EXTENDED REPORT

Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate

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ABSTRACT

Objectives To investigate baricitinib (LY3009104, formerly INCB028050), a novel, oral inhibitor of JAK1/ JAK2 in patients with moderate to severe rheumatoid arthritis (RA) despite treatment with methotrexate.

Methods In this phase IIb study, 301 patients were randomised 2:1:1:1:1 to receive once daily doses of placebo or 1, 2, 4 or 8 mg baricitinib for 12 weeks. Patients assigned to 2, 4 and 8 mg baricitinib continued blinded treatment for an additional 12 weeks. Patients assigned to placebo or 1 mg baricitinib were reassigned to 2 mg twice daily or 4 mg once daily baricitinib between weeks 12–24. The primary endpoint was the proportion of patients in the combined 4 and 8 mg groups achieving an American College of Rheumatology 20% (ACR20) response versus placebo at week 12.

Results Significantly more patients in the combined baricitinib 4 and 8 mg groups compared with placebo achieved an ACR20 response at week 12 (76% vs 41%, p<0.001). At week 12, significant differences versus placebo were also observed in patients achieving ACR50, ACR70 and remission as measured by Disease Activity Score for 28-joint counts, Clinical Disease Activity Index and Simplified Disease Activity Index. Patients receiving 2, 4, or 8 mg baricitinib maintained or improved in all measures through 24 weeks. Similar proportions of patients experienced at least one adverse event in the placebo and baricitinib groups. Serious infections developed in three patients receiving baricitinib. No cases of tuberculosis, herpes zoster, opportunistic infections or deaths were reported. Dose-dependent decreases in haemoglobin were observed with baricitinib.

Conclusions Baricitinib improved the signs and symptoms of RA in methotrexate inadequate responders with active disease. Baricitinib was well tolerated with no unexpected safety findings through week 24.

Trial registration number NCT01185353.

INTRODUCTION

Numerous proinflammatory cytokines use the Janus Kinase (JAK) intracellular signalling pathway.1 2 Inhibition of this pathway represents a novel approach to the treatment of rheumatoid arthritis (RA). Various small molecule JAK inhibitors are in clinical development, each having differing degrees of specificity towards the four identified JAKs (JAK1, JAK2, JAK3 and Tyk2).3

Baricitinib (LY3009104, formerly INCB028050) is an orally administered, potent, selective and reversible inhibitor of JAK1 (IC50=5.9 nM) and JAK2 (IC50=5.7 nM)4 and may inhibit cytokines implicated in RA such as granulocyte-macrophage colony stimulating factor, interferon γ (IFN-γ), IL-6, IL-12, IL-23 and interferon γ.5 In preclinical rodent models of arthritis, baricitinib demonstrated significant anti-inflammatory effects as well as preservation of cartilage and bone.6 In these models, no suppression of humoral immunity or adverse haematological effects were observed. Baricitinib was previously investigated in a phase IIa study in patients with active RA despite treatment with disease-modifying antirheumatic drugs (DMARDs).7 After 12 weeks of treatment, a relatively flat dose–response curve was observed with all doses of baricitinib (ie, 4, 7 or 10 mg administered once daily) resulting in improvements in signs and symptoms compared with placebo. Baricitinib was well tolerated, and the nature of treatment-emergent adverse events (TEAEs) was similar across dose groups.

Study 14V-MC-JADA was a phase IIb, double-blind, randomised, placebo-controlled study conducted in patients with moderately to severely active RA despite treatment with methotrexate (MTX) with or without other conventional DMARDs (cDMARDs). The study was designed to confirm the dose–response relationship observed for baricitinib in the phase IIa study and to identify minimally effective and non-effective doses.

METHODS

Study patients

The study was conducted in 69 centres in nine countries. The number of patients enrolled from each country was the USA (n=95), Mexico (n=47), India (n=43), Poland (n=33), the Ukraine (n=29), the Czech Republic (n=23), Hungary (n=13), Romania (n=11) and Croatia (n=7). Patients aged 18–75 years with a diagnosis of adult-onset RA for at least 6 months and <15 years were eligible for inclusion in the study.8 Moderately to severely active disease was defined by the presence of eight or more tender and eight or more swollen joints (from a 68/66-joint count)9 and either a high-sensitivity C reactive protein (CRP) level >1.2×the upper limit of normal (ULN; >3.6 mg/L) or an erythrocyte sedimentation rate (ESR) >28 mm/h. Regular use of MTX for at least 12 weeks and

