Background: Although reducing inflammation has been associated with pain improvement, the two do not always correlate. Recent studies have suggested that, in addition to its role in inflammation pathogenesis, IL-23 may be involved in pain regulation in a lymphocyte-independent manner. Guselkumab (GUS), a fully human monoclonal antibody that selectively inhibits IL-23, has demonstrated safety and efficacy in treating multiple domains of active PsA in the DISCOVER-1 & DISCOVER-2 trials.1,2

Objectives: To quantify the role of reducing inflammation on the observed relationship between GUS and pain response in PsA patients (pts) using mediation modelling.

Methods: Pooled data from the DISCOVER-1 & DISCOVER-2 studies were analyzed. Pts in D1 had ≥3 swollen and ≥3 tender joints (SJC/TJC) and C-reactive protein (CRP)≥0.3 mg/dL; in D2, pts had ≥3 SJC and ≥3 TJC and CRP≥0.6 mg/dL. 31% of D1 pts received 1-2 prior tumor necrosis factor inhibitors (TNFi); D2 pts were bio-naive. Pts were randomized 1:1:1 to GUS 100 mg Q4W; Δ24 week active placebo (PBO); PBO pts crossed over to GUS 100 mg Q4W at W24. Pts with history of fibromyalgia were excluded from the analysis. Least square mean changes in pt-reported pain (0-100 VAS) through W52 were estimated with a linear mixed model with change in pt-reported pain as the dependent variable; treatment regimen was the independent variable; inflammation, age; sex; and baseline (BL) pain score, BMI, SF-36 MCS score, and NSAID use. were included as covariates. pt-reported pain was the dependent variable; treatment regimen was the independent variable; inflammation, measured by change in SJC or CRP, was the designated mediator; covariates were: age; sex; and baseline (BL) pain score, BMI, SF-36 MCS score, and NSAID use.

Results: Mean (SD) BL pain levels in the GUS Q4W, GUS Q8W, and PBO groups were 60.4 (19.8), 62.0 (20.2), and 61.1 (19.6), respectively. Treatment with GUS was associated with significantly greater pain improvement compared with PBO as early as W4. ΔSJC [95%CI]: -4.9 [-7.6, -2.2]; ΔCRP [95%CI]: -5.2 [-7.9, -2.5] (Figure 1). These between-group differences were further enhanced by W24. ΔSJC [95%CI]: -14.6 [-17.6, -11.7]; ΔCRP [95%CI]: -14.3 [-17.3, -11.2]); by W52, GUS-randomized pts exhibited an approximate 30-point (-50%) decrease in pain. Similar results were observed for TNFi-naïve and TNFi-exp pts. at W24, the indirect effect via SJC improvement represented ≤10% of the GUS treatment effect. No differences were observed between TNFi-naïve and -exp pts at either timepoint.

Consistent results were obtained when using CRP as the mediator variable instead of SJC, whereby ≤29% of GUS effect on pain was mediated by inflammation and 91-98% was direct (Table 1).

Conclusion: GUS induced significant improvement in pt-reported pain as early as W4 of treatment, which was continuously enhanced through W52. While the known mediation effect of SJC and CRP, as markers of inflammation, on pain was confirmed, the majority of GUS’s effect on pain reduction was independent of its effect on these markers, regardless of dosing regimen or prior TNFi experience.

REFERENCES:

Disclosure of Interests: Philip J Mease Speakers bureau: AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, Sun Pharma, and UCB, Consultant of: AbbVie, Aclaris, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Immage, Janssen, Novartis, Pfizer, Sun Pharma, and UCB, Grant/research support from: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Roche, and UCB, Consultant of: AbbVie, Janssen, Novartis, Roche, Grant/ research support from: AbbVie, Janssen, Novartis, Pfizer, Roche, and UCB, Soumya D Chakravarty Shareholder of: Johnson & Johnson, Employee of: Janssen Pharmaceutical Companies of Johnson & Johnson, Peter Nash Speakers bureau: AbbVie, Amgen, Lilly, Janssen, Novartis, Pfizer, Sun Pharma, and UCB, Consultant of: AbbVie, Aclaris, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Sun Pharma, and UCB, Enrique Soriano Speakers bureau: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, Roche, and UCB, Consultant of: AbbVie, Janssen, Novartis, Roche, Grant/ research support from: AbbVie, Janssen, Novartis, Pfizer, Roche, and UCB, Portsmouth D Chakravarty Shareholder of: Johnson & Johnson, Employee of: Janssen Scientific Affairs, LLC and Drexel University College of Medicine, Emamonnal Rampakakis Consultant of: Janssen, Employee of: JSS Medical Research, May Shawi Shareholder of: Johnson & Johnson, Employee of: Janssen Pharmaceutical Companies of Johnson & Johnson, Peter Nash Speakers bureau: Janssen, Abbvie, Amgen, Lilly, Gilde, Roche, Sandoz, Celgene, Sun, Boehringer, and Bristol Myers Squibb, Consultant of: Janssen, Abbvie, Pfizer, Novartis, Lilly, Gilde, Roche, Sandoz, Celgene, Sun, Boehringer, and Bristol Myers Squibb, Grant/research support from: Janssen, Abbvie, Pfizer, Novartis, Lilly, Gilde, Roche, Sandoz, Celgene, Sun, Boehringer, and Bristol Myers Squibb, Grant/research support from: Janssen, Abbvie, Pfizer, Novartis, Lilly, Gilde, Roche, Sandoz, Celgene, Sun, Boehringer, and Bristol Myers Squibb, Proton Rahman Speakers bureau: Janssen, Consultant of: AbbVie, Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Janssen, Merck, Novartis, Pfizer, and UCB, Grant/research support from: Janssen and Novartis


Figure 1.

Mediation analyses demonstrated that the majority of GUS effect on pain at W4 was not attributable to SJC (direct effect), specifically ≤5% was mediated by inflammation as assessed by changes in SJC (indirect effect; Table 1). Similarly, at W24, the indirect effect via SJC improvement represented ≤10% of the GUS treatment effect. No differences were observed between TNFi-naïve and -exp pts at either timepoint.

Consistent results were obtained when using CRP as the mediator variable instead of SJC, whereby ≤29% of GUS effect on pain was mediated by inflammation and 91-98% was direct (Table 1).