Integrated Safety Results of Two Phase-3 Trials of Guselkumab in Patients with Psoriatic Arthritis, Through the Placebo-Controlled Periods

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BACKGROUND

- Guselkumab (GUS) is a fully human monoclonal antibody that specifically binds the p19 subunit of interleukin (IL)-23 and reduces IL-23 activity
- IL-23 is implicated in the pathogenesis of psoriasis and psoriatic arthritis (PsA)[1]
- At Week 24, in two phase-3, randomized, placebo (PBO)-controlled trials of patients with PsA (DISCOVER 1[2] and DISCOVER 2[3]), subcutaneous (SC) GUS 100 mg every 4 or 8 weeks (q4w or q8w) demonstrated significant improvement vs PBO in measures of:
  - o Joint and skin symptoms
  - o Radiographic progression (q4w only)
  - o Physical function
  - o Quality of life
- Continuing GUS treatment showed maintenance of these improvements through Week 52

OBJECTIVE

- To assess the safety of GUS 100 mg SC q8w and q4w in treatment of moderate to severe PsA, using 24-week, integrated safety results from the two phase-3, randomized, controlled DISCOVER trials

METHODS

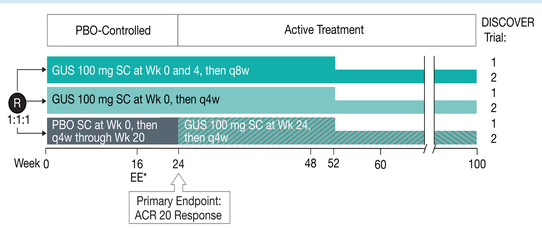
- DISCOVER 1 and 2 study designs are described in Table 1 and Figure 1

Table 1. Study Design

	DISCOVER 1	DISCOVER 2
Study Design	• Randomized, double-blind, PBO-controlled, phase-3 trials	
Study Population	• 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 • N=381	• ≥5 swollen and ≥5 tender joints • CRP ≥0.6 mg/dL • Biologic naïve • N=739
Treatment Groups	• Randomized 1:1:1 to the following treatment groups: – GUS 100 mg SC,q8w – GUS 100 mg SC,q4w – PBO, cross-over to GUS q4W	
Treatment Duration*	52 weeks	100 weeks

*Last dose for DISCOVER 1 was Week 48, for DISCOVER 2 was Week 100. CASPAR, Classification Criteria for Psoriatic Arthritis[4]; CRP, C-reactive protein; GUS, guselkumab; PBO, placebo; PsA, psoriatic arthritis; q4w, every 4 weeks; q8w, every 8 weeks; SC, subcutaneous; TNF, tumor necrosis factor.

Figure 1. 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, American College of Rheumatology; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks; R, randomization; SC, subcutaneous; Wk, week.

Safety Assessments

- Adverse events (AEs) and clinical laboratory test results were recorded

Statistical Methods

- Safety evaluations are reported through the PBO-controlled period, up to Week 24 (and in some instances through a period of safety follow-up [Table 3])
- Patients who received ≥1 dose of the study drug are reported by treatment received
- Events reviewed included AEs, lab reports, and AEs of special interest (Table 5)

RESULTS

- A total of 1121 patients with active PsA were enrolled in DISCOVER 1 and 2
  - o Randomization and treatment: GUS q8w (n=375), GUS q4w (n=373), PBO (n=372)
- Baseline characteristics (Table 2) were similar across treatment groups and trials except that
  - o Patients in DISCOVER 2 had slightly greater number of swollen and tender joints and higher serum C-reactive protein (CRP) (by design, see Table 1)
  - o Patients in DISCOVER 2 also had higher Psoriatic Body Surface Area

