

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/118160/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Choy, Ernest H 2019. Clinical significance of Janus Kinase inhibitor selectivity. *Rheumatology* 58 (6) , pp. 953-962. 10.1093/rheumatology/key339

Publishers page: <http://dx.doi.org/10.1093/rheumatology/key339>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Clinical Significance of Janus Kinase Inhibitor Selectivity

Professor Ernest H Choy

Head of Rheumatology and Translational Research

Division of Infection and Immunity

Director of Arthritis Research UK and Health and Care Research Wales CREATE Centre

Correspondence to: Professor Ernest Choy, CREATE Centre, Section of Rheumatology,
Division of Infection and Immunity, Cardiff University School of Medicine, Tenovus Building,
Heath Park, Cardiff, Wales, United Kingdom CF14 4XN. Email: ChoyEH@cardiff.ac.uk

Key words: rheumatoid arthritis, Janus Kinase, treatment, targeted synthetic DMARDs,
DMARDs

Acknowledgement: The CREATE Centre was funded by Arthritis Research UK and Health and
Care Research Wales.

Statement: This manuscript has no funding supporting.

Key messages:

1. JAKi selectively is relative and not absolute.
2. Current approved JAKi and those in development significantly inhibit JAK1 isoform.
3. JAK1 is an effective target in RA although zoster reactivation is a class effect.

Abstract

Cytokines are key drivers of inflammation in rheumatoid arthritis (RA). Anti-cytokine therapy has improved the outcome of RA. Janus kinases (JAK) are intracellular tyrosine kinases linked to intracellular domains of many cytokine receptors. There are four JAK isoforms: JAK1, JAK2, JAK3 and TYK2. Different cytokine receptor families utilise specific JAK isoforms for signal transduction. Phosphorylation of JAK when cytokine binds to its cognate receptor leads to phosphorylation of other intracellular molecules that eventually leads to gene transcription. Oral JAK inhibitors have been developed as anti-cytokine therapy in RA. Two JAK inhibitors, tofacitinib and baricitinib, have been approved recently for the treatment of RA. Many JAK inhibitors are currently in development. JAK inhibitors inhibit JAK isoforms with different selectivity. This review discusses efficacy and safety of JAKi in RA in particular the potential clinical significance of JAKi selectivity.

Background

During the 1990s, when monoclonal antibodies (mAbs) were trialled in patients with Rheumatoid Arthritis (RA), many rheumatologists questioned whether intravenous or subcutaneous injections could ever be a realistic treatment. At the time, researchers argued that the mAbs were the ideal tools to identify specific therapeutic targets for which oral inhibitors can be developed. This vision was realised when in 2009 the Food and Drug Administration approved the first Janus Kinase Inhibitors (JAKi), tofacitinib, for the treatment of RA. In 2017, tofacitinib and another JAKi, baricitinib, received approval in Europe. Janus Kinases (JAKs) are intracellular molecules involved in signal transduction of type I and II cytokine receptors¹ including interleukin (IL)-6 receptor, a proven therapeutic target in RA². JAKi are classified by European League Against Rheumatism (EULAR) as targeted synthetic Disease Modifying Anti-Rheumatic Drugs (tsDMARDs). There are 4 JAK isoforms: JAK1, JAK2, JAK3 and TYK2, which act in pairs to phosphorylate other intracellular proteins. Other JAKi are being developed for the treatment of RA. Current JAKi, approved and in development for RA, inhibit JAK isoforms with different selectivity. Is JAK selectivity clinically meaningful? This review will discuss efficacy and safety of JAKi in RA as well as potential clinical significance of JAK isoform selectivity.

Cytokine signalling and Biology of JAK/STAT pathway

Cytokines can be classified by the structure of their receptors. Type I cytokine receptors have certain conserved motifs in their extracellular amino-acid domain. These include common γ chain (such as IL-2), gp130 family (such as IL-6), p40 subunit (IL-12 and IL-23), and common β chain cytokine receptors (haemopoietic cytokines such as GM-CSF). Type 2 cytokine receptors are members of the IL-10 and interferon families. Both Type I and II

cytokine receptor families utilise the JAK for signalling transduction. Among these cytokines and cytokine receptors, IL-6 and IL-6R are established therapeutic targets in RA. The role of other JAK signalling cytokines in RA is less well established. JAKs also have essential homeostatic roles, being responsible for signalling of some hormones including prolactin and growth hormone (GH).

JAKs are associated with the membrane proximal regions of cytokine receptors³.

Conformational changes in cytokine receptors induced by ligand binding lead to phosphorylation of JAKs through the reciprocal interaction of two juxta-positioned JAKs (Figure 1). Hence, JAKs activation requires two JAK isoforms either as homodimers or heterodimers to auto-phosphorylate, which allows recruitment and phosphorylation of various signalling molecules including members of the signal transducer and activator of transcription (STAT) family of DNA binding proteins⁴. Phosphorylation of STATs promotes their translocation to the nucleus and gene transcription.

Since, type I and II cytokine receptor families include a large number of cytokines, growth factors and hormones, JAKs are critical to immune function and homeostasis. Consequently, JAKs are highly conserved and JAK isoforms are non-redundant. JAK isoform knock-out animals have severe clinical phenotypes: JAK1⁵ deficient mice die perinatally while JAK2 knockout animals are embryonic lethal due to defective erythropoiesis⁶. JAK3⁷ deficient mice suffer from severe immunodeficiency syndrome and reduced survival. In humans, mutations in JAK3 cause severe combined immune deficiency syndrome^{8,9}. TYK2 deficient mice are viable but susceptible to viral infection due to reduced interferon response¹⁰.

Therapeutic Principle of JAK Inhibition

Evidence from animals and patients with JAK isoform deficiency showed that complete blockade of JAK isoforms is undesirable as it will lead to severe immunodeficiency and abnormal homeostasis. Therefore, the principle of JAKi inhibition differs from cytokine inhibition using biologics in that the objective is not to block specific JAK pathway completely but reversibly reduce the activity of one or more JAK isoforms akin to turning down of a thermostat. One potential clinical advantage of such mode of action is that inhibition can be rapidly reversed with “fast-on” and “fast-off” effects.