1. Keystone EC, Taylor PC, Drescher E, et al. Ann Rheum Dis 2015;74:333–340. 2. Keystone EC, Sneijder M, Taylor PC, et al. Arthritis Rheum 2012;64:1058–68. 3. Keystone EC, Drescher E, Berclaz PY, et al. Ann Rheum Dis 2014;73:1752–60. 4. Varga J. Interferon-gamma and its role in rheumatoid arthritis. J Cell Mol Med 2005;9:107–16. 5. Hanowski RJ, Zhang XM, Gleichman AJ, et al. Baricitinib, a novel Janus kinase inhibitor, suppresses cytokine production in animal models of rheumatoid arthritis and collagen-induced arthritis. Arthritis Rheum 2011;63:429–39. 6. Keystone EC, Sneijder M, Taylor PC, et al. Arthritis Rheum 2012;64:1058–68. 7. Keystone EC, Drescher E, Berclaz PY, et al. Ann Rheum Dis 2014;73:1752–60. 8. Keystone EC, Sneijder M, Taylor PC, et al. Arthritis Rheum 2012;64:1058–68. 9. Keystone EC, Drescher E, Berclaz PY, et al. Ann Rheum Dis 2014;73:1752–60.
treatment at a stable dose of 10–25 mg/week for at least 8 weeks prior to baseline was required. Concurrent treatment with stable doses of hydroxychloroquine (≤400 mg/day), sulfasalazine (≤3000 mg/day), nonsteroidal anti-inflammatory drugs and oral corticosteroids (<10 mg/day of prednisone or equivalent) was permitted. Key exclusion criteria included previous use of biological DMARDs, recent or concurrent infection including active or latent tuberculosis, an estimated glomerular filtration rate (GFR) from serum creatinine of <50 mL/min and any history of chronic liver disease or current serum aspartate aminotransferase or alanine aminotransferase concentration >3× the ULN or total bilirubin ≥1.5×ULN.

Study protocol
Qualifying patients were randomly assigned in a 2:1:1:1:1 ratio to once daily doses of placebo or baricitinib 1, 2, 4 or 8 mg, respectively. After 12 weeks of treatment, patients initially assigned to placebo or baricitinib 1 mg were re-randomised (with randomisation stratified by tender and swollen joint count reductions) to either baricitinib 2 mg twice daily or baricitinib 4 mg once daily for an additional 12 weeks of blinded treatment. Patients initially assigned to baricitinib 2, 4 and 8 mg remained on the same treatment for an additional 12 weeks. Patients who completed the 24-week study entered a 2-year open-label extension or were seen for follow-up 28 days after the last dose of baricitinib.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent. The study (NCT01185353) was designed by the sponsor, Eli Lilly and Company, with input obtained from Incyte Corporation and an academic advisory board in which the non-Lilly authors of this manuscript participated. The study was initiated in October 2010, and the last patient completed 24 weeks of treatment in February 2012. Edward Keystone was the principal investigator and signatory of the clinical study report. Mark Genovese and Edward Keystone wrote the first draft of the introduction and discussion with additional comments provided by Peter Taylor. Douglas Schlichting wrote the first draft of the methods and results. All authors participated in the analysis and interpretation of data, reviewed the draft and final manuscript and provided critical comment.

### Efficacy measures
The primary outcome analysis assumed similar treatment benefit from the 4 and 8 mg baricitinib doses and, therefore, was the aggregate proportion of patients in the combined 4 and 8 mg groups who achieved an American College of Rheumatology 20% response (ACR20)§ compared with placebo at 12 weeks. Secondary outcomes included the rates of ACR50 and ACR70 responses, improvements in individual components of the ACR score, disease activity as assessed by the Disease Activity Score based on 28 tender and swollen joint count, patient’s global assessment of disease activity and the levels of CRP (DAS28-CRP); disease activity as assessed by the European

