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EFFECTS OF THE JAK1-SELECTIVE INHIBITOR FILGOTINIB ON MULTIBIOMARKER DISEASE ACTIVITY SCORES IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO METHOTREXATE

M. C. Genovese[1,*], W. Li[2], L. Goyal[2], Y. Pan[2], A. Van der Aa[3], C. Jamoul[3], P. Harrison[3], C. Tasset[3], R. Galien[4], J. Tarrant[2]

[1]Division of Immunology & Rheumatology, Stanford University School of Medicine, Palo Alto, [2]Gilead Sciences, Foster City, United States, [3]Galapagos NV, Mechelen, Belgium, [4]Galapagos SASU, Romainville, France

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

Objectives: To evaluate the effect of filgotinib compared to placebo on a multi-biomarker disease activity (MBDA) score that measures 12 disease-related biomarkers of inflammation and joint injury in RA patients taking background MTX.

Methods: Serum samples of RA patients who were on a stable dose of MTX and received either placebo (PBO) or filgotinib 100mg or 200mg once daily (QD), were tested for MBDA components (Crescendo Biosciences, CA, US) at baseline, week 4 and week 12. Median % change from baseline for MBDA score and individual components are reported for week 4 and week 12. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups *vs.* PBO.

Results: Baseline MBDA scores and component values (median; interquartile range) were similar in PBO (55; 45-64), 100mg QD (58; 42-66), and 200mg QD (59; 50-67.5) treatment groups. Filgotinib treated patients had reductions in the MBDA score from baseline at both the 100mg and 200mg QD dose levels, but not in the PBO group. At both weeks 4 and 12, these reductions in the filgotinib treated groups were significantly different from the PBO group. Most of the individual components contributed to the decrease in MBDA score, but the largest reductions were observed for serum amyloid A (SAA), C-reactive protein (CRP), and IL-6, and the biomarkers of joint-damage, matrix metalloproteinase 3 (MMP3), MMP1, vascular endothelial growth factor (VEGF), and YKL40 (human cartilage glycoprotein 39). There was an increase in leptin and no change in epidermal growth factor (EGF) concentrations.

Table: Median percent change from baseline of MBDA score and component concentrations

	week 4			week 12		
	PBO (N=62)	filgotinib 100mg QD (N=63)	filgotinib 200mg QD (N=68)	PBO (N=65)	filgotinib 100mg QD (N=62)	filgotinib 200mg QD (N=68)
MBDA SCORE	-1	-20***	-24***	-5	-19***	-24***
CRP	15	-57***	-71***	-8	-66***	-78***
EGF	14	-18 NS	-8 NS	0	-10 NS	0 NS
IL-6	-15	-34**	-60***	-20	-41**	-63***
LEPTIN	0	8 NS	18 NS	6	14 NS	23*
MMP-1	10	-16***	-24***	-6	-18**	-26***
MMP-3	0	-24**	-33***	-9	-25***	-43***
RESISTIN	1	-12**	-22***	-1	-15*	-16***

SAA	8	-45***	-65***	7	-49***	-67***
TNF-RI	0	-11***	-26***	0	-11***	-15***
VCAM-1	5	-10***	-15***	0	-8**	-16***
VEGF	3	-16***	-25***	-2	-16***	-26***
YKL-40	2	-12*	-32***	-7	-17 NS	-33***

p-values comparing % changes between filgotinib and PBO groups NS, $p>0.05$; *$p<0.05$; **$p<0.01$; ***$p<0.001$

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. These findings are consistent with the filgotinib efficacy observed in RA patients over 12 weeks.

References: [1]Westhovens R, et al. Ann Rheum Dis 2016;0:1–11. doi:10.1136/annrheumdis-2016-210104

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