Efficacy and safety of peficitinib (ASP015K) in patients with rheumatoid arthritis and an inadequate response to conventional DMARDs: a randomised, double-blind, placebo-controlled phase III trial (RAJ3)

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ABSTRACT

Objectives To investigate the efficacy and safety of peficitinib, an oral Janus kinase inhibitor, in patients with rheumatoid arthritis (RA).

Methods In this double-blind phase III study, patients with RA and an inadequate response to prior disease-modifying anti-rheumatic drugs (DMARDs) were randomised to peficitinib 100 mg once daily, peficitinib 150 mg once daily, placebo or open-label etanercept for 52 weeks’ treatment; placebo-treated patients were switched at week 12 to peficitinib 100 or 150 mg once daily. The primary endpoint was American College of Rheumatology (ACR20) response at week 12/early termination (ET). Secondary endpoints (assessed throughout) included ACR20, ACR50 and ACR70 response, changes from baseline in disease activity scores (DAS28) and ACR core parameters, adverse events (AEs) and changes in clinical or laboratory measurements.

Results In total, 507 patients received treatment. ACR20 response rates at week 12/ET were significantly higher in the peficitinib 100 mg (57.7%) and 150 mg (74.5%) groups versus placebo (30.7%) (p<0.001). ACR50/70 response rates were also higher for both peficitinib doses versus placebo. Improvements in ACR response were maintained until week 52. Changes from baseline in DAS28-C-reactive protein/erythrocyte sedimentation rate and the ACR core set were significantly greater for both peficitinib doses versus placebo at week 12/ET (p<0.001). AE incidence was similar across treatment arms. Incidence of serious infection and herpes zoster-related disease was higher with peficitinib versus placebo, but with no clear dose-dependent increase.

Conclusions In patients with RA and inadequate response to DMARDs, peficitinib 100 mg once daily or 150 mg once daily was efficacious in reducing RA symptoms and was well tolerated compared with placebo.

Trial registration number NCT02308163.

INTRODUCTION

Rheumatoid arthritis (RA) affects 0.3% to 1% of the population worldwide.1 Biological agents such as tumour necrosis factor (TNF) inhibitors, used in combination with methotrexate (MTX), have been found to be effective in patients who are unresponsive to conventional disease-modifying anti-rheumatic drugs (DMARDs).2 The Janus kinase (JAK) family of non-receptor protein tyrosine kinases is more recently considered a promising alternative target for RA treatment.3-5 Two oral JAK inhibitors, tofacitinib and baricitinib, have so far been approved for use in the USA, the European Union and Japan.6-12 Peficitinib (ASP015K) is an oral JAK inhibitor which inhibits the activity of all JAK family members (JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2))
with similar potency (IC_{50} 0.7 to 5.0 nM). A phase Ib study in Japanese patients with RA showed a dose-dependent, statistically significant improvement after 12 weeks in American College of Rheumatology (ACR)20 response rate (primary endpoint) for once-daily doses of peficitinib 50 mg, 100 mg and 150 mg and an acceptable safety profile. In addition, a dose-dependent increase in mean haemoglobin levels was observed, suggesting that JAK2 was not inhibited in the study even at the highest dose used. Peficitinib also demonstrated similar efficacy in one of two studies in non-Japanese populations; in the other non-Japanese study, most of the improvements in ACR20/50/70 response rates were not significant due to a relatively high response rate in the placebo group.

This study was undertaken to assess the efficacy and safety of peficitinib (100 or 150 mg/day), alone or in combination with DMARDs, in patients who had an inadequate response to prior DMARDs.

METHODS

Study design

This was a randomised, placebo-controlled, double-blind, parallel-group, phase III confirmatory study conducted between August 2014 and November 2017 at 142 sites in Japan, 11 sites in Korea and 12 sites in Taiwan (online supplementary information). Following screening, patients were randomised in a 1:1:1:1:2 ratio to peficitinib 100 mg/day, peficitinib 150 mg/day, placebo or etanercept. The peficitinib doses used in this study were chosen from the upper two doses in former RA studies of peficitinib based on previous efficacy and safety findings (online supplementary methods). In accordance with guidance for this study from a regulatory authority, etanercept was designated as an open-label reference drug, mainly for a safety comparison versus treatment groups (online supplementary methods).

Patients

Patients aged ≥20 years with RA (according to the 1987 American College of Rheumatology criteria (ACR) or the 2010 ACR/European League Against Rheumatism criteria), were enrolled. Eligibility criteria at screening included active RA, defined as ≥6/68 tender/painful joints and ≥6/66 swollen joints, C-reactive protein (CRP) >0.50 mg/dL at screening and an inadequate response to, or intolerance of, at least one DMARD administered for ≥90 days prior to screening (DMARD-IR). Exclusion criteria included an inadequate response to ≥3 biological DMARDs as determined by the investigator, a diagnosis of inflammatory arthritis other than RA and laboratory abnormalities. Further details of inclusion and exclusion criteria can be found in the online supplementary methods.

Outcomes

Efficacy assessments

The primary efficacy endpoint was the response rate according to ACR20 improvement criteria at week 12/early termination (ET). Key secondary endpoints assessed throughout included response rates according to ACR20/50/70 improvement criteria, changes from baseline in 28-joint disease activity score (DAS) based on CRP (DAS28-CRP) and erythrocyte sedimentation rate (ESR) (DAS28-ESR), rates of remission defined as DAS28-CRP<2.6 and DAS28-ESR<2.6, rates of DAS28-CRP≤3.2, changes from baseline in CRP and ESR values, changes from baseline in tender joint count at 68 joints and swollen joint count at 66 joints and changes from baseline in Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Patient and physician-reported outcomes included Subject’s Global Assessment of disease activity (SGA), Subject’s Global Assessment of Pain (SGAP), and Physician’s Global Assessment of disease activity (PGA) using a 100 mm visual analogue scale (VAS) for each, plus Health Assessment Questionnaire – Disability Index (HAQ-DI) scores.

Safety

Treatment-emergent adverse events (TEAEs) were defined as any adverse event (AE), as reported by the investigator, that started or worsened in severity after the initial dose of study or reference drug through week 52 or follow-up period, including the incidence of venous thromboembolism (VTE) (online supplementary figure 1). Serious infections, malignancies and herpes zoster-related disease (including varicella) were assessed per 100 patient-years. Mean (SD) changes from baseline in haematological, biochemical and select laboratory parameters were recorded throughout.

Statistical analyses

Based on the calculation that 62 patients per arm would provide 90% power to detect a significant difference with a two-sided significance level of 0.05, and following guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Japan Ministry of Health, Labour and Welfare on methodology for adequate assessment of AEs (online supplementary methods), the planned sample size was 100 patients for each of the peficitinib 100 mg, peficitinib 150 mg and placebo arms, and 200 patients in the etanercept group, taking into consideration incidence rates for serious infections from post-marketing studies for approved biological drugs and feasibility. As a result of discussions with a regulatory authority, etanercept was set as an open-label anti-TNF reference arm and was not included in statistical comparisons with placebo.