### Table 1 Baseline characteristics and disease activity of patient populations

|                       | Placebo once daily | Baricitinib 1 mg once daily | Baricitinib 2 mg once daily | Baricitinib 4 mg once daily | Baricitinib 8 mg once daily |
|-----------------------|--------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| **Age, years**        | 49±12              | 53±11                       | 51±13                       | 53±10                       | 53±11                       |
| **Gender, % female**  | 87                 | 86                          | 85                          | 71                          | 82                          |
| **Duration of RA, years** | 5.4±4.3          | 5.5±3.9                     | 5.5±4.4                     | 5.3±4.5                     | 6.6±5.0                     |
| **Anti-CCP antibody, † % positive** | 62                | 76                          | 67                          | 71                          | 74                          |
| **RF, % positive**    | 65                 | 71                          | 67                          | 77                          | 80                          |
| **Methotrexate dose, mg/week** | 16.3±4.3         | 18.2±13.4                   | 14.9±4.1                    | 16.3±4.8                    | 15.7±4.2                    |
| **Concomitant cDMARDs for RA, % patients** | 100               | 100                         | 100                         | 98                          | 100                         |
| **Methotrexate**      | 100                | 100                         | 100                         | 98                          | 100                         |
| **Hydroxychloroquine** | 16                | 22                          | 21                          | 13                          | 14                          |
| **Sulfasalazine**     | 14                 | 8                           | 13                          | 17                          | 18                          |
| **Prednisone use, % patients** | 52                | 52                          | 52                          | 38                          | 58                          |
| **Duration of morning joint stiffness, minutes** | 101.7±110.7       | 91.4±78.4                   | 73.1±42.2                   | 103.9±145.1                 | 95.8±97.8                   |
| **Tender joints (68 count)** | 22.2±12.1        | 21.4±10.9                   | 23.0±12.6                   | 19.9±12.7                   | 24.4±13.8                   |
| **Swollen joints (66 count)** | 15.8±8.6         | 15.2±6.6                    | 17.0±9.3                    | 14.8±7.5                    | 16.1±7.9                    |
| **Tender joints (28 count)** | 14.1±6.2         | 14.0±5.5                    | 14.5±6.4                    | 13.1±6.4                    | 15.7±6.2                    |
| **Swollen joints (28 count)** | 11.8±5.4         | 11.9±4.6                    | 12.1±6.0                    | 11.2±4.8                    | 11.6±4.6                    |
| **HAQ-DI§**           | 1.2±0.7            | 1.3±0.6                     | 1.1±0.7                     | 1.0±0.6                     | 1.3±0.7                     |
| **hsCRP, mg/L†**      | 14.0±23.5          | 11.2±12.4                   | 12.0±22.1                   | 11.4±16.9                   | 14.3±15.6                   |
| **ESR, mm/h**         | 39.9±20.9          | 38.2±17.6                   | 36.5±14.6                   | 35.4±17.2                   | 43.3±18.2                   |
| **DAS28-hsCRP**       | 5.5±0.9            | 5.5±0.8                     | 5.4±0.9                     | 5.3±1.0                     | 5.8±0.8                     |
| **DAS28-ESR**         | 6.3±0.8            | 6.3±0.8                     | 6.2±0.8                     | 6.0±0.9                     | 6.6±0.8                     |
| **CDAI**              | 37.1±12.3          | 37.7±10.6                   | 37.7±12.2                   | 35.2±12.2                   | 39.7±12.0                   |
| **SDAI**              | 38.6±12.5          | 38.8±10.8                   | 38.9±12.2                   | 36.3±12.2                   | 41.1±12.1                   |

*Data reported as mean values±SD unless otherwise indicated.
†Anti-CCP antibody positivity (≥ upper limit of normal (ULN)=5 EU/mL).
‡RF positivity (>ULN=14 IU/mL).
§Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability.
¶hsCRP (ULN=3 mg/L).
Anti-CCP, anticyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARDs, conventional disease-modifying antirheumatic drugs; DAS28-ESR, Disease Activity Score for 28-joint counts based on the ESR; DAS28-hsCRP, Disease Activity Score for 28-joint counts based on the hsCRP level; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; hsCRP, high-sensitivity C reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity index.
League Against Rheumatism (EULAR) response criteria based on the 28 joint count (EULAR28) and the duration of morning joint stiffness measured in minutes of joint stiffness on the day prior to the study visit. Clinical Disease Activity Index (CDAI) ≤2.8, Simplified Disease Activity Index (SDAI) ≤3.3 and DAS28-ESR <2.6 were used for post-hoc assessments of remission. A secondary objective assessed the treatment effects of baricitinib 2 mg twice daily or baricitinib 4 mg once daily administered from week 12 through week 24 in the re-randomised population of patients initially treated with placebo or 1 mg of baricitinib.

