



Monotherapy With the JAK1-Selective Inhibitor Filgotinib Displays an Anti-Inflammatory Biomarker Profile in Rheumatoid Arthritis Patients

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J. Tarrant¹, A. Van der Aa², C. Jamoul², A. Kavanaugh³, W. Li¹, L. Goyal¹, Y. Pan¹, P. Harrison², C. Tasset², R. Galien⁴

¹Gilead Sciences, Foster City, United States of America, ²Galapagos NV, Mechelen, Belgium, ³University of California, La Jolla, United States of America, ⁴Galapagos SASU, Romainville, France

Introduction

Janus kinases (JAKs) are key intracellular mediators in the signal transduction of many cytokines and growth factors. The selective JAK1 inhibitor filgotinib (GLPG0634, GS-6034) has been evaluated in a 24-week phase 2B study (DARWIN 2) as monotherapy in active rheumatoid arthritis (RA) patients who were methotrexate inadequate responders and has shown a good safety and efficacy profile¹.

Objective

To gain insight into filgotinib mode of action as monotherapy in RA patients by analyzing the effect of filgotinib compared with placebo on a broad panel of immune modulators in the serum.

Methods

- RA patients received either placebo (PBO), or filgotinib monotherapy at 50 mg, 100 mg or 200 mg once daily (QD). Serum samples were collected at baseline, week 4 and week 12 and analyzed using the multiplex bead-based immunoassay (HSTCMAG-28SK Merck-Millipore) at ABL (Lyon, France) to measure 18 cytokines
- ANCOVA model was fitted for week 4 and 12, respectively, to estimate the log ratio of each cytokine from baseline by treatment group, after adjusting for prior biologic use, region (stratification factors) and the log-transformed baseline cytokine value. The model estimated % change from placebo in the post-baseline ratio of each cytokine per filgotinib treatment arms, and the associated p-values, adjusted for multiplicity per cytokine time point using Hommel's method

Table 1: Baseline (disease) characteristics

	Placebo (N=72)	Filgotinib 50 mg QD (N=72)	Filgotinib 100 mg QD (N=70)	Filgotinib 200 mg QD (N=69)
Age, mean, yrs	52	52	53	52
Female, %	78	86	76	87
Duration of RA, mean, yrs	10	9	9	9
RF positive, %	79	74	73	72
Anti-CCP positive, %	81	78	77	83
DAS28(CRP), mean	6.2	6	6.2	6.1
CRP, mean mg/L	35.3	24.7	25.6	23.2

Reference

¹Kavanaugh A, et al. *Ann Rheum Dis* 2017;76:1009-1019.

Results

- Following treatment with filgotinib, there were significant reductions in cytokines important for the expansion and activity of multiple T-cell subsets and innate immunity compared with PBO
- These changes included decreases in proinflammatory cytokines (IL-6, IL-1 β , and TNF- α), T_H1-related (IL-2, IFN- γ and IL-12), T_H2-related (IL-4, IL-5, and IL-13) and T_H17-related cytokines (IL-1 β , IL-6, IL-17A, IL-21 and IL-23). All doses of filgotinib also reduced the B- and T-cell development cytokine IL-7. In contrast, IL-8 was not affected by filgotinib
- Reductions in MIP-1 α , MIP-1 β and GM-CSF are in line with downmodulation of innate immune activity