JAK Inhibitors

Two JAKi, tofacitinib and baricitinib, in combination with methotrexate (MTX) or as monotherapy, have been approved for the treatment of RA. Both tofacitinib and baricitinib have been examined in large phase III and IV randomised control trials (RCT) in a range of RA patients from csDMARD naïve early patients, csDMARD inadequate responders (IR) to biologic IR. The American College of Rheumatology (ACR) responses in these studies are summarised in Table 1. Tofacitinib is selective for JAK1 for JAK3 while baricitinib is selective for JAK1 and JAK2. In addition, four JAKi are currently in development: the JAK1 selective: upadacitinib and filgotinib, JAK1 and JAK2 inhibitor: peficitinib, and JAK3 selective inhibitor: decernotinib.

In MTX IR, tofacitinib (5 and 10mg bd) in Oral-STANDARD¹¹ and baricitinib (4mg od) in RA-BEAM¹² added to MTX showed superior ACR responses when compared to placebo.

Tofacitinib showed a similar response to adalimumab while baricitinib in RA-BEAM achieved statistically significant higher ACR20 responses than adalimumab (70% vs 61%). However,

the difference was small (<10%) and the sample size was larger in RA-BEAM than Oral-STANDARD. Similar to MTX IR, in csDMARD IR, adding tofacitinib in Oral-SYNC¹³ and baricitinib in RA-BUILD¹⁴ achieved higher ACR responses than placebo. In biologic IR, tofacitinib (5 and 10mg bd) in Oral-Step¹⁵ and baricitinib (2 and 4mg od) in RA-BEACON¹⁶ in combination with MTX achieved higher ACR responses than placebo.

Radiographic damage

In ORAL-SCAN¹⁷, radiographic damage was statistically significantly less in patients treated with tofacitinib 10 mg when compared to placebo-treated patients. Tofacitinib 5 mg treated patients had less radiographic damage than placebo-treated patients but this did not achieve statistical significance. Baricitinib has also been shown to reduce radiographic damage in RA-BUILD¹⁴, RA BEAM¹² and RA-BEGIN¹⁸. In RA-BUILD, baricitinib, both 2 and 4mg in combination with MTX statistically significantly reduced radiographic progression when compared with placebo. In RA-BEGIN, baricitinib 4mg monotherapy treated patients had less radiographic progression than placebo but the difference was not statistically significant.

Monotherapy versus combination therapy with MTX

Since JAKi are not bDMARDs, they do not incite anti-drug antibody response so theoretically concomitant treatment with MTX should be unnecessary. Tofacitinib monotherapy was assessed in Oral SOLO¹⁹ and Oral START²⁰ while baricitinib monotherapy was assessed in RA-BEGIN¹⁸. Tofacitinib (5 and 10mg) and baricitinib 4mg monotherapy were superior to MTX. Baricitinib monotherapy produced similar therapeutic response to 4mg plus MTX. However, the sample size of the study was not powered to compare difference between monotherapy versus combination therapy. Indeed, the sample size of the monotherapy was smaller

(N=159) than the MTX plus baricitinib group (N=215). Furthermore, both Oral-START and RA-BEGIN were trials of patients with early RA while in routine clinical practice, JAKi are used in patients with established disease. These studies showed that JAKi monotherapy is effective, but it is unclear whether monotherapy is as effective as combination therapy. For tofacitinib, this was assessed in ORAL-STRATEGY²¹, a 1-year, double-blind, head-to-head, non-inferiority, RCT comparing tofacitinib (5 mg bd) monotherapy, tofacitinib (5 mg bd) plus MTX, and subcutaneous adalimumab (40 mg fortnightly) plus MTX in MTX IR patients. The primary endpoint was ACR50 response at month 6. This was met by 38%, 46% and 44% of patients in tofacitinib monotherapy, tofacitinib plus MTX and adalimumab plus MTX respectively. Tofacitinib plus MTX was non-inferior to adalimumab plus MTX but non-inferiority was not demonstrated in the tofacitinib monotherapy group suggesting that in patients who can tolerate MTX, combining tofacitinib with MTX is better than switching to monotherapy.

JAKi in development

Phase II RCT data of upadacitinib^{22,23}, filgotinib^{24,25}, peficitinib^{26,27} and decernotinib^{28,29} are summarised in Table 2. Overall, these JAKi demonstrated superior ACR responses than placebo-treated group. Recently, phase III trials of upadacitinib in csDMARD IR (SELECT Next)³⁰ and biologic IR (SELECT Beyond)³¹ patients have been published which confirmed efficacy of upadacitinib (15 and 30mg od).

Safety profile of JAKi

Safety data on JAKi are mostly based on RCT and extension studies. Limited real-world data are available for tofacitinib³². Caution should be exercised when comparing incidence rate

(IR) of adverse event with biologic agents, in which IR from real-world data³³ are available.

In pooled analyses, the IR of serious adverse events was 9.4/100pyrs (95%CI 9.0-0.9) for tofacitinib³⁴. For baricitinib, the IR of severe adverse event has not been reported but IR of specific adverse events are available. The key adverse event data on tofacitinib and baricitinib are summarised in table 3.

Infections

The IR of serious infections was 2.7/100pyrs (95%CI 2.5-3.9)³⁴ and 2.9/100pyrs (95%CI 2.5-3.4)³⁵ for tofacitinib and baricitinib respectively. Both tofacitinib and baricitinib were associated with increased incidence of reactivation of herpes zoster (3-4/100pyrs). This was higher than placebo and exceeded those expected with biologic agents. Risk was highest in Japan and Korea³⁶. Concomitant glucocorticoid was an additional risk factor. Reactivation of herpes zoster appears to be a class effect and may be due to inhibition of interferon and IL-15 which are key anti-viral cytokines which signal through JAK1, JAK2 and JAK3. Response to zoster vaccine prior to JAKi treatment has been evaluated in a RCT³⁷. Zoster vaccine was given to 112 patients with active RA taking MTX 2 weeks before receiving either placebo or tofacitinib for 12 weeks, after which placebo-treated patients received tofacitinib in an open-label extension study. Both humoral and cellular immune responses to the zoster vaccine were similar in placebo and tofacitinib-treated patients. In the open-label extension phase, 5 patients developed reactivation of zoster. All these patients had suboptimal vaccine immune response to the zoster vaccine.

