follow-up through 1 year showed that efficacy improvements were maintained
  - o GUS was well tolerated among patients with moderate to severe PsA after both 24 weeks and 1 year of treatment
- Fatigue is a burdensome symptom among patients with PsA and is recommended as part of the evaluation of treatment effects in randomized controlled trials for PsA[3]
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue is a composite, patient reported outcome measure of fatigue with good content validity, known groups validity, internal consistency, and test-rest reliability in patients with PsA[4]
- Mediation analysis[5] can distinguish between a direct causal effect (eg, direct effect of GUS treatment on an outcome measure such as fatigue) and an indirect effect, influenced by an intermediate factor (eg, GUS treatment leads to improvements in signs and symptoms of arthritis, which lead to improvements in fatigue) (Figure 1)

Figure 1. Causal Diagram of Mediation Analysis



Direct effect = Independent treatment effect on the outcome that is above and beyond its effect on the mediator (ACR 20)

Indirect effect = Treatment effect on the outcome that is mediated (explained) by its effect on the mediator (ACR 20)

ACR 20, American College of Rheumatology 20% improvement criteria

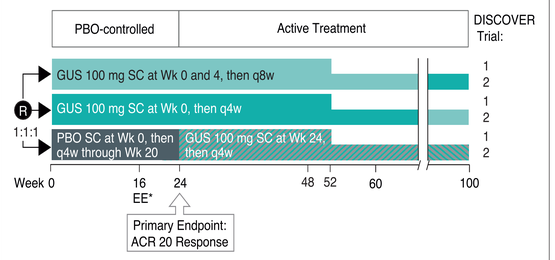
OBJECTIVES

- To evaluate the effect of GUS on fatigue in the DISCOVER 1 & 2 trials using the patient-reported outcome FACIT-Fatigue
- To estimate what proportion of the FACIT-Fatigue response is independent of the ACR 20 efficacy response

METHODS

- DISCOVER 1 & 2 study designs are described in Figure 2 and Table 1

Figure 2. DISCOVER 1 and DISCOVER 2 Study Designs



*EE = early escape; patients were eligible to initiate/increase background medications if <5% improvement from baseline in both tender/swollen joint counts at Week 16.

ACR 20, American College of Rheumatology 20% improvement criteria; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks; R, randomization; SC, subcutaneous; Wk, week.

Table 1. Study Design

	DISCOVER 1	DISCOVER 2
Study Design	• Randomized, double-blind, PBO-controlled, phase-3 trials	
Inclusion Criteria	• Moderate to severe PsA for ≥6 months and fulfillment of CASPAR • Inadequate response to, or intolerance of, standard treatment	
	• ≥3 swollen and ≥3 tender joints • CRP ≥0.3 mg/dL • ~30% of enrolled patients previously treated with 1-2 TNF inhibitors	• ≥5 swollen and ≥5 tender joints • CRP ≥0.6 mg/dL • Biologic naïve
Treatment for 24 weeks	• Randomization (1:1:1) to: – GUS 100 mg SC,q8w – GUS 100 mg SC,q4w – PBO	

CASPAR, Classification Criteria for Psoriatic Arthritis[6]; CRP, C-reactive protein; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor

Statistical methods:

- Analysis of changes from baseline in FACIT-Fatigue scores used Mixed Effect Model Related Measures (MMRM), with factors including treatment group, baseline use of non-biologic disease-modifying antirheumatic drugs, C-reactive protein (CRP) status (>2.0 or ≤2.0 mg/dL), and for DISCOVER 1 only, prior use of tumor necrosis factor inhibitors
- Mediation analysis[5] used linear regression and logistics regression models with bootstrap method

RESULTS

Baseline characteristics:

- Characteristics at baseline (Table 2) were similar across treatment groups and trials, except for the following:
  - o Patients in the DISCOVER 2 trial had higher CRP and slightly greater numbers of swollen/tender joints (by design, see Methods), as well as somewhat greater PASI scores
- FACIT-Fatigue scores did not differ meaningfully between groups or between studies

Table 2. Baseline Characteristics

	DISCOVER1			DISCOVER2		
	GUS q8w (n=127)	GUS q4w (n=128)	PBO (n=126)	GUS q8w (n=248)	GUS q4w (n=245)	PBO (n=246)
Age, years	49 (12)	47 (12)	49 (11)	45 (12)	46 (12)	46 (12)
Male gender, n (%)	68 (54%)	66 (52%)	61 (48%)	129 (52%)	142 (58%)	117 (48%)
BMI, mean kg/m^2	29.9 (6.4)	29.9 (5.5)	29.6 (5.7)	28.7 (6.3)	29.1 (5.9)	29.0 (6.4)
PsA disease duration, years	6.4 (5.9)	6.6 (6.3)	7.2 (7.6)	5·1 (5·5)	5·5 (5·9)	5·8 (5·6)
Number of swollen joints (0-66)	10.9 (9.3)	8.6 (5.8)	10.1 (7.1)	11.7 (6.8)	12.9 (7.8)	12.3 (6.9)
Number of tender joints (0-68)	20.2 (14.5)	17.7 (13.1)	19.8 (14.4)	19.8 (11.9)	22.4 (13.5)	21.6 (13.1)
CRP, median mg/dL (IQR)	0.7 (0.4-1.9)	0.6 (0.3-1.3)	0.8 (0.3-1.5)	1.3 (0.7-2.5)	1.2 (0.6-2.3)	1.2 (0.5-2.6)
PASI Score (0-72)	8.4 (9.8)	9.5 (10.1)	7.7 (8.9)	9.7 (11.7)	10.8 (11.7)	9.3 (9.8)
HAQ-DI	1.2 (0.6)	1.1 (0.7)	1.2 (0.7)	1.3 (0.6)	1.2 (0.6)	1.3 (0.6)
SF-36 PCS	34.1 (7.6)	35.9 (8.3)	33.8 (8.5)	32.6 (7.9)	33.3 (7.1)	32.4 (7.0)
MCS	47.0 (11.1)	46.5 (9.8)	48.7 (9.6)	47.4 (10.8)	48.4 (11.0)	47.2 (12.0)
FACIT-Fatigue	29.5 (11.3)	31.4 (10.1)	30.2 (9.9)	29.3 (9.9)	30.8 (9.6)	29.1 (9.5)