Safety assessments
Clinical laboratory tests, assessments of vital signs and physical examinations were performed at scheduled visits. The incidence and severity of all adverse events (AEs) were recorded. The National Institute of Health Common Terminology Criteria for Adverse Events V4.0 was used to describe postbaseline laboratory changes.

Statistical analysis
All randomised patients, each treated with at least one dose, were included in the primary and secondary analyses, aligned with the intention-to-treat principle. The primary analysis was conducted using a one-sided, 0.10-level test from a logistic regression model including treatment group (baricitinib or placebo) and baseline DAS28-CRP as a continuous covariate. No further control for type I error rate was applied as is typical for a phase II study design. Patients who discontinued the study prior to week 12 were treated as non-responders for the primary analysis, and missing components of the ACR20 index were imputed by last observation carried forward. A sample size of 45 patients per baricitinib group and 90 patients in the placebo group was estimated to provide at least 90% power to detect a difference from placebo of 20% (ACR20).

Figure 1  Primary efficacy analyses. (A–C). The percentage of patients achieving a 20%, 50% or 70% improvement in American College of Rheumatology (ACR) 20 (A), ACR50 (B) or ACR70 (C) over time through 24 weeks. The vertical line at 12 weeks in (A) indicates the primary efficacy time point. (D–F) Assessments of disease activity in patients at weeks 12 and 24. The percentage of patients with Disease Activity Score for 28-joint counts based on C reactive protein (DAS28-CRP) <2.6 or ≤3.2 (D), DAS28 (erythrocyte sedimentation rate (ESR)) <2.6 or ≤3.2 (E), clinical disease activity index (CDAI) ≤2.8 (F), or simplified disease activity index (SDAI) ≤3.3 (F). For ACR and DAS28 responses, data reported as non-responder imputation, *p<0.05, **p<0.01 and ***p<0.001 versus placebo using one-sided Fisher exact test. For CDAI and SDAI, *p<0.05, **p<0.01 and ***p<0.001 using χ² test.

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power for the primary analysis (assuming ACR20 response rates of 35% for placebo and ≥55% for the combined baricitinib 4 and 8 mg groups). The planned and final sample sizes allowed for estimation of response rates with a margin of error of approximately 14% for each baricitinib dose and 10% for placebo.

By-visit analyses of the proportion of patients achieving ACR20, ACR50 and ACR70 responses through 12 weeks were conducted using the Fisher exact test of each dose versus placebo. Individual core components of the ACR indices, assessment of disease activity based on DAS28, assessment of clinical remission based on CDAI and SDAI and duration of morning joint stiffness through 12 weeks were analysed using logistic regression or analysis of covariance, as appropriate. Non-responder imputation was used for the analysis of all categorical response measures, and last observation carried forward used for continuous endpoints. Comparisons of the original baricitinib 2, 4 and 8 mg groups beyond 12 weeks were accomplished through summary statistics.

RESULTS
Patients
From 454 screened patients, a total of 301 patients were enrolled. All randomised patients received at least one dose of their initial assigned treatment (see online supplementary figure S1). The groups were well balanced with respect to demographic characteristics and disease activity (table 1). A total of 16% of the patients in the placebo group, as compared with 10%, 2%, 4% and 2% of the baricitinib 1, 2, 4 and 8 mg groups, respectively, did not complete the study through 12 weeks. The reasons for discontinuation are summarised in online supplementary figure S1.

Table 2 Summary of improvement in American College of Rheumatology (ACR) core components and morning joint stiffness at 12 and 24 weeks