The primary analysis was conducted on the full analysis set (FAS), which consisted of all patients who were randomised and received at least one dose of study or reference treatment. For the ACR20/50/70 responses at week 12/ET, pairwise comparisons with placebo (using a logistic regression model with treatment group as the factor and prior biological DMARD-IR, concomitant DMARD use at baseline and study region as the covariates), multiplicity adjustment and sensitivity analyses were conducted as detailed in the online supplementary methods. The null hypotheses were tested at a two-sided significance level of 0.05. Safety analyses were conducted on the safety analysis set (SAF), which included all patients who received at least one dose of study treatment.

RESULTS

Patient demographics, baseline characteristics and treatment compliance

Of 724 patients screened, 509 were randomised: 102, 104, 102 and 201 to the placebo, peficitinib 100 mg, peficitinib 150 mg and etanercept groups, respectively. Of the randomised patients,
one patient in each of the placebo and etanercept arms did not receive treatment; the SAF/FAS therefore included a total of 507 patients (figure 1). The majority of patients were female (366/507, 72.2%) and the mean age was 55.3 years. Most patients were from Japan (415/507, 81.9%), 54 (10.7%) were from Korea and 38 (7.5%) were from Taiwan (table 1).

For the overall period, the proportion of patients who discontinued the study ranged from 16.9% to 29.8% across the treatment groups: the primary reasons for discontinuation across treatment arms were lack of efficacy (32/509, 6.3%) and AEs (29/509, 5.7%). Reasons for discontinuation in each arm are described in figure 1.

Baseline disease activity and RA history were mostly balanced between the treatment arms. At baseline, a total of 443/507 (87.4%) patients received concomitant DMARDs, of whom 299 (59.0%) received MTX and 144 (28.4%) received DMARDs other than MTX only. An inadequate response to previous biological DMARDs was reported in 36 (7.1%) patients. Mean treatment compliance for the overall study period was 96.44% to 97.70% for all treatment groups.

Efficacy
ACR20/50/70 response rates
The primary efficacy variable, ACR20 response rate at Week 12/ET (last observation carried forward (LOCF)), was 57.7%, 74.5%, 83.3% and 30.7%, in the peficitinib 100 mg, peficitinib 150 mg, etanercept and placebo groups, respectively (figure 2A). Significant differences versus placebo of 27.0% (OR: 3.13, 95% CI 1.76 to 5.38) with peficitinib 100 mg and 43.8% (OR: 6.59, 95% CI 3.56 to 12.20) with peficitinib 150 mg were observed (p<0.001 for both comparisons) (figure 2A).

The primary analysis of the ACR20 response rate was also demonstrated to be robust using sensitivity analyses (online supplementary table 1). Subgroup analyses indicated that both peficitinib doses produced numerically higher ACR20 response rates than placebo regardless of number of prior biological DMARDs, prior biological DMARD-IR, concomitant DMARD use or MTX dose at baseline; however, these subgroup analyses were not powered for statistical comparisons (online supplementary table 1).

ACR50 and ACR70 response rates at week 12/ET were also significantly higher for peficitinib 100 mg and 150 mg compared with placebo (figure 2A; online supplementary figure 3). The increase in ACR20/50/70 response rates versus placebo was maintained throughout the study period in the peficitinib 100 mg group, the peficitinib 150 mg group and the etanercept group (figure 2B–D; online supplementary table 3). For the patients who switched from placebo to peficitinib 100/150 mg at week 12, the response rates were initially lower compared with those in the other treatment arms, but were improved at week 16 and then maintained or increased through week 52 (figure 2B–D).

Key secondary efficacy endpoints
The proportions of patients achieving DAS28-CRP<2.6, DAS28-ESR<2.6 and DAS28-CRP≤3.2 scores at week 12/ET were significantly increased in the peficitinib 100 mg and 150 mg groups compared with placebo, except for the DAS28-ESR<2.6 scores in the peficitinib 100 mg group due to difficulty in estimating the odds ratio. The proportion of patients achieving these criteria was higher at week 52/ET than at week 12/ET (online supplementary figure 2).

The changes from baseline in DAS28-CRP and the ACR core set at week 12/ET (LOCF) were significantly greater in the peficitinib 100 mg and 150 mg groups compared with placebo (p<0.001). In addition, the change from baseline was greater for all outcomes in the peficitinib 150 mg group than in the peficitinib 100 mg group (figure 3).

The proportions of patients with CDAI score ≤2.8, CDAI score ≤10 (low disease activity), SDAI score ≤3.3 and SDAI score ≤11 (low disease activity) were higher with peficitinib 100 mg and 150 mg compared with placebo, although p values could not be estimated in all instances (online supplementary file 1). Changes from baseline in CDAI and SDAI scores were significantly higher with both peficitinib doses than with placebo from week four through to week 12/ET (online supplementary file 1).

Safety
Treatment-emergent adverse events
The incidence of investigator-reported TEAEs from week 0 to week 12 was similar across treatment arms at 53.5% to 59.5% (SAF). For the overall study period, TEAEs were reported in 87.3% to 89.0% patients across all treatment arms, and no major differences in incidence were observed compared with the week 0 to 12 period (table 2A). The majority of investigator-reported TEAEs were mild or moderate in severity (National Cancer Institute Common Terminology Criteria for Adverse Events grades 1 to 2). No deaths were reported during the study. After the end of study, one patient in the etanercept group died from thyroid cancer reported during the study; this event was considered possibly related to etanercept. From baseline to week 12/ET and to the end of the study period, investigator-reported TEAEs leading to permanent discontinuation of study drug occurred in ≥3 patients in each group. An overview of TEAEs from week 12 to week 52 is presented in the online supplementary table 4.

The incidence per 100 patient-years of serious infection, herpes zoster-related disease (including varicella) and malignancies was higher in the groups treated with peficitinib compared with placebo, although there was no clear dose-dependent increase (table 2B). No occurrence of VTE was reported during the study.

Clinical laboratory evaluations
At week 12/ET, reductions in platelet counts and dose-dependent increases in haemoglobin level were observed in the peficitinib 100 mg and 150 mg groups (table 3). Reductions in absolute neutrophil counts were also observed; this parameter also tended to decrease in the placebo group. Dose-dependent increases in creatine kinase, creatinine, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were observed in the peficitinib 100 mg and 150 mg groups until week 12/ET. There were no major changes from week 12/ET to week 52/ET in any of these parameters.

DISCUSSION
This was the first phase III, randomised, double-blind, placebo-controlled trial of peficitinib, a novel oral JAK inhibitor, in patients with RA who had an inadequate response to DMARDs. Results showed statistically significant increases by week 12 in ACR20 response rates compared with placebo for peficitinib doses of 100 mg/day and 150 mg/day. The results for the secondary efficacy variables, including ACR50, ACR70, DAS28-CRP and patient-reported outcomes such as HAQ-DI, supported the results for the primary efficacy variable. ACR20/50/70 showed rapid responses
Figure 1  Patient disposition. *The number of patients who were allocated at randomisation to either peficitinib 100 mg or peficitinib 150 mg starting from week 12. †Discontinuation up to week 12: discontinued at any time from date of randomisation through day 85. ‡Discontinuation for overall period: discontinued at any time from first dose of study drug through the last dose day for overall period.
through the first 4 to 8 weeks of treatment, which were either maintained or improved during long-term treatment up to week 52 (EOT). Even in the placebo group, improvements were observed after switching to peficitinib 100 mg or 150 mg and then maintained during the study. Treatment with etanercept appeared to provide numerically greater response rates than either peficitinib 100 mg or 150 mg, across all outcomes measured.

