

Title: Filgotinib for the treatment of rheumatoid arthritis

Abstract

Introduction

Biologics were the first targeted therapies for rheumatoid arthritis (RA), having in common high clinical efficacy. Being proteins, they are administered parenterally. The first oral targeted small molecules to be approved for RA are competitive inhibitors of the Janus kinase (JAK) enzyme family which mediate signalling for a cytokine subset important in RA pathogenesis.

Areas covered

Several JAK inhibitors have been developed with differing selectivity for the four JAK enzymes with a view to generating oral, multi-cytokine inhibitors. Here we review the pharmacology and clinical trial data for efficacy and safety of filgotinib, an investigational selective JAK1 inhibitor. We contextualise the contemporary approach to RA management and substantial unmet needs that remain.

Expert opinion

The selectivity of filgotinib for JAK1 may have theoretical advantages in terms of limiting toxicity. However, it will be difficult to establish whether this is so before larger numbers of patients are exposed in phase III and beyond in the real world setting. Filgotinib clinical trial

data to date has been encouraging with rapid, sustained efficacy with promising safety and tolerability. It is likely that we will see an expanding choice of approved JAK inhibitors in the clinic but it may not be straightforward to distinguish safety and efficacy differences.

Keywords filgotinib, janus kinase, rheumatoid arthritis, small molecule, treatment.

List of Abbreviations

ACR20	American College of Rheumatology response criteria
ATP	adenosine triphosphate
bDMARDs	biological disease-modifying anti-rheumatic drugs
CDAI	Clinical Disease Activity Index
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
DAS28CRP	Disease Activity Scores based on 28 joints and C-reactive protein value
HAQ-DI	Health Assessment Questionnaire-Disability Index
IL-1	Interleukin-1
JAK	Janus kinase
Jakinibs	JAK inhibitors
JH1	Janus homolog
MTX	methotrexate
RA	Rheumatoid arthritis
SDAI	Simplified Disease Activity Index
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event
TNF	Tumour necrosis factor

1. Introduction and background

Rheumatoid arthritis (RA) is a systemic inflammatory condition with synovitis as its major manifestation leading to progressive joint damage associated with severe disability, morbidity, multisystem involvement and increased mortality. The prevalence of RA is relatively consistent in most populations at 0.5–1.0%. It is more common in women than men and occurs in a wide age range although the incidence generally peaks in late middle years. The aetiology of RA remains poorly understood although it is a polygenic disorder in which gene-environment interactions play a role, one of the best described being smoking [1]. However, there have been significant advances in understanding RA pathology over the last generation and the role of a several key pro-inflammatory cytokines, such as TNF and IL-6, and cell associated targets, such as CD20 and co-stimulation molecules CD80/86, have been validated by the advent of targeted biologic therapies [2].

Contemporary RA treatment recommendations [3,4] emphasise the importance of early therapeutic intervention and treat-to-target strategies in which treatment adjustment is determined by measurement of therapeutic response with the target of remission or low disease activity [5]. Current practice is to initiate treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX) and a short period of glucocorticoids, followed in poor prognosis, refractory patients by parenterally administered biological DMARDs (bDMARDs). However, once RA becomes established, remission is only achieved by a minority of bDMARD treated patients. And even then, troublesome symptoms may remain including pain, fatigue and morning joint stiffness [6]. Furthermore, primary and secondary loss of response to existing therapies, as well as drug discontinuations due to intolerance or adverse effects, means that significant unmet needs remain for alternative therapies.

While biologic originators and biosimilars are in routine clinical use in RA, not all patients respond adequately and there is the risk of immunosuppression and corresponding infectious complications. Therefore, improvements to current treatments remain necessary with a goal of restoring immune homeostasis, more complete symptom resolution and avoidance of the risks of immune suppression [2].