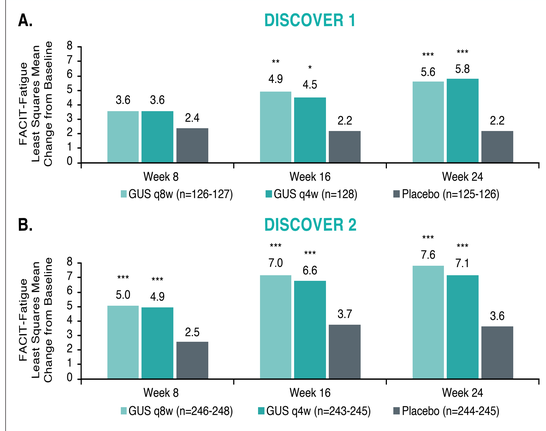
Data are mean (SD) unless otherwise indicated.

BMI, body mass index; CRP, C-reactive protein; FACIT, Functional Assessment of Chronic Illness Therapy; GUS, guselkumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsA, psoriatic arthritis; q4w, every 4 weeks; q8w, every 8 weeks; SF-36 PCS/MCS, 36-item Short-Form physical/mental component summary

Changes from baseline in FACIT-Fatigue:

- Increases from baseline (improvement) in FACIT-Fatigue were greater after treatment with GUS compared with PBO, with both doses of GUS and in both DISCOVER trials (Figure 3)
- Clinically meaningful improvement in FACIT-Fatigue score (≥4 points[4]) was significantly greater after treatment with GUS than PBO, with both doses of GUS and in both DISCOVER trials (Figure 4)
- Improvements were seen as early as Week 16 in DISCOVER 1 and Week 8 in DISCOVER 2

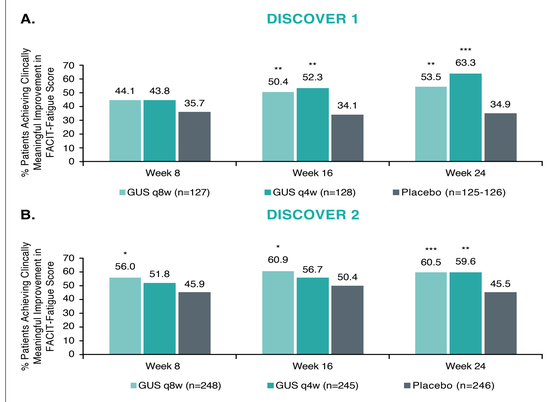
Figure 3. Changes from Baseline in FACIT-Fatigue at Week 24



Unadjusted P values: *P vs placebo <0.05; **P vs placebo <0.01; ***P vs placebo <0.001

FACIT, Functional Assessment of Chronic Illness Therapy; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

Figure 4. Clinically Meaningful Improvement in FACIT-Fatigue Score (≥4 point change in score) at Week 24



Unadjusted P values: *P vs placebo <0.05; **P vs placebo <0.01; ***P vs placebo <0.001

FACIT, Functional Assessment of Chronic Illness Therapy; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

- Mediation analysis of changes from baseline in FACIT-Fatigue in DISCOVER 1 and DISCOVER 2:
  - o The mediation analysis showed that of the total treatment effect on fatigue, 11.7-36.3% in GUS 100 mg q8w, and 68.5-69.7% in GUS 100 mg q4w group were direct effects, indicating additional patient benefit beyond the ACR clinical response

Table 3. Mediation Analysis of the Effect of ACR Response on Change from Baseline in FACIT-Fatigue Score after 24 Weeks of Treatment with Guselkumab

		Mediation Analysis	
	Effect	GUS 100 mg q8w vs. PBO (95% CI)	GUS 100 mg q4w vs. PBO (95% CI)
DISCOVER 1	Total effect	3.1 (1.0, 5.2) (p<0.02)	3.8 (2.0, 5.4) (p<0.02)
	% Direct effect	11.7%	68.5%
	% Indirect effect mediated by ACR 20	88.3%	31.5%
DISCOVER 2	Total Effect	4.0 (2.4, 5.5) (p<0.02)	3.6 (2.1, 5.0) (p<0.02)
	% Direct effect	36.3%	69.7%
	% Indirect effect mediated by ACR 20	63.7%	30.3%

ACR, American College of Rheumatology; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

CONCLUSIONS

- In two phase-3 trials, 24-week treatment with GUS of patients with active PsA led to clinically significant improvements compared to PBO in fatigue
- Mediation analysis revealed substantial effects of GUS on FACIT-Fatigue that were independent of its effects on ACR 20, especially for the q4w dosing group

References

1. Deodhar et al. *Lancet*. 2020;395:1115-1125; **2.** Mease et al. *Lancet*. 2020;395:1126-1136; **3.** Orbai et al. *Ann Rheum Dis*. 2017;76:673-680; **4.** Cella et al. *J Patient Rep Outcomes*. 2019;3:30; **5.** Valeri et al. *Psychologic Meth*. 2013;18:137-150; **6.** Taylor W et al. *Arthritis Rheum*. 2006;54:2665-2673.

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