Of note, ACR20 response rates at week 12 following peficitinib 100 mg or 150 mg treatment were similar to those observed in previous phase III studies of tofacitinib or baricitinib; outcomes may therefore not be compared directly with previous studies evaluating the efficacy of other JAK inhibitors, including tofacitinib and baricitinib outcomes may therefore not be directly comparable with the current study.

Safety analysis indicated that peficitinib was well tolerated for up to 52 weeks. The incidence of TEAEs was similar for both peficitinib arms compared with placebo, and no new safety signals were observed in clinical laboratory results. Of note, a mean decrease in

### Table 1 Patient demographics and baseline characteristics (SAF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
<th>Peficitinib 150 mg (N=102)</th>
<th>Peficitinib 100 mg +150 mg (N=206)</th>
<th>Etanercept (open-label arm) (N=200)</th>
<th>Total (N=507)</th>
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<tr>
<td><strong>Female, n (%)</strong></td>
<td>73 (72.3)</td>
<td>77 (74.0)</td>
<td>78 (76.5)</td>
<td>155 (75.2)</td>
<td>138 (69.0)</td>
<td>366 (72.2)</td>
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<tr>
<td><strong>Age in years, mean (SD)</strong></td>
<td>56.3 (11.7)</td>
<td>54.1 (12.2)</td>
<td>55.0 (12.8)</td>
<td>54.5 (12.5)</td>
<td>55.5 (11.6)</td>
<td>55.3 (12.0)</td>
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<tr>
<td><strong>&lt;65 years, n (%)</strong></td>
<td>71 (70.3)</td>
<td>83 (79.8)</td>
<td>75 (73.5)</td>
<td>158 (76.7)</td>
<td>154 (77.0)</td>
<td>383 (75.5)</td>
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<td><strong>Study region, n (%)</strong></td>
<td></td>
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<td>Japan</td>
<td>83 (82.2)</td>
<td>85 (81.7)</td>
<td>83 (81.4)</td>
<td>168 (81.6)</td>
<td>164 (82.0)</td>
<td>415 (81.9)</td>
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<tr>
<td>Korea</td>
<td>10 (9.9)</td>
<td>11 (10.6)</td>
<td>11 (10.8)</td>
<td>22 (10.7)</td>
<td>22 (11.0)</td>
<td>54 (10.7)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>8 (7.9)</td>
<td>8 (7.7)</td>
<td>8 (7.8)</td>
<td>16 (7.8)</td>
<td>14 (7.0)</td>
<td>38 (7.5)</td>
</tr>
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<td><strong>Body weight in kg, mean (SD)</strong></td>
<td>58.52 (13.00)</td>
<td>59.90 (12.35)</td>
<td>57.69 (11.35)</td>
<td>58.81 (11.89)</td>
<td>58.29 (12.34)</td>
<td>58.54 (12.27)</td>
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<td><strong>RA duration in years, mean (SD)</strong></td>
<td>6.98 (6.57)</td>
<td>8.75 (7.12)</td>
<td>10.39 (8.23)</td>
<td>9.56 (7.71)</td>
<td>9.17 (8.00)</td>
<td>8.89 (7.66)</td>
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<td><strong>Tender joint count (68-joint, mean (SD)</strong></td>
<td>16.2 (10.7)</td>
<td>15.0 (9.4)</td>
<td>15.4 (9.5)</td>
<td>15.2 (9.4)</td>
<td>14.9 (9.3)</td>
<td>15.3 (9.6)</td>
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<td><strong>Swollen joint count (66-joint, mean (SD)</strong></td>
<td>12.9 (7.2)</td>
<td>12.4 (6.3)</td>
<td>12.8 (7.1)</td>
<td>12.6 (6.7)</td>
<td>11.9 (6.8)</td>
<td>12.4 (6.8)</td>
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<td><strong>Physician’s Global Assessment of disease activity (100 mm VAS), mean (SD)</strong></td>
<td>61.93 (19.35)</td>
<td>62.01 (20.11)</td>
<td>58.46 (19.35)</td>
<td>59.34 (19.71)</td>
<td>58.17 (19.87)</td>
<td>59.39 (19.71)</td>
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<td><strong>Subject’s Global Assessment of disease activity (100 mm VAS), mean (SD)</strong></td>
<td>58.99 (25.70)</td>
<td>57.54 (24.78)</td>
<td>59.52 (25.73)</td>
<td>58.52 (25.21)</td>
<td>57.52 (26.92)</td>
<td>58.22 (25.95)</td>
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<td><strong>Prior biological DMARD use only, n (%)</strong></td>
<td>90 (89.1)</td>
<td>90 (86.5)</td>
<td>89 (87.3)</td>
<td>179 (86.9)</td>
<td>162 (81.0)</td>
<td>431 (85.0)</td>
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<td><strong>Prior biological DMARD use only, n (%)</strong></td>
<td>0</td>
<td>0</td>
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<td><strong>Prior non-biological and biological DMARD use, n (%)</strong></td>
<td>11 (10.9)</td>
<td>14 (13.5)</td>
<td>13 (12.7)</td>
<td>27 (13.1)</td>
<td>38 (19.0)</td>
<td>76 (15.0)</td>
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<td><strong>Prior MTX use, n (%)</strong></td>
<td>89 (88.1)</td>
<td>94 (90.4)</td>
<td>92 (90.2)</td>
<td>186 (90.3)</td>
<td>179 (89.5)</td>
<td>454 (89.5)</td>
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<td><strong>Number of prior DMARDs (including biologicals), n (%)</strong></td>
<td></td>
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<tr>
<td><strong>1</strong></td>
<td>14 (13.9)</td>
<td>19 (18.3)</td>
<td>16 (15.7)</td>
<td>35 (17.0)</td>
<td>24 (12.0)</td>
<td>73 (14.4)</td>
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<td><strong>2</strong></td>
<td>56 (55.4)</td>
<td>57 (54.8)</td>
<td>57 (55.9)</td>
<td>114 (55.3)</td>
<td>109 (54.5)</td>
<td>279 (55.0)</td>
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<td><strong>≥3</strong></td>
<td>31 (30.7)</td>
<td>28 (26.9)</td>
<td>29 (28.4)</td>
<td>57 (27.7)</td>
<td>67 (33.5)</td>
<td>155 (30.6)</td>
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<td><strong>Concomitant DMARD at baseline, n (%)</strong></td>
<td>87 (86.1)</td>
<td>91 (87.5)</td>
<td>89 (87.3)</td>
<td>180 (87.4)</td>
<td>176 (88.0)</td>
<td>443 (87.4)</td>
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<td><strong>MTX</strong></td>
<td>57 (56.4)</td>
<td>63 (60.6)</td>
<td>62 (60.8)</td>
<td>125 (60.7)</td>
<td>117 (58.5)</td>
<td>299 (59.0)</td>
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<td><strong>DMARD except for MTX only</strong></td>
<td>30 (29.7)</td>
<td>28 (26.9)</td>
<td>27 (26.5)</td>
<td>55 (26.7)</td>
<td>59 (29.5)</td>
<td>144 (28.4)</td>
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<td><strong>MTX dose at baseline, mg/week</strong></td>
<td>11.35 (3.82)</td>
<td>11.28 (2.98)</td>
<td>10.77 (3.16)</td>
<td>11.03 (3.07)</td>
<td>11.12 (3.78)</td>
<td>11.13 (3.50)</td>
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<td><strong>Prior biological DMARD-IR</strong></td>
<td>5 (5.0)</td>
<td>9 (8.7)</td>
<td>7 (6.9)</td>
<td>16 (7.8)</td>
<td>15 (7.5)</td>
<td>36 (7.1)</td>
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</table>
Figure 2 (Continued)
Rheumatoid arthritis