Malignancies

IR of malignancies excluding non-melanoma skin cancer for tofacitinib³⁴ and baricitinib³⁵ was 0.9/100pyrs (95%CI 0.8-1) and 0.8/100pyrs (95%CI 0.6-1.0) respectively. IR for lymphoma was 0.1/100pyrs (95%CI 0.1-0.2) for tofacitinib and 0.09/100pyrs (95%CI 0.03-0.19) for baricitinib. Non-melanoma skin cancer occurred in 0.6/100pyrs (95%CI 0.5-0.7) for tofacitinib and 0.4/100pyrs (95%CI 0.2-0.5) for baricitinib. However, long-term real-life data will be needed to assess accurately the risk of malignancies.

Gastrointestinal perforation

Gastrointestinal perforation is associated with IL-6 inhibition. IL-6 signals via JAK1, JAK2 and TYK2. Therefore, inhibiting IL-6 signalling by JAKi may be associated with gastrointestinal perforation. IR of gastrointestinal perforation was 0.11/100pyrs (95%CI 0.07-0.17) for tofacitinib and 0.05/100pyrs (95%CI 0.01-0.13) for baricitinib. These were numerically lower than that was observed with tocilizumab reported in registry which was 0.27/100 patient year³⁸. Indeed, a real-world study also suggested the same. Lower gastrointestinal tract perforation was slightly less frequent in tofacitinib-treated than tocilizumab-treated patients, although these are higher than patients treated by TNF inhibitors³⁹

Deep vein thrombosis (DVT) and pulmonary embolus (PE)

Five cases of DVT and/PE was observed with baricitinib (IR 1.2/100pyrs) but none in the placebo-treated patients during RCTs⁴⁰. Overall IR of DVT/PE was 0.5/100pyrs (95%CI 0.3-0.7). There was no association between platelet count and the occurrence of DVT/PE. IR of DVT and PE associated with tofacitinib has not been reported. However, as these adverse events are uncommon, data from registries will be needed to evaluate the association between DVT/PE and JAKi.

Laboratory abnormalities

Haemoglobin (Hb)

One of the extra-articular features of active RA is anaemia of chronic diseases, which is mediated by hepcidin as part of the acute-phase response². Hence, effective suppression of inflammation should increase Hb which has been with biologic treatment^{41,42}. However, haemopoietic cytokines including erythropoietin signals via JAK2⁴³. A consequence of JAK2 inhibition is reduced erythropoiesis. This is reflected by Hb changed associated with baricitinib⁴⁴ in which, there was a statistically significant greater reduction ($p=0.02$) in Hb occurred with baricitinib -0.17 ± 0.02 when compared to placebo-treated patients -0.12 ± 0.02 . Anaemia occurred in 29% of baricitinib-treated versus 26% in placebo-treatment patients. In contrast, a small increase in Hb was observed in a pooled analysis of tofacitinib which has less inhibitory effect on JAK2: 0.47 g/dl and 0.28 g/dl with 5 and 10 mg respectively⁴⁵. The likely reason for a smaller increase in Hb with tofacitinib 10mg is dose-associated inhibition of JAK2 i.e. at low dose (5mg) tofacitinib is selective for JAK1 and JAK3 but at 10mg, this selectivity is diminished and JAK2 is inhibited. Compared to MTX, both doses of tofacitinib were associated with a slightly higher incidence of anaemia although in total <1% of patients experienced major decrease in Hb as defined by decrease from baseline of ≥ 3 g/dl or an absolute haemoglobin level of ≥ 7 g/dl. Nevertheless, Summary of Product Characteristics (SPC) recommended tofacitinib⁴⁶ and baricitinib⁴⁷ should not be used in patients who are anaemic ($Hb < 8$ g/dl) and treatment should be interrupted when Hb drops below 8g/dl.

Neutrophil

Decrease in neutrophil count with occasional cases of neutropenia (Table 3) has been observed with all JAKi. SPCs recommend monitoring of neutrophil count in patients taking JAKi^{46,47}.

Lymphocyte

Lymphopenia can occur in patients treated with JAKi. For tofacitinib, lymphopenia <500 cells/mL occurred in 8.3/100pyrs (95%CI 3.0-18.1)⁴⁵. Multivariate analysis suggested lymphocyte count <500cells/mL was associated with increased risk of serious infection³⁴. Lymphopenia was uncommon (<1% of patients) but has also been observed after treatment with baricitinib⁴⁸. The presence of lymphopenia was associated with a slightly higher overall infection rate, but not for serious infections. Although the lack of association with serious infection may be due to insufficient event and patient number. SPCs recommend interrupting JAKi treatment when lymphocyte count is <500cells/ml^{46,47}.

Platelet

Thrombocytosis is a feature of active disease in RA². Suppression of inflammation should reduce platelet number. Surprisingly, treatment by baricitinib was associated with thrombocytosis⁴⁸. Increases in platelet counts above 600×10^9 cells/L occurred in 2.0% of patients compared with 1.1% of placebo-treated patients⁴⁷. There is no published data on change in platelet count after treatment with tofacitinib.

Biochemistry

Lipids

Increase in both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol occurred after treatment with both tofacitinib⁴⁹ and baricitinib⁵⁰ although there is no change in HDL/LDL ratio. IR of major adverse cardiovascular events was 0.58/100 patients years (95%CI 0.39-0.88) for tofacitinib⁵¹ and 0.5/100 yrs (95%CI 0.4-0.7] for baricitinib⁴⁸. A mechanistic study examined the effect of tofacitinib on cholesterol and lipoprotein transport showed that HDL, LDL and total cholesterol levels were lower in RA patients than in healthy volunteers while cholesterol ester fractional catabolic rate was higher in RA patients⁵² suggesting cholesterol catabolism is increased. Treatment with tofacitinib reduced inflammation and restored cholesterol catabolism.