Low molecular weight, orally available, “small-molecules” which target and inhibit components of the inflammatory signalling cascade have been lately considered as an important alternative to biologic therapies for RA, and several have been developed and tested in clinical trials. Most successful among these to date have been inhibitors of the Janus kinase (JAK) enzymes. The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. JAKs work in pairs to signal through binding to a specific group of so-called Type I and Type II cytokine receptors, which are structurally distinct from other receptors such as those that bind TNF and IL-1. Cytokine-receptor binding leads to receptor oligomerization, which allows the intracellular kinase and JAK binding Janus Homolog (JH1) kinase domains of the receptors to move apart, and permit the activation and autophosphorylation of the different cytoplasmic receptor associated JAK pairs. Different cytokines utilise particular JAK pairings. Because JAKs are phosphotransferases, they catalyse phosphorylation of the receptor, which allows recruitment and tyrosine phosphorylation of members of the signal transducer and activator of transcription (STAT) family of DNA binding proteins. Finally, phosphorylated STAT dimers translocate to the nucleus and regulate the transcription of target genes [7,8].

A number of studies have demonstrated expression of different JAK isoforms and the downstream STAT proteins in synovial tissue and synovial cells [9-11]. Signal transmission of many proinflammatory cytokines involved in RA pathogenesis is dependent on JAK1, notably IL-6. Therefore, several JAK inhibitors (Jakinibs) with variable degrees of selectivity

and specificity for the JAK enzymes have been investigated in inflammatory arthritis. It has been argued that a more selective JAK1 inhibitor might reduce dose-limiting toxicity, even though inhibition of JAK2 and JAK3 might contribute to efficacy [12]. For example, the γ -chain cytokines signal through JAK1,3 heterodimers and erythropoietin and thrombopoietin signal through JAK2 homodimers, as does granulocyte-macrophage colony-stimulating factor (GM-CSF). However, to establish actual safety and benefit in vivo, careful scrutiny of clinical trial and real-world data for efficacy and risk will be necessary for each Jakinib tested. Jakinibs act as competitive inhibitors of the active adenosine triphosphate (ATP) JH1 domain, a structure well conserved among JAKs, making specificity of the new inhibitors more challenging [13,14]. However, new higher resolution crystal structures of the four JAK members, and studies aiming to target specific amino acid interactions within the ATP binding domain allowed the generation of more specific inhibitors [15].

2 Overview of the market

To date, two JAK inhibitors, tofacitinib and baricitinib, have been approved for treatment of RA in certain regions. Tofacitinib, a selective oral JAK1,3 inhibitor with less activity against JAK2 and TYK2 [15], has undergone extensive clinical trials of twice daily dosing in RA [16-21]. It is approved for clinical use in over 80 countries. Tofacitinib is well tolerated, and only the increased risk of viral infections such as herpes zoster seems to distinguish the safety profile of this inhibitor from that of bDMARDS [13]. Baricitinib is a novel, potent and selective oral JAK1,2 inhibitor with moderate activity against TYK2 and significantly less activity against JAK3 [22] that was generated by modifying the structure of tofacitinib. This was achieved by replacing the portion of the molecule which showed JAK1/JAK3 selectivity with a different chemical moiety, resulting in a new structure which exhibited specificity for

JAK1 and JAK2 over JAK 3 in kinase assays [15]. With IC₅₀ values in the nM range, baricitinib was recently approved in Europe for the treatment of RA. Baricitinib is well tolerated and has also been tested in a large phase III programme of once daily dosing [23-26]. Both tofacitinib and baricitinib have demonstrated significant clinical improvements, limitation of structural damage and preservation of function in active RA patients.

A number of other investigational oral Jakinibs with varying selectivity for the four JAK enzymes have been evaluated in phase 2 trials in patients with RA [14]. These include filgotinib and upadacitinib (ABT-494) which have greatest affinity for JAK1; peficitinib, a pan JAK inhibitor with only mild inhibition of JAK2; and decernotinib [27], which is highly selective for JAK3. All of these investigational JAK inhibitors were found to be superior to placebo for improvement of symptoms and signs of RA [28-33]. Safety concerns were raised with respect to decernotinib and the manufacturer, Vertex, decided not to proceed with development of this drug for RA.

3. Introduction to filgotinib

Filgotinib, the first selective JAK 1 inhibitor, was developed by Galapagos by screening a BioFocus kinase-focused library collection against the kinase domain of JAK1 in an *in vitro* biochemical assay. All compounds having a percentage inhibition above 75% were further evaluated in dose response tests with measurement of IC₅₀ values, and the best hit was a compound with a triazolopyridine core structure (Figure 1A). A series of modifications to this compound [15,34] led to the discovery of filgotinib (GLPG0634) (Figure 1C) as a JAK1-selective inhibitor (half maximal inhibitory concentration (IC₅₀): 629 nM or 267 ng/mL),

displaying a 30-fold selectivity for JAK1- over JAK2-dependent signalling in human whole blood [35].