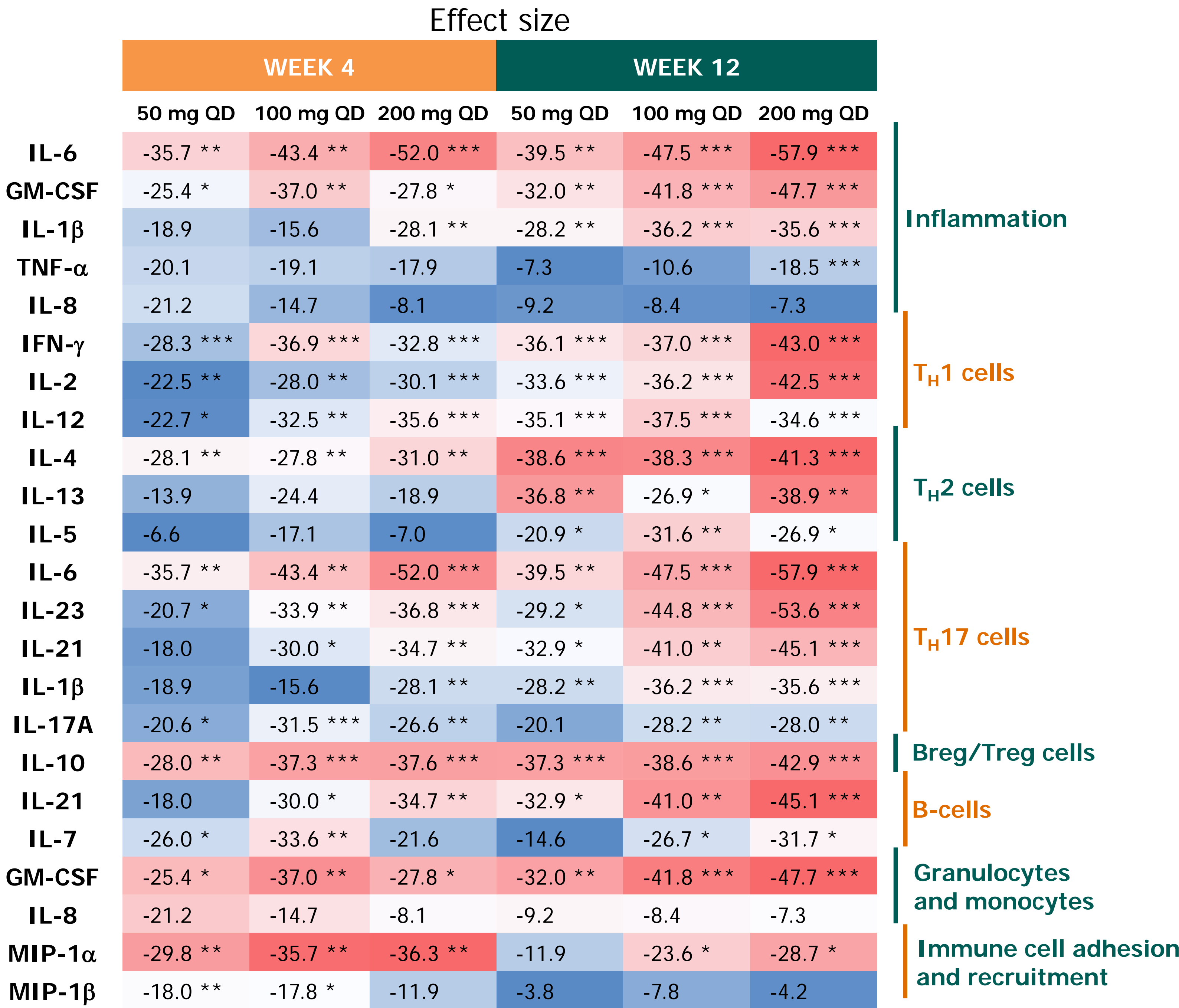


Figure 1: Percentage change from placebo in post-baseline ratio (effect size) and associated p-values for each biomarker, at week 4 and week 12 are presented. Red gradient indicates a greater reduction and darker blue a greater increase. *: p<0.05; **: p<0.01; ***: p<0.001

Conclusions

Treatment of RA patients with filgotinib monotherapy compared with placebo resulted in significant reductions in the levels of a broad range of cytokines related to T_H1, T_H2, T_H17 and potentially B-cells, as well as innate immunity. These findings provide further insights into the filgotinib anti-inflammatory effects in RA patients.