Table 2. Baseline Characteristics

	PBO (n=372)	GUS q8w (n=375)	GUS q4w (n=373)	GUS Combined (n=748)
Age, mean years (SD)	47 (11.5)	46 (11.9)	47 (11.5)	46 (11.7)
Male gender, n (%)	178 (48)	197 (53)	208 (56)	405 (54)
BMI, mean kg/m^2 (SD)	29.2 (6.1)	29.1 (6.3)	29.4 (5.8)	29.2 (6.0)
PsA disease duration, mean years (SD)	6.3 (6.4)	5.6 (5.7)	5.9 (6.1)	5.7 (5.9)
Number of swollen joints (0-66), mean (SD)	11.5 (7.0)	11.4 (7.7)	11.4 (7.5)	11.4 (7.6)
Number of tender joints (0-68), mean (SD)	21.0 (13.5)	19.9 (12.8)	20.8 (13.6)	20.4 (13.2)
CRP, mean mg/dL (SD)	1.9 (2.5)	1.9 (2.4)	1.6 (2.0)	1.7 (2.2)
Psoriatic body surface area, mean % (SD)	15.4 (18.9)	15.7 (20.0)	17.1 (19.7)	16.4 (19.9)
IGA ≥ 2, n (%)	301/371 (81)	295 (79)	311 (83)	606 (81)
Previous TNF inhibitor use, n (%)	39 (10)	41 (11)	38 (10)	79 (11)
Drug use for PsA at baseline, n (%):				
Methotrexate	227 (61.0)	209 (55.7)	218 (58.4)	427 (57.1)
Oral corticosteroids	69 (18.5)	68 (18.1)	62 (16.6)	130 (17.4)
NSAIDs	245 (65.9)	236 (62.9)	240 (64.3)	476 (63.6)

BMI, body mass index; CRP, C-reactive protein; GUS, guselkumab; IGA, investigators global assessment of psoriasis (cleared=0, minimal=1, mild=2, moderate=3, severe=4); NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; PsA, psoriatic arthritis; q4w, every 4 weeks; q8w, every 8 weeks; SD, standard deviation; TNF, tumor necrosis factor; VAS, visual analog scale

Adverse Events (Table 3)

- Percentages of patients with ≥1 AE and ≥1 serious AE were comparable among treatment groups in the integrated safety analysis
- Incidence of infections was similar among groups
  - o Serious infections were infrequent
- Two deaths occurred in the PBO group of patients (cardiac failure and pneumonia)
- Discontinuations due to AEs were low and comparable across groups
- AEs reported by ≥5% of GUS-treated patients were increases in hepatic transaminases, nasopharyngitis, and upper respiratory infection

Table 3. Adverse Events Pooled from the DISCOVER 1 and 2 Trials

	GUS 100 mg q8w (n=375)	GUS 100 mg q4w (n=373)	GUS Combined (n=748)	PBO (n=372)
AEs, n (%)*				
≥1 AE	182 (48.5)	182 (48.8)	364 (48.7)	176 (47.3)
≥1 Serious AE	7 (1.9)	8 (2.1)	15 (2.0)	12 (3.2)
≥1 Infection	73 (19.5)	80 (21.4)	153 (20.5)	77 (20.7)
≥1 Serious Infection	1 (0.3)	3 (0.8)	4 (0.5)	3 (0.8)
Death	0	0	0	2 (0.5)*
Discontinuation due to AE	5 (1.3)	8 (2.1)	13 (1.7)	7 (1.9)
AEs Reported by ≥5% of Patients in Any Treatment Group				
Increased ALT	23 (6.1)	28 (7.5)	51 (6.8)	14 (3.8)
Nasopharyngitis	26 (6.9)	19 (5.1)	45 (6.0)	17 (4.6)
Increased AST	23 (6.1)	14 (3.8)	37 (4.9)	9 (2.4)
Upper Respiratory Tract Infection	13 (3.5)	23 (6.2)	36 (4.8)	17 (4.6)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GUS, guselkumab; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks
*Data collected through the final safety follow-up visit are included in this period.

- Incidence of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Increase and Neutrophil Decrease (Table 4)
  - o ALT/AST increases
    - – Increases in serum ALT and AST were slightly more frequent in the combined GUS than PBO group
    - – Increases were mostly low grade, generally transient, resolved spontaneously, did not result in study drug discontinuation, and were not associated with clinically significant increases in bilirubin
    - – ALT increases were slightly more frequent in patients receiving methotrexate (MTX) at baseline (q4w 48.1%, q8w 39%) than not (q4w 40.4%, q8w 33.5%); AST elevations more frequent with MTX (36.6%) than not (24%) in the q4w group
  - o Neutrophil count decrease
    - – Decreases in neutrophil count were seen more frequently in the GUS than PBO group
    - – Most cases were low grade, transient, resolved spontaneously, and were not associated with infection