Figure 1. Development of Filgotinib. A). Triazolopyridine core structure. B). Best hit compound. C. filgotinib (GLPG0634) structure. D) structure of active metabolite after dosing and loss of cyclopropyl carboxylic moiety.

3.1 Pharmacodynamics, pharmacokinetics and metabolism of filgotinib

Preclinical investigations in a collagen-induced arthritis model confirmed filgotinib to have an efficacy that was comparable to that of etanercept [35]. Filgotinib is metabolized to form an active metabolite. This is mediated by carboxylesterases and the loss of the cyclopropyl carboxylic acid group (figure 1D). The metabolite exhibits a similar JAK1 selectivity as the parent compound although it is about 10 times less potent than filgotinib [36].

The pharmacokinetic (PK) profile of filgotinib was evaluated in two early phase trials in healthy volunteers. In the first trial, filgotinib was administered as single doses from 10 mg up to multiple daily doses of 200 mg. In the second trial, daily doses of 300 and 450 mg for 10 days were evaluated. After filgotinib dosing, active metabolite concentrations peaked within 3–5 h and then slowly decreased with an apparent elimination half-life of about 23 h leading to up to 4-fold accumulation after twice-daily dosing. The time to peak and the decline in plasma levels of the metabolite are much longer than those of filgotinib, suggesting that metabolite elimination rather than the formation may be the rate-limiting step. As a result, exposure to the active metabolite exceeds that of filgotinib by a factor of 16–20 within

a dose range of 50- to 200-mg daily. These observations suggested that filgotinib has the potential to demonstrate clinical efficacy in both twice-daily and once-daily dosing regimens, a hypothesis that has subsequently been confirmed. The high exposure of active metabolite results in clinical exposures above whole blood IC_{50} values for inhibition of JAK1, despite its low potency, so that it contributes to the overall pharmacodynamic (PD) effects of filgotinib, resulting in a relatively long duration of JAK1 inhibition. However, after one week of treatment, the plasma levels of the metabolite are at steady state such that there is no further increase or accumulation in plasma and tissues. Available safety data on filgotinib cover much longer exposure than one week and therefore take into account the accumulation of the metabolite.

The overall PD activity for filgotinib and its active metabolite was assessed in whole blood using IL-6-induced phosphorylation of signal-transducer and activator of transcription 1 (STAT-1) as a biomarker for JAK1 activity. Non-linear mixed-effects modelling to investigate a PK/PD relationship suggested that a maximal PD effect would be achieved at a daily dosing of 200 mg of filgotinib. Therefore, this dose was selected as the highest to be tested in the phase IIB program in patients with RA [37,38].

In order to evaluate any genetic influence on drug metabolism and the potential for different dosing, PK and PD profiles of filgotinib and its main active metabolite were also assessed in the whole blood of Japanese and Caucasian healthy volunteers after repeated dosing of 200 mg filgotinib or placebo for 10 days. Filgotinib showed comparable PK, PD and safety profiles between both ethnic groups [39].

3.2 Clinical efficacy of filgotinib

In healthy volunteer studies, dose regimens of filgotinib up to 450mg/day were well tolerated with no effect on JAK2 signaling [40].

Clinical proof of concept for the efficacy and safety of filgotinib in patients with RA was initially investigated in a 4-week phase IIA trial reported in 2012 in which 36 patients with insufficient response to MTX received either filgotinib 100mg twice daily, 200mg once daily or placebo for 4 weeks [41]. Significant improvements in American College of Rheumatology response criteria (ACR20) and Disease Activity Scores based on 28 joints and C-reactive protein value (DAS28CRP), were observed compared to placebo for both doses of filgotinib. Subsequently, a second double-blind Phase IIA study compared filgotinib at 30, 75, 150 and 300 mg once-daily versus placebo in a total of 91 patients with insufficient response to MTX and naïve to bDMARDs. Filgotinib showed minimal clinical efficacy at the lower dose compared to daily doses of 75 to 300 mg, all of which demonstrated similar effects in terms of improvements in CRP and DAS28 [42]. The results achieved at 300 mg are similar to those with 200 mg QD in the prior proof of concept study (DAS28: -2.2, with 33% <3.2 at week 4). The high response rate observed in the second study in the placebo group (DAS28: -1.2, with 18% <3.2 at week 4) may have been related to a lower disease activity at baseline. Most adverse events (AEs) were mild and one serious AE was reported. No patient discontinued due to AEs. No anemia was observed but rather a dose related improvement in hemoglobin. There was a limited decrease in absolute neutrophil count, no neutropenia, and no impact on lymphocyte subsets. No consistent changes in LDL were observed. ALT/AST was stable with no elevations >1.5 times ULN.