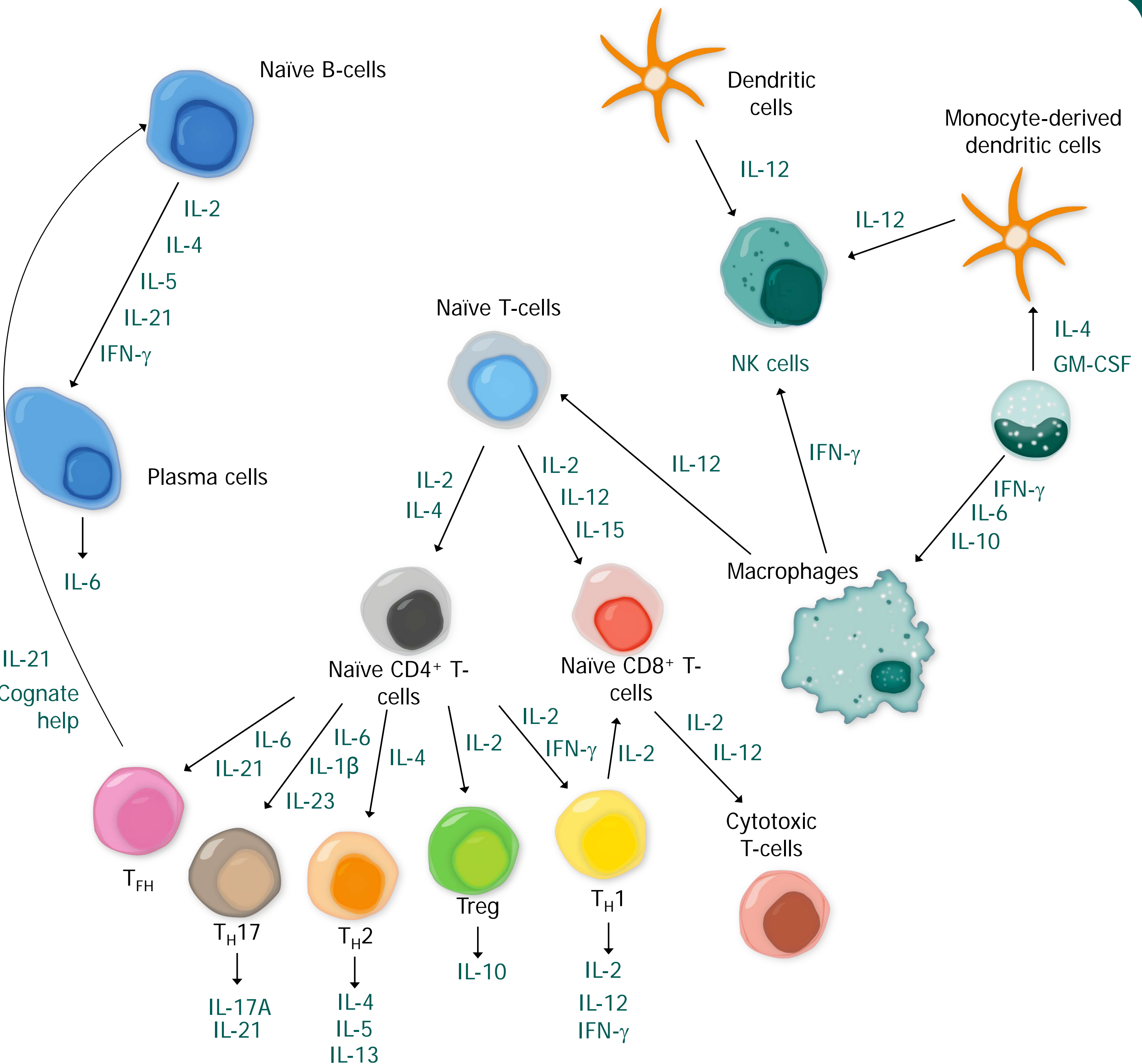


Figure 2: Schematic representation of the effects of filgotinib on the development and activity of immune cells. Only cytokines impacted by filgotinib monotherapy treatment in RA patients compared with placebo are depicted