Table 4. Incidence of ALT/AST Increases and Neutrophil Decreases by Grade

	GUS 100 mg q8w (n=373)	GUS 100 mg q4w (n=371)	GUS Combined (n=744)	PBO (n=370)
ALT Increased, n (%)				
Grade* 1	105 (28.2)	130 (35.0)	235 (31.6)	111 (30.0)
2	4 (1.1)	10 (2.7)	14 (1.9)	5 (1.4)
3	3 (0.8)	4 (1.1)	7 (0.9)	2 (0.5)
4	0	0	0	1 (0.3)
AST Increased, n (%)				
Grade* 1	70 (18.8)	80 (21.6)	150 (20.2)	74 (20.0)**
2	6 (1.6)	6 (1.6)	12 (1.6)	2 (0.5)
3	2 (0.5)	6 (1.6)	8 (1.1)	4 (1.1)
4	0	0	0	0
Neutrophil Count Decreased, n (%)				
Grade* 1	21 (5.6)	22 (5.9)	43 (5.8)**	12 (3.2)
2	6 (1.6)	6 (1.6)	12 (1.6)	3 (0.8)
3	0	0	0	1 (0.3)
4	0	1 (0.3)	1 (0.1)	0

*National Cancer Institute toxicity Grades. **N=369 for the PBO AST-increased series.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GUS, guselkumab; N, numbers of patients with ≥1 post-baseline data point; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

- AEs of special interest (Table 5)
  - o Infections and serious infections were of similar incidence among all treatment groups
  - o There were no incidences of opportunistic infections or active tuberculosis (TB)
  - o There were no safety signals for malignancy, inflammatory bowel disease (IBD), or major adverse cardiac events (MACE)
  - o Low rates of injection-site reactions were higher with GUS than PBO
  - o Low incidence of anti-GUS antibodies was comparable between patients receiving q8w and q4w
    - – 6.7% of antibody positive patients (1/15) had neutralizing antibodies

Table 5. Adverse Events of Special Interest During 24-weeks of Treatment

Patients, n (%) with:	GUS 100 mg q8w (n=373)	GUS 100 mg q4w (n=371)	GUS Combined (n=744)	PBO (n=370)
Infection	73 (19.5)	80 (21.4)	153 (20.5)	77 (20.7)
Serious Infection	1 (0.3)	3 (0.8)	4 (0.5)	3 (0.8)
Opportunistic Infection	0	0	0	0
Active Tuberculosis	0	0	0	0
Malignancy	2 (0.5)	0	2 (0.3)	1 (0.3)
MACE	0	1 (0.3)	1 (0.1)	1 (0.3)
IBD	0	0	0	1 (0.3)
Injection-site Reaction	5 (1.3)	4 (1.1)	9 (1.2)	1 (0.3)
Anti-GUS Antibody Positive	6 (1.6)	9 (2.4)	15 (2.0)	NA

GUS, guselkumab; IBD, inflammatory bowel disease; MACE, major adverse cardiac events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke); NA, not applicable; PBO, placebo; q4w, every 4 weeks; q8w, every 8 weeks

SUMMARY

- Incidence of patients with AEs was similar between GUS and PBO
- There were no cases of TB or opportunistic infections
- Incidences of malignancy, IBD or MACE were low and generally comparable between GUS and PBO
- The most common AEs occurring in ≥5% of the GUS-combined group of patients included nasopharyngitis, upper respiratory tract infection, and hepatic aminotransferase enzyme elevations
  - o Most infections were not serious
  - o Enzyme elevations were predominantly of low NCI toxicity grade
- Lab abnormalities included decreased neutrophil count
  - o Most were of low NCI toxicity grade and not associated with infection
- Injection-site reactions were infrequent
- Incidence of anti-GUS antibodies was low
  - o Largely not GUS-neutralizing antibodies

CONCLUSIONS

- GUS was safe and well tolerated through the PBO-controlled period in two randomized, phase-3 trials of patients with active PsA
- There were no meaningful safety differences between the q8w and q4w groups, no significant safety issues identified when comparing GUS to PBO, and no safety signals with regards to infections, malignancy, MACE, or IBD
- The safety profile of GUS in PsA patients is generally comparable with the previously established safety profile of GUS

References

1. Veale D, et al. *Lancet*. 2018; 391:2273-2284; **2.** Deodhar A, et al. *Lancet*. 2020;395:1115-1125; **3.** Mease P, et al. *Lancet*. 2020;395:1126-1136; **4.** Taylor W, et al. *Arthritis Rheum*. 2006;54:2665-2273.

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