The Phase IIB studies started in July 2013. The first study (DARWIN 1), evaluated efficacy and safety of different doses and regimens of filgotinib as add on therapy to MTX in patients with moderate to severe active RA who had inadequate response to MTX [28]. In this 24-

week study involving 594 patients on background MTX, subjects were randomised (1:1:1:1:1:1:1) to receive placebo or a total daily dose of 50 mg, 100 mg or 200 mg filgotinib, administered as either a once daily (QD) or twice daily (BD) regime. At the end of week 12, the ACR20 primary end point of the study was achieved, with response rates of 64 % at 100mg QD ($p=0.0435$), 69 % at 200mg QD ($p=0.0068$), and 79% at 100mg BD dose ($p<0.0001$), compared with 44 % in the placebo group (Table1). At week 12, a dose dependent statistically significant improvement was also reported in most of the secondary endpoints including ACR50, ACR-N, DAS28-CRP, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI)], compared with placebo. Responses were maintained through to week 24. For Health Assessment Questionnaire-Disability Index (HAQ-DI), significant improvements were noted as early as week 2 in the filgotinib 200mg QD group compared to placebo and by week 8, similar improvement were also observed in the filgotinib 100mg QD group. Furthermore, early onset of effect from week 1 onwards was observed as assessed by DAS28-CRP, at the 100mg and 200-mg daily dose groups. There was no significant difference in efficacy between QD and BD dosing regimens.

The second study (DARWIN 2) evaluated the efficacy and safety of 50, 100 or 200 mg filgotinib once daily as monotherapy versus placebo (after a ≥ 4 -week washout from MTX) in patients with active RA who had inadequate response to MTX [24] This was also a 24-week study, involving 283 patients. At week 12, significantly more patients receiving filgotinib at any dose achieved the primary endpoint of ACR20 responses versus placebo; 67% of the 50mg QD dose, 66 % of the 100mg QD dose, and 73 % of the 200-mg QD dose, compared with 31 % of placebo group ($p < 0.001$). (Table 1). Similarly, at week 12 statistical significance verses placebo was reported for all filgotinib dose groups for different composite measures of disease remission or response to treatment, including ACR-N, DAS28-CRP,

SDAI and European League Against Rheumatism (EULAR) ‘good’ response. A fast kinetic of clinical response was observed with improvements in DAS28-CRP and CDAI at week 1 across all filgotinib treatment groups compared to placebo and improvements at week 2 in HAQ-DI measures. In terms of, higher doses of filgotinib were associated with greater reductions in disease activity and higher remission rates.

Table 1 Summary of results of phase II trials on the effects of filgotinib in treating patients with rheumatoid arthritis.

3.3 Safety and tolerability of filgotinib

JAK/STAT signalling is essential to host defence, including mediating responses to viruses and pathogens such as *mycobacterium tuberculosis* [13]. Furthermore, JAK signalling pathways are involved in mediating cellular homeostasis, including lymphocyte proliferation, erythropoiesis and platelet production [43]. JAK3 has a more restricted cellular expression (hematopoietic and epithelial cells) than that of other members of the JAK family. Mutations that abrogate JAK3 function result in severe combined immunodeficiency disease, therefore complete inhibition of JAK3 is not desirable. Similarly, complete blockade of erythropoietin signals through JAK2 and loss of its function would be expected to be deleterious. Selectivity for JAK1 might also minimise potential toxicities associated with inhibition of other JAK family members. However, while differing enzyme selectivity is attributed to the JAK inhibitors for which clinical data is currently available, there is significant overlap in terms of their safety profiles and to date, at a cohort level, there are no clearly distinguishing adverse events characterising any particular JAK selectivity.