Figure 2  (A) ACR20, ACR50 and ACR70 response rates at week 12/ET (FAS). (B) Response rates for ACR20 from baseline until week 52 and EOT (FAS). (C) Response rates for ACR50 from baseline until week 52 and EOT (FAS). (D) Response rates for ACR70 from baseline until week 52 and EOT (FAS). For all timepoints except for week 12/ET and EOT, observed data are plotted. For week 12/ET and EOT, in the case of early termination, ACR components were analysed using the LOCF method first, and then ACR20/50/70 responses were calculated. A pairwise comparison with the placebo group was performed using a logistic regression model with treatment group as the factor and inadequate response to prior biological DMARD use, concomitant DMARD use during the study period and region as covariates. P values were calculated using Wald’s Chi-square test with a closed testing procedure for multiplicity adjustment for ACR20 and no multiplicity adjustment for ACR50/70. 95% CI were based on a normal approximation to the binomial distribution (continuity corrected). Etanercept was an open-label reference arm and was not included in statistical comparisons with placebo.

*The odds ratio for the treatment difference in ACR70 between peficitinib 100 mg and placebo was not estimable with the planned logistic regression model (p=0.009 with an ad-hoc analysis using a logistic regression model with treatment group as the only explanatory variable). †Includes LOCF.

ACR, American College of Rheumatology; DMARD, disease-modifying anti-rheumatic drugs; EOT, end of treatment; ET, early termination; FAS, full analysis set; LOCF, last observation carried forward; N/E, not estimable.
**Rheumatoid arthritis**

**Figure 3** (Continued)
Figure 3 (Continued)
Although rates remained within the range approximately doubled with peficitinib compared with etanercept arms, for ethical reasons; comparisons between placebo and peficitinib arms are therefore limited. In addition, the study design did not allow for a statistical comparison of treatment differences in the open-label etanercept arm relative to the other arms. No radiographical assessments were conducted for this study, and it is therefore uncertain whether peficitinib inhibits radiographical progression in this population. Moreover, the patient population was drawn from Japan, Korea and Taiwan. Statistical comparisons with placebo were performed using analysis of covariance with no multiplicity adjustment. Etanercept was an open-label reference arm and was not included in statistical comparisons with placebo. *p<0.05; **p<0.01; ***p<0.001. ACR, American College of Rheumatology; ANCOVA, analysis of covariance; CRP, C-reactive protein; DAS28-CRP, Disease Activity Scores in 28 joints using CRP; DMARD, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; ET, early termination; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; IR, inadequate response; LOCF, last observation carried forward; PGA, Physician’s Global Assessment of disease activity; SGA, Subject’s Global Assessment of disease activity; SGAP, Subject’s Global Assessment of Pain; SJC66, swollen joint count at 66 joints; TJC68, tender joint count at 68 joints.

Figure 3 Changes from baseline to week 12/ET in DAS28-CRP scores and ACR core parameters (CRP, ESR, HAQ-DI, SGA, SGAP, PGA, TJC68 and SJC66) (FAS). For all timepoints except for week 12/ET, observed data are plotted. For week 12/ET, in the case of early termination, the LOCF method was used. Data were plotted as least-squares means with 95% CI based on ANCOVA model: change from baseline = treatment + baseline value + prior biological DMARD-IR + concomitant DMARD use + study region (Japan, Korea or Taiwan). Statistical comparisons with placebo were performed using analysis of covariance with no multiplicity adjustment. Etanercept was an open-label reference arm and was not included in statistical comparisons with placebo. *p<0.05; **p<0.01; ***p<0.001. ACR, American College of Rheumatology; ANCOVA, analysis of covariance; CRP, C-reactive protein; DAS28-CRP, Disease Activity Scores in 28 joints using CRP; DMARD, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; ET, early termination; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire – Disability Index; IR, inadequate response; LOCF, last observation carried forward; PGA, Physician’s Global Assessment of disease activity; SGA, Subject’s Global Assessment of disease activity; SGAP, Subject’s Global Assessment of Pain; SJC66, swollen joint count at 66 joints; TJC68, tender joint count at 68 joints.

haemoglobin levels, which might be attributable to JAK2 inhibition, was not observed even with the highest dose of 150 mg/day. These safety results are consistent with those from short-term (12 week) treatment with 25 to 150 mg/day peficitinib monotherapy.13

With regard to TEAEs of special interests, no apparent dose dependency was observed in the incidence of herpes zoster-related disease (including varicella), serious infections or malignancies. Previous safety data for the use of tofacitinib suggest that Asian populations may be specifically at risk of developing herpes zoster when receiving JAK inhibitors.22 In line with this, the incidence of herpes zoster-related disease was approximately doubled with peficitinib compared with etanercept in our study, although rates remained within the range previously observed with tofacitinib and baricitinib in Japanese/Korean/Taiwanese populations.22-25 As historical data of vaccination for herpes zoster or varicella in each patient were not captured in this study, the relationship between the observed incidence and vaccination rate is unknown and further investigation would be required to elucidate this. Lastly, although previous studies have shown an association between JAK inhibitors and VTE,26 no incidence of VTE was observed in our study.

Greater clinical improvements were observed with peficitinib 150 mg versus peficitinib 100 mg. In this study, no marked increase in AEs was observed with peficitinib 150 mg compared with 100 mg and both doses demonstrated efficacy and tolerability, thus broadening the potential treatment options for those with refractory disease. However, further evaluation is needed to establish whether peficitinib >150 mg/day may provide even greater clinical benefits, without additional safety concerns.