| Week 12 Baricitinib | Placebo once daily (N=98) | 1 mg once daily (N=49) | 2 mg once daily (N=52) | 4 mg once daily (N=52) | 8 mg once daily (N=50) | Week 24 Baricitinib | 2 mg once daily (N=52) | 4 mg once daily (N=52) | 8 mg once daily (N=50) |
|---------------------|--------------------------|-----------------------|-----------------------|-----------------------|-----------------------|---------------------|-----------------------|-----------------------|-----------------------|
| Tender joints (68 count) | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change |
| Placebo once daily (N=98) | 31 | -7.6 | 70 | 7.5 |
| 1 mg once daily (N=49) | 32 | -8.4 | 11.3 |
| 2 mg once daily (N=52) | 41 | -11.3 | 12.2** |
| 4 mg once daily (N=52) | 60*** | -12.2** |
| 8 mg once daily (N=50) | 59** | -14.7** |
| Mean % improvement | 12.4 |
| Mean change | -14.0 |
| Swollen joints (66 count) | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change | Mean % improvement | Mean change |
| Placebo once daily (N=98) | 40 | -6.7 | 48 | -8.1 |
| 1 mg once daily (N=49) | 49 | -8.9 | 14.2 |
| 2 mg once daily (N=52) | 51 | -9.6*** |
| 4 mg once daily (N=52) | 68*** |
| 8 mg once daily (N=50) | 62** |
| Mean % improvement | 10.0 |
| Mean change | -10.5 |
| Pain (0–100) | Mean change | Mean change | Mean change | Mean change | Mean change | Mean change |
| Placebo once daily (N=98) | -8.8 |
| 1 mg once daily (N=49) | -22.8*** |
| 2 mg once daily (N=52) | -14.2 |
| 4 mg once daily (N=52) | -25.0** |
| 8 mg once daily (N=50) | -25.3*** |
| Mean change | -29.8*** |
| PhGA (0–100) | Mean change | Mean change | Mean change | Mean change | Mean change | Mean change |
| Placebo once daily (N=98) | -10.3 |
| 1 mg once daily (N=49) | -24.9*** |
| 2 mg once daily (N=52) | -16.2 |
| 4 mg once daily (N=52) | -25.4** |
| 8 mg once daily (N=50) | -29.8*** |
| Mean change | -33.5*** |
| PhGA (0–100) | Mean change | Mean change | Mean change | Mean change | Mean change | Mean change |
| Placebo once daily (N=98) | -19.0 |
| 1 mg once daily (N=49) | -23.9 |
| 2 mg once daily (N=52) | -25.0 |
| 4 mg once daily (N=52) | -30.4*** |
| 8 mg once daily (N=50) | -33.5*** |
| Mean change | -37.8 |
| HAQ-DI (0–3) | Mean change | Mean change | Mean change | Mean change | Mean change | Mean change |
| Placebo once daily (N=98) | -0.10 |
| 1 mg once daily (N=49) | -0.35** |
| 2 mg once daily (N=52) | -0.18 |
| 4 mg once daily (N=52) | -0.33*** |
| 8 mg once daily (N=50) | -0.39** |
| Mean change | -0.18 |
| Median (min) | Median (min) | Median (min) | Median (min) | Median (min) | Median (min) | Median (min) | Median (min) | Median (min) | Median (min) |
| Placebo once daily (N=98) | 45.0 |
| 1 mg once daily (N=49) | 30.0 |
| 2 mg once daily (N=52) | 30.0 |
| 4 mg once daily (N=52) | 10.0 |
| 8 mg once daily (N=50) | 15.0 |
| Mean change | -33.9 |

Data reported as mean change from baseline unless otherwise noted and last observation carried forward. No significant differences in baseline measures between treatment groups were observed.
*p<0.05, **p<0.01 and ***p<0.001 versus placebo; p values derived using two-sided analysis of covariance with treatment as the fixed factor and the baseline value as a covariate for pain/wrist comparisons of each baricitinib dose versus placebo.
†Mean percent improvement from baseline.
‡Percent of patients achieving MCID (≥0.22) for HAQ-DI.
§Mean change from baseline.
ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; hsCRP, high-sensitivity C reactive protein; MCID, minimal clinically important difference (≥0.22); PhGA, physician’s global assessment of disease activity; PtGA, patient’s global assessment of disease activity.