Overall the safety profiles of JAK inhibitors are similar to those of biologic agents currently in use, with exception of few notable differences in relation to risk of infections, particularly to viral infections and changes in laboratory parameters [13]. A potential advantage of Jakinibs over that of bDMARDs with respect to infection risk is the relatively short half-life of JAK inhibitors; in the event of an infection, the drug can be stopped and the immunomodulatory effect is transient.

Most of the safety data available to date are from tofacitinib, with approximately 15,000 person-years of exposure from long term extension studies [13]. The most commonly observed adverse events with the use of tofacitinib include infections, elevations in cholesterol, transaminases and creatinine, as well as reduced neutrophil counts [44]. One of the most prominent infectious events observed with JAK inhibition is reactivation of varicella zoster virus (herpes zoster), especially with the use of tofacitinib (1.5-2 fold higher than expected for RA patients), with even higher rates reported in certain Asian populations compared with bDMARDs [45].

Limited safety and tolerability data are available for filgotinib from the two phase IIb studies. In DARWIN 1, all doses evaluated were tolerated and treatment-emergent adverse events (TEAEs) were similar across all doses and treatment regimens. Study drug related TEAEs were observed more frequently in the filgotinib groups (20.9%) compared with placebo (10.7%). Fifteen patients had ≥ 1 serious TEAE, with one death due to pneumonia and septic shock in the filgotinib 100mg BD group. Serious TE infections were observed in one patient in the placebo group and five patients in the filgotinib group. Treatment discontinuation rates were low, with one patient in placebo group and five patients receiving filgotinib withdrawing secondary to infection. Herpes zoster infections were observed in four patients receiving filgotinib and one patient in the placebo group [28]. (Table 2).

In DARWIN 2, all doses of filgotinib evaluated were tolerated and comparable numbers of patients had TEAEs in the placebo and filgotinib groups. Nine serious TEAEs were reported (seven in the treatment group and two in the placebo group), four of which were serious infections (pneumonia, cellulitis, gastroenteritis and pyelonephritis). There was only one case of herpes zoster infection in a patient receiving filgotinib 50mg QD [29]. (Table 2).

In both DARWIN studies, dose-dependent changes in laboratory parameters were observed, including decreases in mean neutrophil count and mild elevation in creatinine, both without clinical consequence. Initial decreases in platelet count were observed which plateaued at week 4 and remained stable thereafter. Increases were reported in mean haemoglobin level, consistent with the anti-inflammatory efficacy of filgotinib and absence of JAK2 inhibition. Furthermore, there were no reductions in counts of absolute lymphocytes or natural killer cells. Only minimal effects on liver enzymes were observed, even when filgotinib was co-administered with MTX. As with other JAK inhibitors and bDMARD inhibitors of the IL6 pathway, dose dependent elevation in both HDL and LDL cholesterol were observed in all filgotinib groups, however the LDL:HDL ratio was reduced.

No cases of tuberculosis or opportunistic infections, lymphoma or cancer was reported in either of the studies. In terms of risk for malignancies, experience with filgotinib is limited and long-term safety data will be needed to evaluate the true risk.

Table 2 Summary of treatment emergent adverse events reported in phase II clinical trials on filgotinib in treating patients with rheumatoid arthritis

Given that polypharmacy is commonplace for RA patients, possible drug-drug interactions of filgotinib with cytochrome P450 enzymes and with key drug transporters have been evaluated

in vitro and in clinical studies [46]. The potential for interaction of filgotinib with CYP3A4 was examined in an open-label study in healthy volunteers, with simultaneous evaluation of the impact of filgotinib on co-administered midazolam, a CYP3A4-sensitive substrate. Potential interactions with MTX were investigated in the proof of concept Phase IIA study in RA patients. Collectively, the *in vivo* and *in vitro* data on drug-metabolizing enzymes and key drug transporters, support co-administration of filgotinib with commonly used drugs for RA patients without the need for dose adjustments.