The strengths of this study include the 52-week treatment period, which allowed for assessment of long-term efficacy and safety. The study population comprised patients who previously had an inadequate response or intolerance to either conventional synthetic or biological DMARDs, thus representing a patient population with more restricted treatment options. One limitation of this study is that placebo treatment was of shorter duration (12 weeks) compared with the peficitinib and etanercept arms, for ethical reasons; comparisons between placebo and peficitinib arms are therefore limited. In addition, the study design did not allow for a statistical comparison of treatment differences in the open-label etanercept arm relative to the other arms. No radiographical assessments were conducted for this study, and it is therefore uncertain whether peficitinib inhibits radiographical progression in this population. Moreover, the patient population was drawn from Japan, Korea and Taiwan and although the results reflect populations of more than one country, they lack global diversity. The baseline HAQ-DI score of 1.0 for the study population was low, especially considering the mean DAS-CRP/ESR of 3.3 to 6.0 and mean RA duration of almost 9 years, but these parameters are in line with findings from previous studies of tofacitinib27,28 and baricitinib29 in Japanese populations.

As previously described, kinase assays showed peficitinib inhibits the activity of all JAK family members with similar
### Table 2A  TEAEs for weeks 0 to 12 and overall period (SAF)

<table>
<thead>
<tr>
<th></th>
<th>Weeks 0 to 12</th>
<th>Overall period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=101)</td>
<td>Peficitinib 100 mg (N=104)</td>
</tr>
<tr>
<td>All TEAEs</td>
<td>54 (53.5)</td>
<td>59 (56.7)</td>
</tr>
<tr>
<td>Drug-related TEAEs*</td>
<td>29 (28.7)</td>
<td>33 (31.7)</td>
</tr>
<tr>
<td>SAEs</td>
<td>4 (4.0)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Drug-related SAEs*</td>
<td>3 (3.0)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>≥Grade 3 TEAE†</td>
<td>8 (7.9)</td>
<td>6 (5.8)</td>
</tr>
</tbody>
</table>

**SAEs leading to permanent discontinuation of study drug or reference drug**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>4 (4.0)</td>
<td>6 (5.8)</td>
<td>3 (2.9)</td>
<td>9 (4.4)</td>
</tr>
<tr>
<td>Drug-related*</td>
<td>1 (1.0)</td>
<td>4 (3.8)</td>
<td>2 (2.0)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>SAEs</td>
<td>2 (2.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Drug-related SAEs*</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

Treatment-emergent adverse events are defined as any adverse event that started or worsened in severity after initial dose of study drug or reference drug through the follow-up period. All values are n (%).

*Possible or probable, as assessed by the investigator or records where relationship is missing.
†Based on National Cancer Institute Common Terminology Criteria for Adverse Events grading; grade 3 = severe or medically significant, grade 4 = life threatening, grade 5 = death related to AE.
AE, adverse event; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

### Table 2B  Incidence of serious infections, herpes zoster-related disease and malignancy per 100 patient-years, from week 0 to week 52 (SAF)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-years</td>
<td>22.6</td>
<td>88.2</td>
<td>92.1</td>
<td>180.3</td>
</tr>
<tr>
<td>Incidence rate/100 patient-years (95% CI)</td>
<td>0.0</td>
<td>1.1 (0.2 to 8.1)</td>
<td>2.2 (0.5 to 8.7)</td>
<td>1.7 (0.5 to 5.2)</td>
</tr>
</tbody>
</table>

**Herpes zoster-related disease (including varicella)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-years</td>
<td>22.6</td>
<td>86.8</td>
<td>90.9</td>
<td>177.7</td>
</tr>
<tr>
<td>Incidence rate/100 patient-years (95% CI)</td>
<td>0.0</td>
<td>5.8 (2.4 to 13.8)</td>
<td>4.4 (1.7 to 11.7)</td>
<td>5.1 (2.6 to 9.7)</td>
</tr>
</tbody>
</table>

**Malignancies**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
<th>Placebo (N=101)</th>
<th>Peficitinib 100 mg (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-years</td>
<td>22.6</td>
<td>88.1</td>
<td>92.8</td>
<td>180.9</td>
</tr>
<tr>
<td>Incidence rate/100 patient-years (95% CI)</td>
<td>0.0</td>
<td>2.3 (0.6 to 9.1)</td>
<td>0.0 (- to -)</td>
<td>1.1 (0.3 to 4.4)</td>
</tr>
</tbody>
</table>

Patient-years was calculated from initial dose up to first incidence of the event for patients who had at least one event, and from initial dose through follow-up for patients who had no events; incidence rate is calculated as (100 × number of patients who had at least one incidence/total patient-years).

*Included adverse events occurring during treatment with peficitinib in patients who were initially treated with placebo and switched to peficitinib at week 12.
SAF, safety analysis set.
In conclusion, peficitinib at doses of 100 mg/day and 150 mg/day was superior to placebo in reducing RA symptoms, and these improvements were maintained throughout the study period. Peficitinib was generally well tolerated in long-term treatment up to 52 weeks. Peficitinib may therefore be a viable treatment option for patients who fail to respond to previous lines of therapy with other biological and non-biological DMARDs.

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Contributors All authors met the following criteria for authorship: substantial contributions to the acquisition of data; analysis and interpretation of data for the work; contribution to drafting the work and revising it critically; giving the final approval of the version submitted and agreeing to be accountable for all aspects of the work.

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Table 3 Change from baseline in haematological and bioclinical parameters to week 12/ET and week 52/ET (SAF)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline result</th>
<th>Week 52/ET (SAF)</th>
<th>Week 12/ET (SAF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count (10⁹/L)</td>
<td>5.6 (3.9–7.4)</td>
<td>5.6 (3.9–7.4)</td>
<td>5.6 (3.9–7.4)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>13.1 (12.0–14.4)</td>
<td>13.1 (12.0–14.4)</td>
<td>13.1 (12.0–14.4)</td>
</tr>
<tr>
<td>Platelets (10⁹/L)</td>
<td>273 (197–354)</td>
<td>273 (197–354)</td>
<td>273 (197–354)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>59.6 (40.2–90.2)</td>
<td>59.6 (40.2–90.2)</td>
<td>59.6 (40.2–90.2)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>23.1 (12.8)</td>
<td>23.1 (12.8)</td>
<td>23.1 (12.8)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.77 (0.87)</td>
<td>2.77 (0.87)</td>
<td>2.77 (0.87)</td>
</tr>
</tbody>
</table>

| Adverse event * | Astellas Pharma Inc, Tokyo, Japan |

12 JAK inhibition may contribute to the clinical efficacy of peficitinib in RA patients. However, the clinical significance of the mouse model findings is unclear and additional investigation is necessary to elucidate the involvement of TYK2 in the pathogenesis of RA.

In conclusion, peficitinib at doses of 100 mg/day and 150 mg/day was superior to placebo in reducing RA symptoms, and these improvements were maintained throughout the study period. Peficitinib was generally well tolerated in long-term treatment up to 52 weeks. Peficitinib may therefore be a viable treatment option for patients who fail to respond to previous lines of therapy with other biological and non-biological DMARDs.
Rheumatoid arthritis

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Patient consent for publication Not required.

Ethics approval This study was conducted in accordance with Good Clinical Practice, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and local laws and regulations. The protocol and amendments were approved by an Institutional Review Board at each study site, and safety data were reviewed by the independent Data and Safety Monitoring Board. Each patient provided written informed consent prior to treatment initiation.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data are available upon reasonable request.