Liver transaminases

Increases in liver transaminases (>3x ULN) occurred in up to 2% of patients receiving tofacitinib⁵³ and 1.4% of patients treated with baricitinib⁴⁷. Most cases were transient and asymptomatic. Liver function tests should be monitored in patient taking JAKi and when liver transaminases increase significantly, treatment should be temporarily discontinued.

Increase in creatinine levels

Small increase in serum creatinine by 2-4 µmol/L was observed in RCTs when compared with placebo for tofacitinib⁵⁴ and baricitinib⁵⁵. This plateaued after 3 months and was not associated with significant renal side effects.

Increase in creatine phosphokinase (CPK)

Increase in CPK (>5 x the upper limit of normal) occurred in up to 1% of patients treated with either tofacitinib⁴⁶ or baricitinib⁴⁷. In most cases, CPK elevation was transient, asymptomatic and did not require treatment discontinuation.

Safety of JAKi in development

Exposure is too low to assess major clinical safety such as serious infection. For laboratory measures, changes in biochemistry measures have been observed with all JAKi suggesting that these are class effects (Table 3).

For haematology measures, decrease in neutrophil and lymphocyte count including neutropenia and lymphopenia, have been observed with all JAKi suggesting these are also class effects. However, JAKi have different effects on Hb and platelet count. Filgotinib and decernotinib increased Hb but peficitinib and upadacitinib especially at high doses decreased Hb. Therefore, filgotinib and decernotinib are similar to tofacitinib while peficitinib and upadacitinib are more akin to baricitinib. The most likely explanation for these differences is inhibition of JAK2 which is expected with in vitro profile of baricitinib and peficitinib. Another potential differentiating feature among JAKi is the effect on platelet count, both filgotinib and peficitinib decrease platelet numbers while baricitinib increased platelet number. Effect of upadacitinib and decernotinib on platelet number was not reported.

JAK isoform Selectivity

Structurally, JAKs are composed of seven homologous regions JH1-7. JH5-7 are critical for the association of the JAKs with their cognate receptors while JH1 kinase is the active

catalytic domain and the main target for JAKi. Because the JH1 domains of the JAK isoforms exhibit a high degree of homology, JAKi are **selective** but not specific.

JAKi selectivity is assessed by in vitro assay of cytokine release and/or pSTAT activation. It is important to note that results from these assays depend on assay substrates/cell lines and cytokines measured. Furthermore, JAK1, JAK2 and TYK2 are ubiquitously expressed but JAK3 is predominantly expressed by hematopoietic cells and is highly regulated with cell development and activation.

JAK isoform selectivity is dose dependent

Table 4 showed the IC50 (concentration needed to inhibit 50% of activation) of different JAKi. Low IC50 value implies higher potency. JAK isoform selectivity is determined by ratio and difference between IC50s for different JAK isoforms. Table 4 showed not IC50 but also the ratio of IC50s. One may consider the ratio as the **“JAK selectivity dose window”**.

Conventional pharmacology will select compound with high potency. However, in the case of JAKi, potency affects JAK selectivity dose window. Highly potent compound will have narrow windows whilst low potency compound will have larger selectivity window.

Therefore, the clinical impact of JAK isoform selectivity is therefore dependent on dose, cell type, tissue penetration and genetics of the individual patient. This is probably best illustrated by the change in Hb in tofacitinib 5mg-treated patients with less Hb increase in the 10mg group.

JAK isoforms as therapeutic targets in RA

Since JAK isoforms are important in the signal transduction of multiple cytokines, different JAKi might inhibit different cytokines, which could be important in tailoring treatment to

patients. All current JAKi approved and in development have significant effect on JAK1. Even for the “JAK3 selective decernotinib”, the ratio between JAK3 and JAK1 inhibition is only 0.6. JAK1 is involved in the signalling transduction of IL-6, interferon and the common gamma-chain cytokines including IL-2 and IL-15. Amongst these, IL-6 is a proven therapeutic target in RA. Some of the side effects associated with IL-6 inhibition such as increase in liver transaminases and lipids, neutropenia as well as gastrointestinal perforation are also associated with JAKi suggesting inhibiting IL-6 is a significant mode of action. However, JAKi differ from IL-6 inhibitors in that CRP whilst reduced did not normalise suggesting that inhibition of IL-6 activity is incomplete⁴⁵. A phase II RCT with very small patient number suggested that anti-interferon- γ may be effective in RA⁵⁶. Whether interferon suppression is an important contributor to the therapeutic benefit of JAK1 inhibitors is unclear. However, interferon- γ is important in anti-viral immunity which is a potential explanation for herpes zoster reactivation. Nevertheless, current evidence suggests that JAK1 is an important therapeutic target in RA.

Whether JAK2 is a good therapeutic target in RA is less clear. Pro-inflammatory cytokines such as GM-CSF signals via JAK2. A phase II RCT of anti-GM-CSF α monoclonal antibody showed benefit in RA⁵⁷. A head to head trial suggested of anti-GM-CSF α monoclonal antibody was as efficacious as TNF inhibitor⁵⁸. Therefore, inhibiting both JAK1 and JAK2 may produce greater anti-inflammatory effect by inhibiting GM-CSF. The disadvantage of inhibiting JAK2 is potential side effects associated with inhibiting haematopoietic cytokines including erythropoietin, IL-3 and IL-5 and hormones such as prolactin and growth hormone. The clinical significance of long-term JAK2 inhibition remains unknown. It will be prudent to investigate whether JAK2 inhibition leads to increase in platelet count and the rare cases of

DVT/PE. In vitro experiment has shown that JAK2 is involved in platelet activation. JAK2 inhibitor attenuated collagen-induced platelet aggregation in a dose-dependent manner⁵⁹, so an association between thrombosis and JAK2 via effect on platelet seems counterintuitive. Aside from the hitherto unknown effect of JAK2 inhibition and thrombosis, small molecule inhibitors, unlike mAbs, are more likely to have off-target side effects that may not be associated with JAK inhibition but are compound-specific.

Based on available data, it is unclear whether JAK3 and TYK2 are desirable therapeutic targets in RA.