4. Conclusion

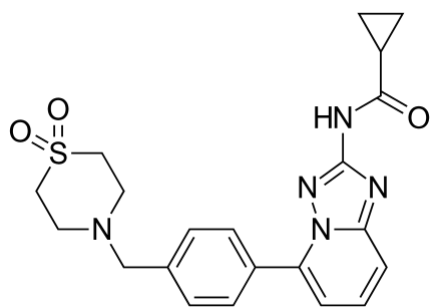
Filgotinib is being developed as a selective JAK1 inhibitor. It has an active metabolite with similar JAK1 selectivity but a relatively longer elimination half-life compared to the parent so that it contributes to the overall PD effects of filgotinib. To date, filgotinib has been tested in early phase IIA proof-of-concept and dose-ranging studies and subsequently in two phase IIB randomised, placebo-controlled trials in active RA refractory to methotrexate as an add on to methotrexate or as a monotherapy. Doses of 100-200mg QD or 50-100mg BD were efficacious for symptoms and signs with a rapid kinetic of onset and overall acceptable safety profile. Although infections were the most frequent adverse event, they were low in number and few were serious. Of note, there was no reduction in lymphocyte or NK cell counts and haemoglobin increased. Phase III studies in RA are ongoing.

5. Expert opinion

The selectivity of filgotinib for JAK1 may have theoretical advantages over broader JAK inhibition in terms of limiting toxicity although the heterodimeric pairing of JAK enzymes and the unique pharmacological profile of filgotinib makes toxicity difficult to predict. Although there may be some differences with respect to certain haematological parameters, it will not be possible to judge clinical safety relative to other JAK inhibitors until much larger numbers of patients are exposed to filgotinib and assessment of relative efficacy would require a head to head trial. Nonetheless, to date, filgotinib clinical trial data has been encouraging and within the efficacy range observed in other Jakinib studies. It is likely that we will see an expanding choice of approved JAK inhibitors in the clinic but it may not be straightforward to distinguish safety and efficacy differences. Perceived convenience of dosing schedule, with once daily often preferred, and cost effectiveness will have a marked influence on the potential future uptake of filgotinib. The latter will be all the more important as earlier generation Jakinibs come off patent. However, market competition within the Jak inhibitor class will encourage cost competitiveness and there will be close scrutiny of emerging real-world data for safety and sustained efficacy for currently approved and future drugs. It is anticipated that filgotinib will join other Jak inhibitors for clinical use in the management of RA within the next 5 years.

5.1 Drug summary box

Drug name (generic)	Filgotinib (GLPG0634 and GS-6034)
Phase (for indication under discussion)	Phase IIB trials in RA completed. Phase III trials ongoing
Indication (specific to discussion)	Rheumatoid arthritis discussed in this article. Also in development for Crohn's disease, ulcerative colitis, cutaneous lupus erythematosus, Sjogren's disease, ankylosing spondylitis and psoriatic arthritis
Pharmacology description/mechanism of action	Oral selective JAK1 inhibitor with active metabolite contributing to prolonged PD effects on inhibition of IL6-driven JAK STAT signalling.
Route of administration	Oral
Chemical structure	$C_{21}H_{23}N_5O_3S$



Pivotal trial(s)

Phase IIB DARWIN 1: Double blind, randomised placebo controlled trial of filgotinib plus MTX in moderate to severe, active RA MTX inadequate responders (MTX-IR).

1:1:1:1:1:1:1 randomisation to placebo or 50 mg QD, 100 mg QD, 200 mg QD, 25mgBD, 50mgBD or 100mg BD filgotinib. Primary endpoint ACR20 at 12 weeks.

Phase IIB DARWIN 2: Double blind, randomised placebo controlled trial of filgotinib monotherapy in moderate to severe, active RA MTX inadequate responders (MTX-IR).

1:1:1:1 randomisation to placebo, 50, 100 or 200 mg QD filgotinib. Primary endpoint ACR20 at 12 weeks.

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Key PhIII clinical trial describing efficacy of tofacitinib as a monotherapy in RA

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Key PhIII clinical trial designed to investigate disease modifying capability of tofacitinib. It missed its radiographic primary endpoint because the rate of structural damage progression in the comparator group was very low.

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Key PhIII trial comparing methotrexate plus tofacitinib at 5mg BD or 10mgBD with methotrexate plus placebo or methotrexate plus adalimumab. Trial was not designed to provide head-to-head comparative efficacy and should not be interpreted as evidence of superiority or noninferiority to adalimumab. The co-primary outcomes were met (%ACR20 month 6, Change HAQ-DI at month 6 and proportion DAS28ESR<2.6 at month 6).

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