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10 US Food and Drug Administration. NDA approval for Xeljanz (tofacitinib) 5 mg tablets, 2012. Available: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/203214Orig1s000ltpdf
26 Scott IC, Hider SL, Scott DL. Tromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? Drug Saf 2018;41:645–53.
SUPPLEMENTARY METHODS

Randomisation

Randomisation was conducted by study region using a biased-coin minimisation procedure with study centre, inadequate response to previous biological DMARDs, and concomitant DMARD use at treatment initiation as stratification factors.

Patient inclusion and exclusion criteria

Inclusion criteria

Patients were eligible for the study if all of the following applied:

1. Received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study obtained
2. A man or woman aged ≥20 years at the time of informed consent.
3. Had RA diagnosed according to the 1987 ACR criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria.
4. Did not receive the following drugs, or received the drugs with stable dosage for at least 28 days prior to the baseline (start of treatment) for RA treatment: NSAIDs (excluding topical formulations), oral morphine or equivalent opioid analgesics (≤30 mg/day), acetaminophen or oral corticosteroids (≤10 mg/day in prednisolone equivalent).
5. At screening, had active RA as evidenced by both of the following:
   - ≥6 tender/painful joints (using 68-joint assessment)
   - ≥6 swollen joints (using 66-joint assessment)
6. CRP >0.50 mg/dL at screening.
7. Met the ACR 1991 Revised Criteria for the Classification of Global Functional Status in RA Class I, II or III at screening.
8. Inadequate responder to (including patients who were intolerant of) at least 1 DMARD administered for at least 90 days prior to screening.
9. When the following DMARDs were concomitantly administered to patient, the drugs had to be administered for at least 90 days prior to screening, and had to be stable from at least 28 days prior to screening until the end of the administration period of study drug or reference drug.
   - MTX
32. Hydroxychloroquine
33. Salazosulfapyridine
34. Gold
35. D-penicillamine
36. Lobenzarit
37. Actarit
38. Bucillamine
39. Iguratimod
40. Willing and able to comply with the study requirements.

Exclusion criteria

Patients were excluded from participation if any of the following applied:

1. Receipt of a biological DMARD within the specified period:
   - Anakinra: within 28 days prior to baseline
   - Adalimumab, infliximab: within 56 days prior to baseline
   - Golimumab, certolizumab pegol: within 70 days prior to baseline
   - Abatacept, tocilizumab: within 84 days prior to baseline
   - Denosumab: within 150 days prior to baseline
   - Rituximab: within 180 days prior to baseline
   - Etanercept (regardless of timeframe)

2. Inadequate responder to at least 3 biological DMARDs as determined by investigator/subinvestigator.

3. Receipt of a non-biological DMARD listed below or other drugs used in the treatment of RA within 28 days prior to baseline. Leflunomide was prohibited within 180 days prior to baseline. Alternatively, leflunomide was prohibited within 28 days prior to baseline if washout with cholestyramine for at least 17 days was completed at least 28 days prior to baseline. However, topical drugs other than those for the treatment of RA could be used concomitantly.
   - Leflunomide
   - Tacrolimus
   - Cyclosporine
   - Cyclophosphamide
   - Azathioprine
   - Minocycline
   - Mizoribine
4. Receipt of tofacitinib or other JAK inhibitors (including other investigational drugs), regardless of timeframe.

5. Receipt of intra-articular, intravenous, intramuscular or endorectal (excluding suppositories for anal diseases) corticosteroid within 28 days prior to baseline.

6. Prior participation in any study of peficitinib and had received peficitinib or placebo.

7. Receipt of other investigational drugs within 90 days or within 5 half-lives, whichever was longer, prior to baseline.

8. Receipt of plasma exchange therapy within 60 days prior to baseline.

9. Had undergone joint drainage, had received local anaesthesia and nerve block, or had received articular cartilage protectant at the assessed joint within 28 days prior to baseline.

10. Had undergone surgery and had residual effects in the assessed joints at the discretion of investigator/subinvestigator, or was scheduled to undergo surgery that could affect the study evaluation of the assessed joints at the discretion of investigator/subinvestigator.

11. A diagnosis of inflammatory arthritis (psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, sarcoidosis, etc.) other than RA.

12. Any of the following laboratory values during the screening test period:

   - Haemoglobin <9.0 g/dL
   - Absolute neutrophil count <1000/μL
   - Absolute lymphocyte count <800/μL
   - Platelet count <75000/μL
   - Alanine aminotransferase (ALT) ≥2 × upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) ≥2 × ULN
   - Total bilirubin ≥1.5 × ULN
   - Estimated glomerular filtration rate (eGFR) ≤40 mL/min as measured by the modification of diet in renal disease method
   - β-D-glucan >ULN [in case of Japan: ≥11 pg/mL]
   - Positive hepatitis B surface (HBs) antigen, hepatitis B core (HBe) antibody, HBs antibody or HBV-DNA quantitation (However, patient with negative HBs antigen and HBV-DNA quantitation, and positive HBe antibody and/or HBs antibody was eligible if HBV-DNA was monitored by HBV-DNA quantitation at every scheduled visit after initiation of study drug or reference drug administration)
   - Positive hepatitis C virus antibody
13. A history of or concurrent active tuberculosis. Eligibility criteria for tuberculosis are tabulated at the end of this section.

14. Any of the following in terms of infections except for tuberculosis:

- History of or concurrent severe herpes zoster (associated with Hunt syndrome or having ulcerative lesions) or disseminated herpes zoster
- History of multiple recurrences (at least twice) of localised herpes zoster
- Serious infection requiring hospitalisation within 90 days prior to baseline
- Had received intravenous antibiotics within 90 days prior to baseline.
  (However, prophylactic antibiotics were allowed)
- With high risk of infection (e.g., patient with urinary catheter) at the discretion of investigator

15. A history of or concurrent interstitial pneumonia and investigator judged that it was inappropriate for the patient to participate in this study.

16. A history of or concurrent malignant tumour (except for successfully treated basal cell carcinoma).

17. Receipt of live or live attenuated virus vaccination within 56 days prior to baseline.
   (Inactivated vaccines including influenza and pneumococcal vaccines were allowed).

18. A history of or concurrent demyelinating disorders.

19. Any ongoing severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, infectious or autoimmune disease except for RA (excluding Sjogren’s syndrome and chronic thyroiditis), or any ongoing illness which would make the patient unsuitable for the study as determined by the investigator.

20. A history of clinically significant allergy (including allergies such as systemic urticaria induced by specific antigens and drugs, anaphylaxis, and allergy associated with shock necessitating hospitalised treatment).

21. Had received medications that were cytochrome P450 3A substrates with narrow therapeutic range within 14 days prior to baseline, including dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus and disopyramide.

22. A history of or concurrent cardiac failure, defined as New York Heart Association classification Class III or higher.

23. A history of or concurrent prolonged QT syndrome, defined as QTc ≥500 ms, at screening

24. A history of positive human immunodeficiency virus infection.

25. Was a woman who was pregnant or might be pregnant, was nursing, wished to conceive for a period running from the time informed consent was given within 60
days after the EOT (including reference drug), or for whom the possibility of pregnancy could not be ruled out as a result of the serum pregnancy test given at the time of screening.