Conclusion

JAK isoform selectivity of JAKi is relative and not absolute. It is dose and tissue dependent. Current approved JAKi and those in development significantly inhibit JAK1, which is an effective therapeutic target in RA, although herpes zoster reactivation is probably a class effect of JAK1 inhibitors. The balance of benefit and risk of inhibiting JAK2, JAK3 and TYK2 is uncertain and should be evaluated in the future. The exact role of JAKi in the treatment pathway of RA should be further assessed by head-to-head and strategy trials. The manufacturing cost of JAKi is substantially less than biologics. With the potential of generic JAKi in the future, wider access to more effective treatment for RA is becoming tangible.

Conflict of Interest: has received research grants and/or served as member of advisory boards and speaker bureaus of Abbvie, Allergan, Amgen, AstraZeneca, Bio-Cancer, Biogen, BMS, Boehringer Ingelheim, Celgene, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring

Pharmaceutical, GSK, Hospira, ISIS, Jazz Pharmaceuticals, Janssen, MedImmune, Merrimack
Pharmaceutical, MSD, Napp, Novimmune, Novartis, ObsEva, Pfizer, Regeneron, Roche, R-
Pharm, Sanofi, SynAct Pharma, Synovate, Tonix and UCB.

Table 1: ACR responses at Primary Endpoints in Tofacitinib and Baricitinib RCTs

| | Controls | | | JAKi | | | Active comparator | | |
|--|------------------------------|------------------------------|------------------------------|-------|-------|-------|-------------------|-------|-------|
| | ACR20 | ACR50 | ACR70 | ACR20 | ACR50 | ACR70 | ACR20 | ACR50 | ACR70 |
| MTX IR | | | | | | | | | |
| Oral-Standard ¹¹ Tofacitinib (5mg bid) | 26 | 7 | 2 | 61 | 34 | 12 | 56 | 24 | 9 |
| Oral-Standard ¹¹ Tofacitinib (10mg bid) | | | | 59 | 28 | 15 | | | |
| RA Beam ¹² Baricitinib (4mg qd) | 40 | 17 | 5 | 70 | 45 | 19 | 61 | 35 | 13 |
| cDMARD-IR | | | | | | | | | |
| Oral-Sync ¹³ Tofacitinib (5mg bid) | 27 | 10 | 2 | 56 | 27 | 8 | | | |
| Oral-Sync ¹³ Tofacitinib (10mg bid) | | | | 65 | 34 | 14 | | | |
| RA-Build ¹⁴ Baricitinib (2mg qd) | 39 | 13 | 3 | 66 | 34 | 18 | | | |
| RA-Build ¹⁴ Baricitinib (4mg qd) | | | | 62 | 33 | 18 | | | |
| bDMARD-IR | | | | | | | | | |
| Oral-Step ¹⁵ Tofacitinib (5mg bid) | 24 | 8 | 2 | 42 | 27 | 14 | | | |
| Oral-Step ¹⁵ Tofacitinib (10mg bid) | | | | 48 | 28 | 11 | | | |
| RA Beacon ¹⁶ Baricitinib (2mg qd) | 27 | 8 | 2 | 49 | 20 | 13 | | | |
| RA Beacon ¹⁶ Baricitinib (4mg qd) | | | | 55 | 28 | 11 | | | |
| MTX naive | | | | | | | | | |
| Oral Start ²⁰ Tofacitinib (5mg bid) | 51 (MTX as control) | 27 (MTX as control) | 12 (MTX as control) | 71 | 47 | 26 | | | |
| Oral Start ²⁰ Tofacitinib (10mg bid) | | | | 76 | 56 | 38 | | | |
| RA-Begin ¹⁸ Baricitinib (4mg | 62 (MTX as | 43 (MTX as control) | 21 (MTX as control) | 78 | 63 | 40 | | | |

| | | | | | | | | | |
|--|------------------------------|---------------------------|---------------------------|----|----|----|--|--|--|
| qd)+MTX | control) | | | | | | | | |
| Monotherapy | | | | | | | | | |
| Oral Solo ¹⁹ Tofacitinib (5mg bid) | 27 | 13 | 6 | 60 | 31 | 15 | | | |
| Oral Solo ¹⁹ Tofacitinib (10mg bid) | | | | 66 | 37 | 20 | | | |
| RA-Begin ¹⁸ Baricitinib (4mg qd) | 62 (MTX as control) | 43 (MTX as control) | 21 (MTX as control) | 77 | 60 | 42 | | | |

Legend: Numbers are percentage

Table 2: Results of Phase II RCT of JAKi in Development

| | | Controls | | | JAKi | | |
|---|------------|----------|-------|-------|-------|-------|-------|
| | | ACR20 | ACR50 | ACR70 | ACR20 | ACR50 | ACR70 |
| JAK1 Selective | | | | | | | |
| Filgotinib DARWIN 1 ²⁴ (+ MTX) | 50mg qd | 44 | 15 | 8 | 56 | 33 | 16 |
| | 100mg qd | | | | 64 | 38 | 21 |
| | 200mg qd | | | | 69 | 43 | 24 |
| Filgotinib DARWIN 2 ²⁵ (Monotherapy) | 50mg qd | 29 | 11 | 4 | 67 | 35 | 8 |
| | 100mg qd | | | | 67 | 36 | 19 |
| | 200mg qd | | | | 72 | 43 | 13 |
| Upadacitinib BALANCE 2 ²³ (MTX-IR) | 6mg bid | 46 | 18 | 6 | 68 | 46 | 28 |
| | 12mg bid | | | | 80 | 50 | 16 |
| | 18mg bid | | | | 64 | 40 | 26 |
| Upadacitinib BALANCE 1 ²² (TNF-IR) | 6mg bid | | | | 58 | 36 | 26 |
| | 12mg bid | | | | 71 | 42 | 22 |
| | 18mg bid | | | | 67 | 38 | 22 |
| Moderate JAK3 Selective | | | | | | | |
| Dercernotinib ²⁹ | 100md qd | 18 | 7 | 3 | 47 | 23 | 10 |
| | 150mg qd | | | | 67 | 39 | 11 |
| | 200mg qd | | | | 57 | 35 | 10 |
| | 100mg bid | | | | 68 | 39 | 22 |
| Dercernotinib Monotherapy ²⁸ | 25mg bid | 29 | 7 | 2 | 39 | 17 | 7 |
| | 50 mg bid | | | | 61 | 32 | 12 |
| | 100 mg bid | | | | 65 | 38 | 18 |
| | 150 mg bid | | | | 66 | 49 | 22 |
| Peficitinib ²⁷ | 25mg qd | 44 | 26 | 11 | 44 | 18 | 9 |
| | 50 mg qd | | | | 62 | 33 | 15 |
| | 100 mg qd | | | | 46 | 33 | 17 |
| | 150 mg qd | | | | 57 | 37 | 19 |
| Peficitinib ²⁶ | 25mg qd | 29 | 10 | 8 | 22 | 15 | 7 |
| | 50 mg qd | | | | 37 | 25 | 16 |
| | 100 mg qd | | | | 48 | 28 | 19 |
| | 150 mg qd | | | | 56 | 28 | 11 |

