Effects of the JAK1-Selective Inhibitor Filgotinib on Multibiomarker Disease Activity Scores in Patients with Active Rheumatoid Arthritis and an Inadequate Response to Methotrexate


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Introduction
Filgotinib (GLPG0634, GS-6034) is an oral selective JAK1 inhibitor that has been evaluated in a 24-week phase 2B study (DARWIN 1) on a background of methotrexate (MTX) treatment in active rheumatoid arthritis (RA) patients who were MTX inadequate responders1.

Objectives
To evaluate the effect of filgotinib compared to placebo (PBO) in combination with MTX treatment on a Multi-Biomarker Disease Activity (MBDA) score that measures 12 disease-related serum biomarkers of inflammation and joint injury in RA patients.

Methods
• Available serum samples from RA patients who were on a stable dose of MTX receiving either PBO (n=67), or filgotinib 100 mg (n=63), or 200 mg (n=69) once daily (QD), were analyzed for MBDA (Crescendo Biosciences, CA, US) at baseline, week 4 and 12.
• Median % change from baseline for MBDA score and components are reported for week 4 and 12. Wilcoxon rank-sum test assessed the significance between filgotinib treated groups vs. PBO (p-values adjusted for multiplicity using Hommel’s method).

Conclusions
• RA patients treated with filgotinib in combination with MTX had significant reductions in the MBDA score that was driven by key RA biomarkers encompassing both inflammation and joint injury. Together, these findings support systemic anti-inflammatory effects and amelioration of localized pathogenic mechanisms of matrix-turnover and joint damage following treatment with filgotinib.
• The favorable effects on the MBDA score and component biomarkers are consistent with the filgotinib efficacy observed in RA patients1.

Results
• Patient (disease) characteristics and MBDA scores were balanced between the treatment groups at baseline (Table 1).
• MBDA score reductions from baseline were observed for both filgotinib treatment groups, but not for the PBO group (Figure 1). Median scores for 100 mg and 200 mg QD at week 4 (47, 42) and week 12 (42, 41), were significantly different from PBO (p<0.001).
• Most of the individual components contributed to the decrease in MBDA score, but the largest reductions were observed in key biological processes contributing to RA, specifically markers of inflammation, joint damage and matrix remodeling (Figure 2).
• The proinflammatory biomarkers serum amyloid A (SAA), C-reactive protein (CRP), and IL-6 showed the greatest reduction in response to filgotinib (p<0.001).
• Biomarkers of joint-damage and remodeling, comprising matrix metalloproteinase 3 (MMP-3), MMP-1, vascular endothelial growth factor (VEGF), and YKL40 (human cartilage glycoprotein 39), were also strongly reduced (p<0.001).
• There was an increase in leptin (p<0.05) and no change in epidermal growth factor (EGF) concentrations.

References