(STAT3), and plasma markers of inflammation, writing that the "data lends support to the widely held assumption that the JAK2 activating mutation and consequent activation of STAT3 leads to **increased inflammatory cytokines** in the plasma … and that treatment with ruxolitinib reversed this." Focusing more on the drug's mechanism of action, the reviewer added that, "measurement of pSTAT3 activation is a surrogate for JAK2 [Janus kinase] activation, … [t]his is a demonstration that ruxolitinib is inhibiting the enzymatic activity of JAK2 in vivo in patients on the ruxolitinib arm."

FDA's analysis of the study drug's influence on CRP is reflected in the *Pharmacodynamics* section of the package insert. Although the package insert did not mention CRP, it did mention part of the pathway (STAT3 activation) that provides inflammatory responses. The package insert for ruxolitinib (Jakafi) read:

> Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF patients. Jakafi administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 10 hours in both healthy subjects and myelofibrosis patients (118).

To conclude, the *Medical Review* illustrates how clinical trial data, which made use of the CRP biomarker, were included in the *Pharmacodynamics* section of the package insert.

d. C-Reactive Protein and Atherosclerosis

In addition to expression by hepatocytes, CRP is also expressed by cells in atherosclerotic lesions. CRP is found in the plasma, as well as in the extracellular matrix at the site of inflammation, such as atherosclerotic lesions (119). Expression of CRP by these lesions can result in local concentrations of CRP that are far in excess of plasma concentrations (120).

If CRP is eventually proven to contribute to the mechanism of atherosclerosis, it is likely that these high, local concentrations of CRP are a source of CRP's proinflammatory and proatherogenic effects (121). One possible mechanism of CRP, which is central to the established mechanism for atherosclerosis, is CRP's ability to mediate uptake of oxidized LDLs by macrophages (122). In atherosclerosis, it is a firmly established fact that chronic uptake of oxidized LDLs by macrophages results in the conversion of macrophages to foam cells, and eventually to formation of the atherosclerotic lesion (123,124). Singh et al.

[118]Package insert for JAKAFI™ (ruxolitinib) tablets, for oral use; November 2011 (23 pp.).

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