Legend: Numbers are percentage. bid: bis in die (twice per day) qd: quaque die (once per day)

Table 3: Safety of Tofacitinib and Baricitinib: Incidence Rate per 100 patient years (95% confidence intervals)

| | Tofacitinib (JAK, JAK3) | Baricitinib (JAK1, JAK2) | Peficitinib (JAK1, JAK2) | Fligotinib (JAK1) | Upadacitinib (JAK1) | Decernotinib (JAK3) |
|--|---|----------------------------------|-----------------------------|--|---------------------------|------------------------|
| Serious Infection | 2.7 (2.5-3.9) | 2.9 (2.5-3.4) | | | | |
| Herpes Zoster | 3-4 | | | | | |
| Malignancies | 0.9(0.8-1) | 0.8 (0.6-1.0) | | | | |
| Lymphoma | 0.1 (0.1-0.2) | 0.09(0.03-0.19) | | | | |
| Non-melanoma skin cancer | 0.6 (0.5-0.7) | 0.4 (0.2-0.5) | | | | |
| Gastrointestinal perforation | 0.11 (0.07-0.17) | 0.05(0.01-0.13) | | | | |
| DVT/PE | | 0.5 (0.3-0.7) | | | | |
| Changes in Laboratory Tests (mean ± SD) | | | | | | |
| Haemoglobin (g/dl) | +0.47±0.05 (5mg) +0.28±0.05 (10mg) | -0.17 | Decrease | Increase | Decreases at higher doses | Increase |
| Neutrophil (x10³/mm³) | -1.09±0.1 (5mg) -1.49±0.1 (10mg) | -1.08 ±0.07 | Decrease | Decrease | Decrease | Decrease in high dose |
| Lymphocyte count (x10³/mm³) | -0.24±0.03 (5mg) -0.36±0.03 (10mg) | -0.01 (2mg) -0.05 (4mg) | Decrease | No change Some patients developed lymphopenia | Decrease | Decrease |
| Platelets | -30% | Increase | Decrease | Decrease | NR | NR |
| Liver transaminase | Increase up | Increase | Increase in high dose group | Increase | Increase | Increase |
| Cholesterol | Increase | Increase | Increase | Increase | Increase | Increase |
| Creatinine | Increase | Increase) | Increase | Increase | Increase | Increase |
| Creatinine Phosphokinase | Increase | Increase | Increase | NR | Increase | Increase |

Legend: Safety data are incidence rate per 100 patient years with 95% confidence intervals. Laboratory results are mean ± SD unless stated otherwise. NR: Not reported

Table 4: In vitro JAK isoform selectivity

| Compound | Enzyme assay IC ₅₀ (nM) | | | | JAK2:JAK1 | JAK3:JAK1 | TyK2:JAK1 |
|---------------------|------------------------------------|------|---------|---------|-----------|-----------|-----------|
| | JAK1 | JAK2 | JAK3 | TyK2 | | | |
| Tofacitinib | 15.1 | 77.4 | 55.0 | 489 | 5.1 | 3.6 | 32.4 |
| Baricitinib | 4.0 | 6.6 | 787 | 61 | 1.5 | 196.8 | 15.3 |
| Filgotinib | 363 | 2400 | >10,000 | 2,600 | 6.6 | >27.5 | 7.2 |
| Upadacitinib | 8 | 600 | 139 | NA | 75 | 17.4 | NA |
| Peficitinib | 3.9 | 5.0 | 0.7 | 4.8 | 1.3 | 0.2 | 1.2 |
| Decernotinib | 112 | 619 | 74.4 | >10,000 | 5.5 | 0.67 | >89 |

Legend: JAK: Janus kinase, IC₅₀: half maximal inhibitory concentration, TyK: Non-receptor Tyrosine-protein Kinase

Figure 1: Cytokine signalling via JAK isoforms and their inhibitors

Legend to Figure 1: IL: interleukin, JAK: janus kinase, p: phosphate

References

- ¹ Yamaoka K, Saharinen P, Pesu M, Holt VE, 3rd, Silvennoinen O, O'Shea JJ. The Janus kinases (Jaks). *Genome Biol.* 2004;5(12):253.
- ² Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology (Oxford).* 2010 Jan;49(1):15-24.
- ³ Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. *J Cell Sci.* 2004 Mar 15;117(Pt 8):1281-3.
- ⁴ Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects. *Drugs.* 2017 Apr;77(5):521-546.
- ⁵ Rodig SJ, Meraz MA, White JM, et al. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell.* 1998;93(3):373-83.
- ⁶ Parganas E, Wang D, Stravopodis D, et al. Jak2 is essential for signaling through a variety of cytokine receptors. *Cell.* 1998 May 1;93(3):385-95.
- ⁷ Thomis DC, Gurniak CB, Tivol E, Sharpe AH, Berg LJ. Defects in B lymphocyte maturation and T lymphocyte activation in mice lacking Jak3. *Science.* 1995 Nov 3;270(5237):794-7.
- ⁸ Macchi P, Villa A, Giliani S, et al. Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID). *Nature.* 1995;377(6544):65-8.
- ⁹ Russell SM, Tayebi N, Nakajima H, et al. Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. *Science.* 1995;270(5237):797-800
- ¹⁰ Karaghiosoff M, Neubauer H, Lassnig C, Kovarik P, Schindler H, Pircher H, McCoy B, Bogdan C, Decker T, Brem G, Pfeffer K, Müller M. Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity.* 2000 Oct;13(4):549-60.
- ¹¹ van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med.* 2012 Aug 9;367(6):508-19.
- ¹² Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med.* 2017 Feb 16;376(7):652-662.
- ¹³ Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253-61.
- ¹⁴ Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis.* 2017 Jan;76(1):88-95.
- ¹⁵ Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Soma K, Bradley J, Mebus C; Oral-Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet.* 2013 Feb 9;381(9865):451-60.
- ¹⁶ Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243-52.
- ¹⁷ van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, Cardiel MH, Cohen S, Nash P, Song YW, Tegzová D, Wyman BT, Gruben D, Benda B, Wallenstein G, Krishnaswami S, Zwillich SH, Bradley JD, Connell CA; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum.* 2013 Mar;65(3):559-70.
- ¹⁸ Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, Gurbuz S, Dickson C, de Bono S, Schlichting D, Beattie S, Kuo WL, Rooney T, Macias W, Takeuchi T. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. *Arthritis Rheumatol.* 2017 Mar;69(3):506-51
- ¹⁹ Fleischmann R1, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, Wallenstein GV, Zwillich SH, Kanik KS; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012 Aug 9;367(6):495-507.

