from CareRA baseline of DAS28-CRP and HAQ was assessed via linear mixed models. All adverse events (AEs), considered to be clinically relevant by investigators, and DMARD/GCs therapy were registered.

Results: Of 322 eligible patients, 252 (78%) were included in CareRA-plus, of which 203 (81%) completed the study. Characteristics and outcomes at the CareRA closing visit (year 2) did not differ between patients entering CareRA-plus or not. DAS28-CRP<2.6 at year 5 in high-risk patients was 72%, 77% and 64% in the Classic, Slim and Avant-Garde group respectively (p=0.403). In the longitudinal analyses, all treatment arms in the high-risk group had comparable DAS28-CRP (p=0.111) and HAQ scores over time (p=0.540). In the low-risk population, 83% of patients in the Slim and 82% in the TSU arm had DAS28-CRP<2.6 at year 5 (p=0.945). Low-risk patients starting Cobra-Slim had lower DAS28-CRP scores over 5 years than those receiving TSU (p=0.002). HAQ score over time did not differ (p=0.129). In high-risk patients, the total numbers of AEs throughout CareRA-plus, were 70 in 36 Classic, 95 in 48 Slim and 80 in 36 Avant-Garde patients (p=0.162). In the low-risk group there were 16 AEs in 10 Slim and 36 in 17 TSU patients (p=0.048). During the 5-year study biology was initiated in 22% of all patients: 23% of Classic, 23% of Slim high-risk, 25% of Avant-Garde, 17% of Slim low-risk, and 15% of TSU patients. At the year 5 visit, 71%, 61% and 50% of high-risk patients were on csDMARD monotherapy (mostly MTX) in Classic, Slim and Avant-Garde respectively. Of the low-risk group, 65% in COBRA-Slim and 62% in TSU were taking a single csDMARD.

At the year 5 visit, 9% of all participants received chronic oral GC therapy (>3 months).

Conclusion: All intensive treatment strategies resulted in excellent long-term clinical outcomes. Initial Cobra Slim therapy showed comparable 5-year effectiveness as Cobra Classic and Avant-Garde in high-risk early RA patients and better efficacy and safety than conservative step up treatment in low-risk patients.

References:

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**Figure 1.** Mean disease activity by DAS28-CRP or mean functionality by HAQ index scores for high-risk or low-risk patients.
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Background: Filgotinib (FIL), an oral selective JAK1 inhibitor, has shown efficacy and safety in multiple phase 3 studies in adults with moderately-to-severely active rheumatoid arthritis (RA), including those who are naive to methotrexate (MTX) therapy (FINCH3; NCT02886728).

Objectives: A longitudinal study of protein biomarkers related to JAK signaling, bone biology, immune cell migration, and inflammation was conducted in FINCH3 pts to identify disease relevant biomarkers that are altered by FIL vs MTX.

Methods: MTX-naïve RA pts enrolled in FINCH3 received a stable dose of MTX (MTX mono), FIL200mg monotherapy (FIL200mg mono) or one of two doses of FIL once daily with MTX (FIL100mg+MTX, FIL200mg+MTX). Up to 27 disease relevant biomarkers were evaluated. Baseline (BL) correlation between biomarkers and clinical response measures were analyzed by Spearman Rank. Multiscale bootstrap resampling was used to evaluate significant intra-cluster biomarker membership. Mean changes in biomarker levels from BL to wks 4, 12 and 24 were compared between arms using MTX-adjusted estimates from a linear mixed effects model, adjusted for age, sex, race and BL biomarker level. A false discovery rate of 5% was applied for all analyses.

Results: At BL, distinct clusters (CL) of biomarkers differentiated by JAK signaling were identified. The strongest intra-group correlations were biomarkers upstream of JAK2 signaling (CL1; Rho range 0.88–0.98) and cytokines associated with JAK1 signaling (CL2; Rho range 0.72–0.77). Within MTX-naïve RA pts, there were significant BL correlations between 15 biomarkers and clinical measures. The strongest associations observed were between DAS28CRP and L6, CXCL10, TNFRF, YKL-40, and CXCL13 (Rho >0.3).

Relative to MTX mono, 23 biomarkers exhibited significant early responses to treatment (any arm, wk 4). The strongest treatment effect observed at wk 4 was a reduction by FIL+MTX (regardless of dose) and FIL200mg alone for CXCL13 (FIL100mg+MTX: -28.2%, FIL200mg-MTX: -40%, FIL200mg: -34%). This reduction was sustained in each arm through 24 wks, with the greatest reduction by FIL200mg-MTX (-37.8%).

Dose differences were observed relative to FIL100mg-MTX, where FIL200mg-MTX led to an early (wk 4) and significantly greater reduction of 9 biomarkers. There was a significant dose difference as a delayed response (wk 24) with a greater reduction by FIL200mg-MTX for 8 biomarkers.

FIL200mg mono produced a greater effect on 18 biomarkers vs MTX mono, remaining significant through wk 24. The greatest effect in FIL200mg mono were reductions by wk 24 in CTX1 (-29.1%), CXCL13 (-33.2%), and IL6 (-29.5%), all of which were biomarkers associated with DAS28CRP at BL. Effects observed at any time point were largely similar between FIL200mg as a mono or in combination with MTX. Four biomarkers were uniquely different between FIL200mg mono and FIL200mg+MTX arms by wk 24: greater increase of MMP7 and decrease of GMCSF in FIL200mg-MTX; greater decrease of TRAPS1 and ICAM1 in FIL200mg alone.

Conclusion: Treatment through 24 weeks with FIL200mg (mono or with MTX) reduced many of the disease-relevant biomarkers tested; markers related to JAK signaling, bone biology, inflammation, and immune cell migration in the MTX-naïve RA setting. Changes were significantly reduced relative to MTX mono at wk 4, supporting the rapid onset of FIL clinical efficacy. The current study identified significant reductions of RA-associated disease markers that were unique to FIL mono, supporting the FIL mechanisms of action in the treatment of RA.

References:

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Figure. Treatment-emergent Adverse Events Through 72 Weeks (E/100 Pts, 95% CI).