26. Was a man who could not practice at least 2 types of contraception from the time of informed consent to 90 days after the EOT (including reference drug), or patient was a woman with childbearing potential who could not practice at least 2 types of contraception from the time of informed consent to 60 days after the EOT (including reference drug).

27. Male patient who did not agree not to donate sperm starting at informed consent and through the treatment period and for at least 90 days after final study drug (or reference drug) administration. Female patient who did not agree not to donate ova starting at informed consent through the treatment period and for 60 days after final study drug (or reference drug) administration.

28. Judged unsuitable to participate in the study for other reasons by the investigator.

29. A history or complication of lymphatic diseases such as lymphoproliferative disorder, lymphoma and leukaemia.

30. A history of or current congenital short QT syndrome, defined by QTc <330 msec.

**Tuberculosis history and eligibility for enrolment**

<table>
<thead>
<tr>
<th>History of active tuberculosis</th>
<th>Chest X-ray for tuberculosis</th>
<th>Tuberculosis infection(a)</th>
<th>Exposure to patients with infective tuberculosis (interview)</th>
<th>Eligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Not eligible</td>
</tr>
<tr>
<td>Absent</td>
<td>Abnormal (active)</td>
<td>-</td>
<td>-</td>
<td>Not eligible</td>
</tr>
<tr>
<td>Abnormal (old)(^a)</td>
<td>Abnormal (active)</td>
<td>Either exposed or not exposed</td>
<td>Eligible if prophylaxis was given(^c)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Positive</td>
<td>Either exposed or not exposed</td>
<td>Eligible if prophylaxis was given(^c)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Exposed</td>
<td>Eligible if prophylaxis was given(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Not exposed</td>
<td>Eligible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Old tuberculosis was evidenced if chest X-ray reveals pleural thickening, band-like shadow and calcification ≥5 mm. A chest X-ray within 90 days prior to baseline could substitute for the screening test.

\(^b\)T-spot or Quantiferon Gold test was first priority. When the result was equivocal or invalid, a retest including other test methods was allowed. If a retest was not performed, the criteria for positive results were followed.

\(^c\)When T-spot or Quantiferon Gold test was not feasible, tuberculin test was performed. Tuberculin was defined as...
positive with a red spot covering an area of ≥20 mm (10 mm for Korea, 5 mm for Taiwan), or induration. Tests
carried out within 90 days prior to baseline could be used for diagnosis.

*For Japan and Korea, patient had to receive or have received prophylaxis with isoniazid or rifampicin for 6 to 9
months, starting from at least 21 days prior to baseline. For Taiwan, patient had to receive or have received
prophylaxis with isoniazid for 9 months, starting from at least 21 days prior to baseline.

**Prior medication**

Prior medication recorded included DMARDs and prohibited concomitant medications taken
≤90 days prior to baseline, and restricted concomitant medications and rescue medications
taken ≤28 days prior to baseline. The following biological DMARDs were prohibited within
the stated periods before baseline: etanercept (regardless of timeframe); anakinra (≤28
days); adalimumab and infliximab (≤56 days); golimumab and certolizumab pegol (≤70
days); abatacept and tocilizumab (≤84 days); denosumab (≤150 days); or rituximab (≤180
days).

Non-biological DMARDs were prohibited within 28 days of baseline, with the exception of:
MTX (with concomitant folic acid whenever possible); hydroxychloroquine;
salazosulfapyridine; gold; D-penicillamine; lefunzol; actarit; bucillamine; and iguratimod.
Medications used to treat RA (including biological and non-biological DMARDs, tacrolimus,
cyclosporine, cyclophosphamide, azathioprine, and minocycline) were also prohibited ≤28
days before baseline, with the exception of topical drugs.

Patients were not permitted to have received treatment with the following drugs, unless
received on a stable dosage for ≥28 days prior to baseline and within the following specified
doses: NSAIDs (excluding topical formulations), oral morphine or equivalent opioid
analgesics (≤30 mg/day), acetaminophen or oral corticosteroids (≤10 mg/day in prednisolone
equivalent).

Receipt of the following drugs and therapies was also prohibited: oral corticosteroids at
doses >10 mg/day prednisolone equivalent and corticosteroids administered via other routes
(excepting topical corticosteroid) ≤28 days prior to baseline; tofacitinib or another JAK
inhibitor regardless of timeframe; lefunomide ≤180 days prior to baseline, or ≤28 days prior
to baseline if washout with cholestyramine for ≥17 days was completed ≥28 days prior to
baseline; other study drugs within 90 days or 5 half-lives, whichever was longer, prior to
baseline; CYP3A substrates with a narrow therapeutic range, such as dihydroergotamine,
ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide ≤14 days prior to
baseline; live or live attenuated virus vaccinations ≤56 days prior to baseline; and other
surgical treatments that could affect the evaluation of peficitinib.
The following rescue medications could be used ≤28 days prior to baseline, and within the following specified time periods, but not within 24 h of baseline joint assessment and only for the treatment of an AE: NSAIDs: for ≤3 days, and analgesics other than NSAIDs for ≤7 consecutive days.

Concomitant medication

With the exception of etanercept given as the reference drug, the following biological DMARDs were prohibited during study treatment: adalimumab, anakinra, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, rituximab, etanercept and denosumab. Patients receiving allowed non-biological DMARDs (see above) were required to maintain the same dosage and administration schedule from ≥28 days before screening until the end of the study. The only other permitted concomitant therapies were rescue medications, such as NSAIDs, oral morphine (≤30 mg/day or equivalent of other opioid analgesics), acetaminophen, oral corticosteroids (prednisolone or equivalent, ≤10 mg/day), and topical drugs other than those used to treat RA. Following a protocol amendment in April 2015, MTX was included in the permitted concomitant DMARDs.

Sample size determination

From the results of RAJ1 and studies of other RA drugs, it was calculated that 62 patients per treatment arm would provide 90% power to detect a significant difference with a two-sided significance level of 0.05, assuming ACR20 response rates at Week 12 of 25%, 54.5% and 65.5% in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively. Additionally, ICH guidelines [18] and the Japan Ministry of Health Labour and Welfare guidelines on methodology for clinical assessment of antirheumatic drugs [19] states that 100 patients per treatment arm is required to observe delayed AEs at a frequency of 0.5–5% and to determine if there is an increase in high-frequency AEs during later treatment stages. The sample size of the etanercept reference group was set as 200 in order to give 95% probability of detecting at least one patient with an AE occurring at an incidence rate of 1.5%

Statistical analyses

For the primary analysis of ACR20 response at Week 12/ET, pairwise comparisons to placebo were performed at each peficitinib dose level by using a logistic regression model with treatment group (placebo, peficitinib 100 mg and peficitinib 150 mg) as the factor and prior biological DMARD-IR, concomitant DMARD use at baseline, and study region (Japan,
Korea and Taiwan) as the covariates. Multiplicity adjustment in the primary analysis was carried out using the following closed testing procedure:

Step 1. ACR20 response at Week 12/ET: peficitinib 150 mg vs placebo
Step 2. ACR20 response at Week 12/ET: peficitinib 100 mg vs placebo

To assess the robustness of findings from the primary efficacy analyses, the following sensitivity analyses were performed for the ACR20 response at Week 12/ET: using the last observation carried forward (LOCF) method for components and non-responder imputation for response; using the LOCF method for components and the per protocol set (all patients in the FAS who received study or reference treatment for at least 8 weeks with a treatment compliance of ≥75% and had no major protocol violations) as the analysis set; using data as collected with no imputation or multiplicity adjustment; using multiple imputation assuming missing randomisation mechanism; using placebo multiple imputation; and a re-randomisation test.