-
- ²⁰ Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, Koncz T, Krishnaswami S, Wallenstein GV, Zang C, Zwillich SH, van Vollenhoven RF; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014 Jun 19;370(25):2377-86.
- ²¹ Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, DeMasi R, Soma K, Zhang R, Takiya L, Tatulych S, Mojcik C, Krishnaswami S, Menon S, Smolen JS; ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet*. 2017 Jul 29;390(10093):457-468.
- ²² Kremer JM, Emery P, Camp HS, Friedman A, Wang L, Othman AA, Khan N, Pangan AL, Jungerwirth S, Keystone EC. A Phase IIb Study of ABT-494, a Selective JAK-1 Inhibitor, in Patients With Rheumatoid Arthritis and an Inadequate Response to Anti-Tumor Necrosis Factor Therapy. *Arthritis Rheumatol*. 2016 Dec;68(12):2867-2877.
- ²³ Genovese MC, Smolen JS, Weinblatt ME, Burmester GR, Meerwein S, Camp HS, Wang L, Othman AA, Khan N, Pangan AL, Jungerwirth S. Efficacy and Safety of ABT-494, a Selective JAK-1 Inhibitor, in a Phase IIb Study in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate. *Arthritis Rheumatol*. 2016 Dec;68(12):2857-2866
- ²⁴ Westhovens R, Taylor PC, Alten R, Pavlova D, Enríquez-Sosa F, Mazur M, Greenwald M, Van der Aa A, Vanhoutte F, Tasset C, Harrison P. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). *Ann Rheum Dis*. 2017 Jun;76(6):998-1008.
- ²⁵ Kavanaugh A, Kremer J, Ponce L, Cseuz R, Reshetko OV, Stanislavchuk M, Greenwald M, Van der Aa A, Vanhoutte F, Tasset C, Harrison P. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis*. 2017 Jun;76(6):1009-1019.
- ²⁶ Genovese MC, Greenwald M, Codding C, Zubrzycka-Sienkiewicz A, Kivitz AJ, Wang A, Shay K, Wang X, Garg JP, Cardiel MH. Peficitinib, a JAK Inhibitor, in Combination With Limited Conventional Synthetic Disease-Modifying Antirheumatic Drugs in the Treatment of Moderate-to-Severe Rheumatoid Arthritis. *Arthritis Rheumatol*. 2017 May;69(5):932-942
- ²⁷ Kivitz AJ, Gutierrez-Ureña SR, Poiley J, Genovese MC, Kristy R, Shay K, Wang X, Garg JP, Zubrzycka-Sienkiewicz A. Peficitinib, a JAK Inhibitor, in the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients With an Inadequate Response to Methotrexate. *Arthritis Rheumatol*. 2017 Apr;69(4):709-719.
- ²⁸ Fleischmann RM, Damjanov NS, Kivitz AJ, Legedza A, Hooek T, Kinnman N. A randomized, double-blind, placebo-controlled, twelve-week, dose-ranging study of decernotinib, an oral selective JAK-3 inhibitor, as monotherapy in patients with active rheumatoid arthritis. *Arthritis Rheumatol*. 2015 Feb;67(2):334-43.
- ²⁹ Genovese MC, van Vollenhoven RF, Pacheco-Tena C, Zhang Y, Kinnman N. VX-509 (Decernotinib), an Oral Selective JAK-3 Inhibitor, in Combination With Methotrexate in Patients With Rheumatoid Arthritis. *Arthritis Rheumatol*. 2016 Jan;68(1):46-55.
- ³⁰ Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018; 391: 2503–12.
- ³¹ Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018; 391: 2513–24.
- ³² Cohen S, Curtis JR, DeMasi R, et al. Worldwide, 3-Year, Post-Marketing Surveillance Experience with Tofacitinib in Rheumatoid Arthritis. *Rheumatol Ther* 2018;5:283–291.
- ³³ Codreanu C and Damjanov N. Safety of biologics in rheumatoid arthritis: data from randomized controlled trials and registries. *Biologics: Targets and Therapy* 2015;9 1–6.
- ³⁴ Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, Winthrop KL, Charles-Schoeman C, Thirunavukkarasu K, DeMasi R, Geier J, Kwok K, Wang L, Riese R, Wollenhaupt J. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis*. 2017 Jul;76(7):1253-1262.
- ³⁵ Genovese MC, Smolen JS, Takeuchi T, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 5.5 years: an updated integrated safety analysis. Presented at the ACR/ARHP Annual Meeting, San Diego, CA, USA, 3–8 November 2017; Abstr. 511.