Efficacy
Significantly, more patients in the combined baricitinib 4 and 8 mg groups compared with placebo met the criteria for ACR20 response at week 12 (76% vs 41%, p<0.001). The treatment effect was consistent across geographical regions. Significantly more patients receiving 1, 4 or 8 mg achieved an ACR20 response compared with placebo at the first postrandomisation assessment at 2 weeks (29%, 42% and 44%, respectively, vs 11%, all p<0.01; figure 1A). An increase in the ACR20 response over time was observed that appeared to plateau by 8 weeks in the 4 and 8 mg groups. At 4 weeks, significantly more patients in the 4 and 8 mg groups obtained ACR50 and ACR70 responses compared with placebo; these responses persisted through 12 weeks (figure 1B, C). The ACR20, ACR50 and ACR70 response rates were maintained or continued to improve through 24 weeks in the patients initially assigned to the 2, 4 and 8 mg groups (figure 1A–C). Significantly more patients in the 4 and 8 mg groups achieved DAS28 scores ≤3.2 or <2.6 by 12 weeks compared with placebo (figure 1D, E). The proportions of patients who achieved these disease activity states were maintained or increased through 24 weeks (figure 1D, E). Remission as measured with CDAI (≤2.8) or SDAI (≤3.3) was also observed in a significantly greater proportion of patients in the 4 and 8 mg groups at 12 weeks and was maintained or increased in these groups through 24 weeks (figure 1F). Using the EULAR28 measure of good or moderate response, significantly more patients receiving baricitinib 2, 4 or 8 mg achieved a good/moderate response at 12 weeks compared with placebo (see online supplementary figure S2). Similar good/moderate responses were observed at 24 weeks in these dose groups (see online supplementary figure S2). Improvements in the ACR20, ACR50 and ACR70 responses as well as DAS28 scores ≤3.2 or <2.6 were observed for patients initially assigned
from baseline for selected laboratory analytes through week 12 in the study. No cases of tuberculosis, herpes zoster, opportunistic infections or deaths were reported through 24 weeks. Physical function was significantly improved in patients receiving 4 or 8 mg baricitinib versus placebo, as measured by the Health Assessment Questionnaire Disability Index (≥0.22) from baseline to 12 weeks (see online supplementary figure S3). Significant improvements were observed in most components of the ACR index and in morning joint stiffness duration at 12 weeks in patients receiving 4 or 8 mg baricitinib (table 2).

Table 3

| Weeks 0–12 Baricitinib | Weeks 12–24 Baricitinib | Weeks 0–24 Baricitinib |
|------------------------|-------------------------|------------------------|
| Placebo once daily (N=98) | 1 mg once daily (N=49) | 2 mg once daily (N=52) | 4 mg once daily (N=52) | 8 mg once daily (N=50) | Combined 2 mg twice daily*† | Combined 4 mg once daily† | Weeks 0–24 Baricitinib |
| TEAE, n (%) | 45 (46) | 20 (41) | 24 (46) | 22 (42) | 26 (52) | 29 (48) | 27 (44) | 31 (60) | 32 (62) | 36 (72) |
| SAE, n (%) | 3 (3) | 0 | 3 (6) | 0 | 1 (2) | 3 (5)† | 1 (2)† | 3 (6) | 0 | 4 (8) |
| Serious infection, n (%) | 0 | 0 | 2 (4) | 0 | 0 | 0 | 0 | 2 (4) | 0 | 1 (2) |
| Discontinuations due to AEs, n (%) | 5 (5) | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 0 | 1 (2) | 1 (2) |

* Patients originally assigned to placebo or baricitinib 1 mg once daily at study entry and re-randomised to receive baricitinib 2 mg twice daily or 4 mg once daily for an additional 12 weeks.
† Data for baricitinib combined 2 mg twice daily or combined 4 mg once daily are reported for weeks 12–24.
‡ One SAE in each of the baricitinib combined 2 mg twice daily (hyperglycaemia) or combined 4 mg once daily (haematuria) groups began prior to week 12 and continued into weeks 12–24.

AE, adverse event; N, number of patients randomised and treated; n, number of patients with event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Table 4 Summary of laboratory data at weeks 12 and 24

