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EVALUATION OF POTENTIAL MECHANISMS UNDERLYING THE SAFETY OBSERVATIONS OF FILGOTINIB IN CLINICAL STUDIES IN RA

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Inflammatory Bowel Diseases
IBD: Uncontrolled Therapeutic Observations in Humans Non-Biologic
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Background: Inhibitors of the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway have demonstrated efficacy in the treatment of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Differences in selectivity of JAK inhibitors for JAK1, JAK2, JAK3 and TYK2 may influence their respective safety profiles, and the mechanisms responsible are not currently known. Filgotinib (FIL), a JAK1 inhibitor, did not negatively impact haemoglobin, LDL:HDL ratios or natural killer (NK) cell counts in clinical trials. Here, we compare the *in vitro* mechanistic profiles of four JAK inhibitors at clinically relevant doses.

Methods: JAK inhibitors (FIL, FIL metabolite [GS-829845], baricitinib [BARI], tofacitinib [TOFA], and upadacitinib [UPA]) were evaluated *in vitro* in human-cell-based assays. Growth of erythroid progenitors from human cord blood $CD34^+$ cells was assessed using a HemaTox™ liquid expansion assay, NK cell proliferation was induced by IL-15 and LXR agonist-induced cholesteryl ester transfer protein (CETP) expression was assessed in the hepatic cell line, HepG2. Using assay-generated IC50 values and the reported human plasma concentrations from clinical studies, we calculated the target coverage for each JAK inhibitor at clinically relevant doses. The activity of FIL in humans was based on PK/PD modeling of FIL + GS-829845.

Results: Inhibition of cellular activity was calculated for each JAK inhibitor based on *in vitro* dose-response data, human exposure data and modeled PK/PD relationships. At clinically relevant doses, FIL resulted in lower calculated inhibition of NK cell proliferation compared with other JAK inhibitors. FIL 100 mg and 200 mg also reduced CETP expression, whereas other JAK inhibitors had no effect. There was no difference in the effect of FIL vs. other JAK inhibitors on erythroid progenitor cell differentiation or maturation.

Conclusion: FIL, a JAK1 inhibitor, resulted in less inhibition of NK cell proliferation compared with BARI, TOFA, and UPA. FIL also reduced LXR agonist-induced CETP expression, while the other inhibitors did not alter these levels. These results provide a potential mechanistic link between the observed reduction of CETP concentration following FIL treatment and the previously observed reduction in the LDL:HDL ratio in RA patients.

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Calculated Inhibition of Cellular Activity at Clinical Exposures (% inhibition over 24h)								
JAK inhibitor	FIL[a]		BARI		TOFA		UPA	
Dose (mg)	100	200	2	4	5	10	15	30
Early erythroid progenitor	18.9	30.5	17.6	38.2	17.6	28.5	31.1	42.4
Mature erythroid progenitor	42.1	50.4	33.0	45.1	36.7	45.0	46.3	54.7
NK cell proliferation	38.9	52.3	51.7	78.9	75.4	86.0	74.2	84.2
Inhibition of LXR agonist-induced CETP expression	17.3	27.4	Inactive					

[a] FIL + GS-829845 composite PD effect

Disclosure: A. Clarke: Gilead Sciences, Inc.: Employment; J. Di Paolo: Denali: Employment; Gilead Sciences: Employment, Employment; B. Downie: Gilead Sciences: Employment, Employment; A. Meng: Gilead Sciences: Employment, Employment; N. Mollova: Gilead Sciences, Inc.: Employment, Stock Shareholder; Y. Yu: Gilead Sciences, Inc: Employment; P. Han: Gilead: Employment;