WHOLE BLOOD TRANSCRIPTIONAL CHANGES FOLLOWING SELECTIVE INHIBITION OF JANUS KINASE 1 (JAK1) BY FILGOTINIB IN MTX-NAÏVE ADULTS WITH MODERATELY-TO-SEVERELY ACTIVE RHEUMATOID ARTHRITIS (RA) (FINCH3).

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Background: Filgotinib (FIL), an oral selective JAK1 inhibitor, has shown safety and efficacy in multiple phase 3 studies in adults with moderately-to-severely active rheumatoid arthritis (RA). We have previously described the molecular response to FIL in large-scale RNA sequencing studies of gene expression in other RA populations[1-3] and conducted a similar study in MTX-naïve RA patients (pts) (FINCH3).

Objective: Identify gene transcripts and biological pathways associated with RA and those altered in response to filgotinib treatment.

Methods: MTX-naive RA pts who were enrolled in FINCH3 (Clinicaltrials.gov NCT02886728) received a stable dose of MTX (PBO+MTX), FIL 200mg alone (FIL200mg monotherapy) or one of two doses of FIL once daily (QD) together with MTX (FIL100mg+MTX, FIL200mg+MTX). Whole blood samples were collected from pts using PAXgene tubes at baseline, week 4, week 12, and week 24. RNA from these samples was extracted and sequenced on the Illumina HiSeq 2500 platform following globin RNA depletion. Correlations between baseline gene expression and disease measurements were performed using Spearman's rank partial correlation to account for covariates. Differentially expressed genes (DEGs) were identified using voom-limma. Biological pathway analysis was performed on v6.1 of the Molecular Signature Database using single sample GSEA. A false-discovery rate of 5% was applied for all analyses.

Results: Differential gene expression analyses comparing baseline samples with after-treatment samples revealed rapid onset of transcriptional changes in FIL-treated pts, most notably for the two FIL200mg arms (Table 1). Fewer DEGs were observed at all timepoints in PBO+MTX treated patients with a peak number at week 24, an observation consistent with the clinical response kinetics of MTX[4]. Up to 3x as many significant DEGs were observed in the FIL200mg+MTX arm compared to the FIL100mg+MTX arm, a finding consistent with the superior clinical efficacy of the FIL 200mg dosage. As with other FIL clinical trial RNA-seq studies and the selective MoA of FIL, JAK-STAT pathway-induced genes SOCS2 and CISH were significantly downregulated across FIL treatment arms and timepoints, but not PBO+MTX. RA disease activity associated genes[2-3] FAM20A and METTL7B were significantly reduced at all timepoints in FIL treated pts, but only at week 24 in PBO+MTX pts. While no significant changes in KEGG immune signaling pathways were observed in the PBO+MTX arm, a dose dependent effect on pathway modulation was observed in the filgotinib arms, including reductions in JAK/STAT, toll-like receptor, chemokine, and RIG-I like receptor signaling.

Conclusions: We observe a more rapid onset and sustained changes of transcriptional activity after FIL treatment compared to PBO+MTX. Furthermore, dose-dependent changes in the whole blood transcriptional profile of RA pts were observed following FIL treatment, most notably in the KEGG JAK/STAT signaling pathway. These observations confirm an inhibition of JAK-STAT signaling by FIL and are consistent with the observed clinical efficacy of FIL in these pts. These observations confirm

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References

1. P. C. Taylor, *et al* (EULAR 2018). http://dx.doi.org/10.1136/annrheumdis-2018-eular.3759
2. P. C. Taylor, *et al* (ACR 2018). https://doi.org/10.1093/rheumatology/kez105.001
3. P. C. Taylor, *et al* (EULAR 2019). http://dx.doi.org/10.1136/annrheumdis-2019-eular.2509
4. Taylor PC *et al. J Clin Med*. 2019;8: pii: E515. doi: 10.3390/jcm8040515