|                     | Placebo once daily (N=50) | 1 mg once daily (N=49) | 2 mg once daily (N=52) | 4 mg once daily (N=52) | 8 mg once daily (N=50) | Baricitinib once daily (N=52) | 2 mg once daily (N=52) | 4 mg once daily (N=52) | 8 mg once daily (N=50) |
|---------------------|---------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------------|---------------------------|-----------------------|-----------------------|
| Neutrophil count, 10^6 cells/mm^3 | -0.02±1.51 | -0.43±1.42 | -0.59±1.66* | -0.30±1.79 | -0.68±2.06* | -0.25±1.18 | -0.21±2.02 | -1.37±2.33 |
| Lymphocyte count, 10^6 cells/mm^3 | -0.18±0.60 | -0.01±0.65 | -0.05±0.48 | 0.06±0.62* | 0.16±0.74 | -0.01±0.50 | -0.03±0.66 | 0.10±0.61 |
| Platelet count, 10^9 cells/mm^3 | 9.6±4.33 | -4.1±45.0 | 13.7±37.0 | 31.1±59.8* | 50.2±64.5*** | 18.9±36.8 | 33.5±66.1 | 48.5±59.9 |
| Haemoglobin, g/dL | 8.4±6.2 | 0.12±0.75* | -0.09±0.67 | -0.15±0.80 | -0.54±0.92** | -0.28±1.10 | -0.24±0.91 | -0.44±1.04 |
| ALT, IU/L | 3.5±20.7 | 0.2±15.3 | 3.6±14.6 | 7.5±33.8 | 2.8±15.4 | 2.2±1.6 | 2.5±12.7 | 2.8±23.0 |
| HDL, mg/dL | 0.7±8.5 | 3.3±9.1 | 3.0±12.2 | 7.3±12.9*** | 8.1±13.9*** | 3.5±10.0 | 5.7±12.6 | 10.0±1.15 |
| LDL, mg/dL | -4.7±25.1 | 3.4±24.2 | 8.0±24.1*** | 9.5±30.3** | 11.8±23.5*** | 11.5±22.8 | 8.8±32.6 | 14.0±30.9 |
| Creatinine, mg/dL | 0.01±0.08 | 0.02±0.10 | 0.04±0.10* | 0.11±0.36* | 0.08±0.27* | 0.04±0.10 | 0.05±0.08 | 0.07±0.13 |
| Creatine phosphokinase, U/L | 17±307 | 15±38 | 21±59 | 49±96 | 70±133 | 25±66 | 41±81 | 70±89 |

Data represented as mean change from baseline±SD.

*P<0.05, **P<0.01 and ***P<0.001 versus placebo; p values derived using two-sided t test comparing the baricitinib dose versus placebo.

ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**DISCUSSION**

At both weeks 12 and 24, the 2 mg dose of baricitinib produced disease activity and remission in terms of ACR20 and ACR50, low disease activity and remission in terms of ACR70 and ACR100, and low disease activity in terms of ACR50, ACR70, ACR100, and ACR200. Secondary efficacy endpoints, such as ACR70 and ACR100, showed similar effectiveness in both treatment groups. At both weeks 12 and 24, the 2 mg dose of baricitinib was associated with improvements in all efficacy measures, including low disease activity and remission, low disease activity, and ACR70. Secondary efficacy endpoints, such as ACR70 and ACR100, showed similar effectiveness in both treatment groups. At both weeks 12 and 24, the 2 mg dose of baricitinib was associated with improvements in all efficacy measures, including low disease activity and remission, low disease activity, and ACR70. Secondary efficacy endpoints, such as ACR70 and ACR100, showed similar effectiveness in both treatment groups.
Among the limitations of the study, the length of the placebo control was limited to 12 weeks by ethical concerns of continuing placebo in patients with active RA. While the placebo control group ended at 12 weeks, the study remained double blind through the completion of 24 weeks to assess efficacy and safety in this later period, as well as the effects of dose change. This study restricted enrolment to the tumour necrosis factor α inhibitor/biologically naïve population on background MTX, thus limiting the ability to extrapolate efficacy and safety to biologically experienced subjects or to assess the safety of baricitinib with other background DMARDs commonly combined in RA treatment. Finally, the length and size of the study were limited to 24 weeks and 301 patients based on its phase II dose-ranging nature.

In conclusion, the results of this phase IIb study with baricitinib demonstrate that selective inhibition of JAK1 and JAK2 is effective and well tolerated in patients with active RA taking background MTX. Further studies are underway to determine safety and efficacy in other RA populations such as those patients refractory to biological treatments as well as to further delineate any mechanistic and clinical differences and longer term ramifications of JAK1/JAK2 inhibition.

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REFERENCES
1 Leonard W, O’Shea JJ. Jaks and STATs: biological implications. Ann Rev Immunol 1998;16: 293–322.
2 O’Shea JJ, Holland SM, Staudt LM. Mechanisms of disease: JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med 2013;368:161–70.
3 O’Shea JJ, Kontizas A, Yamaoka K, et al. Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis 2013;72: S111–15.
4 Fridman JS, Scherer PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INC8028050. J Immunol 2010;184:5298–307.