-
- ³⁶ Winthrop KL, Curtis JR, Lindsey S et al. Herpes Zoster and Tofacitinib. Clinical Outcomes and the Risk of Concomitant Therapy. *Arthritis Rheumatol.* 2017; 69: 1960–1968.
- ³⁷ Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, Biswas P, Needle E, Passador S, Mojcik CF, Rigby WF. The Safety and Immunogenicity of Live Zoster Vaccination in Patients With Rheumatoid Arthritis Before Starting Tofacitinib: A Randomized Phase II Trial. *Arthritis Rheumatol.* 2017 Oct;69(10):1969-1977.
- ³⁸ Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, Aringer M, Meißner Y, Zink A, Listing J. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis.* 2017 Mar;76(3):504-510.
- ³⁹ Xie F, Yun H, Bernatsky S, Curtis JR. Brief Report: Risk of Gastrointestinal Perforation Among Rheumatoid Arthritis Patients Receiving Tofacitinib, Tocilizumab, or Other Biologic Treatments. *Arthritis Rheumatol.* 2016 Nov;68(11):2612-2617.
- ⁴⁰ Weinblatt M, Taylor PC, Burmester G, et al. Cardiovascular safety during treatment with baricitinib in patients with rheumatoid arthritis. Presented at the ACR/ARHP Annual Meeting, San Diego, California, USA, 3–8 November 2017; Abstr. 499.
- ⁴¹ Doyle MK, Rahman MU, Han C, Han J, Giles J, Bingham CO 3rd, Bathon J. Treatment with infliximab plus methotrexate improves anemia in patients with rheumatoid arthritis independent of improvement in other clinical outcome measures—a pooled analysis from three large, multicenter, double-blind, randomized clinical trials. *Semin Arthritis Rheum.* 2009 Oct;39(2):123-31.
- ⁴² Paul SK, Montvida O, Best JH, Gale S, Pethoe-Schramm A, Sarsour K. Effectiveness of biologic and non-biologic antirheumatic drugs on anaemia markers in 153,788 patients with rheumatoid arthritis: New evidence from real-world data. *Semin Arthritis Rheum.* 2018 Feb;47(4):478-484.
- ⁴³ Kurt D, Wojchowski DM. Emerging EPO and EPO receptor regulators and signal transducers. *Blood* 2015;125(23):3536–41.
- ⁴⁴ Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis: an integrated analysis. Presented at European League Against Rheumatism (EULAR), London, UK, 8–11 June 2016; Poster THU0166.
- ⁴⁵ Schulze-Koops H, Strand V, Nduaka C, DeMasi R, Wallenstein G, Kwok K, Wang L. Analysis of haematological changes in tofacitinib-treated patients with rheumatoid arthritis across phase 3 and long-term extension studies. *Rheumatology (Oxford).* 2017 Jan;56(1):46-57.
- ⁴⁶ Tofacitinib. Summary of Product Characteristics. European Medicine Agency. 2017.
- ⁴⁷ Baricitinib. Summary of Product Characteristics. European Medicine Agency. 2017.
- ⁴⁸ Kremer JM, Checn L, Saifan CG, et al. Analysis of neutrophils, lymphocytes, and platelets in pooled phase 2 and phase 3 studies of baricitinib for rheumatoid arthritis. Presented at European League Against Rheumatism (EULAR), Madrid, Spain, 14–17 June 2017b; poster 1325.
- ⁴⁹ Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, Boy M, Geier J, Luo Z, Zuckerman A, Riese R. Effects of tofacitinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. *Semin Arthritis Rheum.* 2016 Aug;46(1):71-80.
- ⁵⁰ McInnes IB, Kremer J, Emery P, Zuckerman SH, Ruotolo G, Saifan C, Chen L, Thanabalasundrum S, Witt S, Macias W. Lipid Profile and Effect of Statin Treatment in Pooled Phase 2 and Phase 3 Baricitinib Studies. 2016 ACR/ARHP Annual Meeting abstract no 3023.
- ⁵¹ Charles-Schoeman C, Wicker P, Gonzalez-Gay MA, Boy M, Zuckerman A, Soma K, Geier J, Kwok K, Riese R. Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor. *Semin Arthritis Rheum.* 2016 Dec;46(3):261-271
- ⁵² Charles-Schoeman C, Fleischmann R, Davignon J, Schwartz H, Turner SM, Beysen C, Milad M, Hellerstein MK, Luo Z, Kaplan IV, Riese R, Zuckerman A, McInnes IB. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol.* 2015 Mar;67(3):616-25.
- ⁵³ Fleischmann R, Wollenhaupt J, Takiya L, Maniccia A, Kwok K, Wang L, van Vollenhoven RF. Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies. *RMD Open.* 2017 Dec 18;3(2):e000491.
- ⁵⁴ Isaacs JD, Zuckerman A, Krishnaswami S, Nduaka C, Lan S, Hutmacher MM, Boy MG, Kowalski K, Menon S, Riese R. Changes in serum creatinine in patients with active rheumatoid arthritis treated with tofacitinib: results from clinical trials. *Arthritis Res Ther.* 2014 Jul 25;16(4):R158.

-
- ⁵⁵ Keystone EC, Taylor PC, Drescher E, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis.* 2015 Feb; 74(2): 333–340.
- ⁵⁶ Sigidin YA, Loukina GV, Skurkovich B, Skurkovich S. Randomized, double-blind trial of anti-interferon-gamma antibodies in rheumatoid arthritis. *Scand J Rheumatol.* 2001;30(4):203-7.
- ⁵⁷ Burmester GR, McInnes IB, Kremer J, et al. A randomised phase IIb study of mavrimumab, a novel GM-CSF receptor alpha monoclonal antibody, in the treatment of rheumatoid arthritis. *Ann Rheum Dis.* 2017 Jun;76(6):1020-1030.
- ⁵⁸ Weinblatt ME, McInnes IB, Kremer JM, Miranda P, Vencovsky J, Guo X, White WI, Ryan PC, Godwood A, Albulescu M, Close D, Burmester GR. A Randomized Phase IIb Study of Mavrimumab and Golimumab in Rheumatoid Arthritis. *Arthritis Rheumatol.* 2018 Jan;70(1):49-59.
- ⁵⁹ Lu WJ, Lin KC, Huang SY, Thomas PA, Wu YH, Wu HC, Lin KH, Sheu JR. Role of a Janus kinase 2-dependent signaling pathway in platelet activation. *Thromb Res.* 2014 Jun;133(6):1088-96.