Table 5 Summary of laboratory abnormalities of special interest through weeks 12 and 24

|                | Weeks 0–24 | Weeks 0–24 |
|----------------|------------|------------|
|                | Baricitinib | Baricitinib |
|                | Placebo    | 1 mg once  | 2 mg once  | 4 mg once  | 8 mg once  | 2 mg once  | 4 mg once  | 8 mg once  |
|                | daily (N=98)| daily (N=49)| daily (N=52)| daily (N=52)| daily (N=50)| daily (N=52)| daily (N=52)| daily (N=50)|
| Decreased neutrophils, n (%) |            |            |            |            |            |            |            |            |
| Grade 1: 1500 cells/mm³ to less than LLN* | 3 (3) | 4 (8) | 3 (6) | 2 (4) | 6 (12) | 4 (8) | 1 (2) | 5 (10) |
| Grade 2: ≥ 1000 to <1500 cells/mm³ | 1 (1) | 1 (2) | 1 (2) | 2 (4) | 5 (10) | 3 (6) | 5 (10) | 9 (18) |
| Grade 3: ≥ 500 to <1000 cells/mm³ | 0 | 0 | 1 (2) | 0 | 1 (2) | 1 (2) | 0 | 1 (2) |
| Decreased lymphocytes, n (%) |            |            |            |            |            |            |            |            |
| Grade 1: ≥ 800 cells/mm³ to less than LLN | 13 (13) | 6 (12) | 5 (10) | 9 (18) | 6 (12) | 6 (12) | 10 (20) | 10 (20) |
| Grade 2: ≥ 500 to <800 cells/mm³ | 3 (3) | 2 (4) | 4 (8) | 3 (6) | 5 (10) | 5 (10) | 7 (14) | 10 (20) |
| Decreased haemoglobin, n (%) |            |            |            |            |            |            |            |            |
| Grade 1: ≥ 10.0 g/dL to less than LLN | 29 (30) | 17 (35) | 11 (21) | 11 (22) | 21 (42) | 14 (27) | 17 (33) | 23 (46) |
| Grade 2: ≥ 8.0 to <10.0 g/dL | 5 (5) | 0 | 3 (6) | 6 (12) | 4 (8) | 4 (8) | 6 (12) | 6 (12) |
| Elevated platelets, n (%) |            |            |            |            |            |            |            |            |
| Platelet count >600 000 cells/µL | 1 (1) | 1 (2) | 0 | 2 (4) | 0 | 0 | 2 (4) | 0 |
| Elevated ALT, n (%) |            |            |            |            |            |            |            |            |
| Grade 1: >ULN and ≤ 2.5× ULN | 19 (19) | 10 (20) | 9 (17) | 11 (22) | 10 (20) | 11 (21) | 14 (27) | 13 (26) |
| Grade 2: >2.5× ULN and ≤ 5× ULN | 3 (3) | 0 | 2 (4) | 2 (4) | 0 | 2 (4) | 3 (6) | 1 (2) |
| Grade 3: >5× ULN and ≤ 10× ULN | 0 | 0 | 0 | 1 (2) | 1 (2) | 0 | 1 (2) | 1 (2) |

*Laboratory grades defined using Common Terminology Criteria for Adverse Events V4.0. Grades are based on the worst single value through the time period.

† Incidence of protocol-defined thrombocytosis in patients with platelet counts >600 000 cells/µL.
5 Greenwald MK, Fidelus-Gort R, Levy R, et al. A randomized dose-ranging, placebo-controlled study of INCB028050, a selective JAK1 and JAK2 inhibitor in subjects with active rheumatoid arthritis [abstract]. *Arthritis Rheum* 2010;62(Suppl 10):2172.

6 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.

7 Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. *Arthritis Rheum* 1995;38:38–43.

8 Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.

9 Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005;23(Suppl 39):S93–9.

10 van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum* 1998;41:1845–50.

11 Aletaha D, Ward MM, Machold KP, et al. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005;52:2625–36.

12 Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23(Suppl. 39):5100–8.

13 Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient’s perspective. *J Rheumatol* 1993;20:557–60.

14 Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000;43:1478–87.

15 Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.

16 van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.

17 Burmester GR, Blanco R, Charles-Schoeman C, et al. 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;381:451–60.

18 FDA News Release. FDA approves Xeljanz for rheumatoid arthritis. November 6, 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm327152.htm (accessed 21 Nov 2013).