The other analyses for primary and secondary endpoints, which include continuous variables, raw value and change from baseline at each visit (baseline, Weeks 4, 8, 12, 12/ET), were conducted using the analysis of covariance model with treatment group (placebo, peficitinib 100 mg and 150 mg) as the factor and the prior biological DMARD-IR, concomitant DMARD at baseline use, study region (Japan, Korea and Taiwan), and baseline value as the covariates.

Categorical variables at each visit were also analysed using the logistic regression model, as described for the primary efficacy variable, unless otherwise specified in the statistical analysis plan.

For missing data, the last observation carried forward (LOCF) method was used for efficacy and laboratory variables at Week 12/ET and Week 52/ET. All outliers were included in the analysis.

SUPPLEMENTARY RESULTS

Incidence of malignancies

A total of four patients experienced malignancies: three treated with peficitinib (including one patient who switched from placebo) and one treated with etanercept.
A 65-year-old female receiving peficitinib 100 mg developed a gastric adenocarcinoma at Day 147 (Week 21). Her medical history included iron deficiency anaemia and left ventricular hypertrophy. Concomitant medications included DMARDs (oral hydroxychloroquine, 400 mg/day; oral MTX, 15 mg/week; oral sulphasalazine, 1000 mg/day), isoniazid, pyridoxine HCl, tramadol and acetaminophen, prednisolone, Celebrex and folic acid. On Day 100 (Week 14), the patient presented with epigastralgia, poor appetite and occasional nausea. Peficitinib treatment was suspended on Day 119 (Week 17), and a gastric ulcer was revealed by upper gastrointestinal panendoscopy. The patient was discharged on Day 120 and peficitinib treatment resumed on Day 128. On Day 147 (Week 21), adenocarcinoma was diagnosed by pathological biopsy and peficitinib treatment permanently discontinued on Day 152 (Week 21). Endoscopic mucosal resection was conducted on Day 183 (Week 26) and the adenocarcinoma and gastric ulcer were considered to be resolving at Day 281 (Week 40). Other adverse events experienced by the patient during the study included renal function impairment, alanine aminotransaminase elevation and cough. The investigator judged the gastric ulcer and adenocarcinoma to be possibly related to peficitinib.

An 86-year-old male receiving peficitinib 100 mg developed advanced colon cancer at Day 140 (Week 20). The patient had a medical history of hypertension, type 2 diabetes mellitus, dyslipidemia, prior cerebral infarction and eczema. The patient concomitantly received DMARDs (oral salazosulfapyridine, 1000 mg/day; oral MTX, 6 mg/week), enalapril maleate, glimepiride, linagliptin, clopidogrel sulfate, pitavastatin calcium, amlodipine besilate, famotidine, metformin hydrochloride, folic acid and loxoprofen sodium. A decrease in haemoglobin (99 g/L; normal range 135–175 g/L) was noted on Day 83 (Week 11) and advanced colon cancer diagnosed on Day 140 (Week 20). Peficitinib was discontinued on Day 142 (Week 20) and MTX reduced to 5 mg/week due to concerns of folate deficiency anaemia. Following laparoscopic rectal resection on Day 182 (Week 26), the patient experienced post-operative anastomotic leakage and peritonitis, which began to resolve on Day 210 (Week 30). The patient was discharged from hospital on Day 223 (Week 31). The investigator considered the colon cancer likely to have been present prior to the study and its development unrelated to peficitinib treatment.

A 55-year-old female who switched from placebo to peficitinib 100 mg at Day 86 (Week 12) developed breast cancer at Day 216 (Week 30). The patient had a medical history of spondylosis deformans, erosive gastritis, atypical psychosis, hypertension, sinusitis, herpes zoster (Mar-2015) and osteoporosis. Concomitant
medications included oral MTX (16 mg/week), celecoxib, prednisolone, isoniazid, folic acid, carbocisteine, lansoprazole, loxoprofen sodium, alfacalcidol, magnesium oxide, zolpidem tartrate, valsartan, risperidone, trihexyphenidyl hydrochloride, zotepine and clarithromycin. Following diagnosis with left breast cancer on Day 216 (Week 30), peficitinib was immediately discontinued. Left mastectomy was performed on Day 258 (Week 37) and chemotherapy begun on Day 292 (Week 41). The breast cancer was judged to be resolving on Day 467 (Week 66). The event was considered by the investigator to be possibly related to peficitinib.

- A 46-year-old female receiving etanercept developed thyroid cancer during follow up. The patient had a medical history of pericarditis, dilated cardiomyopathy, chronic cystitis, fatty liver disease and anaemia. Concomitant medications included DMARDs (oral bucillamine, 200 mg/day; oral MTX, 12 mg/week), prednisolone, folic acid, celecoxib, diclofenac sodium, rabeprazole sodium, alendronate, Baktar, spironolactone and bisoprolol fumarate. Other adverse events experienced by the patient during the study included bradycardia, common cold, chest pain and cough. Treatment with MTX was discontinued on Day 297 (Week 42) following development of the persistent cough. The patient completed the course of etanercept on Day 358 (Week 51). Anaplastic thyroid cancer was diagnosed on Day 381 (Week 54) and treatment with bucillamine discontinued on Day 394 (Week 56). The patient developed multiple metastases and died on Day 547 following a thoracic aorta rupture due to cancer invasion. The investigator considered the development of thyroid cancer possibly related to etanercept.
## SUPPLEMENTARY TABLES

### Supplementary Table 1. Sensitivity analysis of ACR20 response

<table>
<thead>
<tr>
<th></th>
<th>Number of responders, n (%)</th>
<th>Treatment difference versus placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Difference (%)^*</td>
<td>Odds ratio†</td>
</tr>
<tr>
<td><strong>ACR20 response at Week 12/ET (LOCF and non-responder imputation) (FAS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (N=101)</td>
<td>29 (28.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg (N=104)</td>
<td>57 (54.8)</td>
<td>26.1</td>
<td>3.08</td>
</tr>
<tr>
<td>Peficitinib 150 mg (N=102)</td>
<td>71 (69.6)</td>
<td>40.9</td>
<td>5.68</td>
</tr>
<tr>
<td>Etanercept (open-label arm) (N=200)</td>
<td>163 (81.5)</td>
<td>52.8</td>
<td>-</td>
</tr>
<tr>
<td><strong>ACR20 response at Week 12/ET (LOCF) (re-randomisation test§) (FAS)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Peficitinib 150 mg versus placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg versus placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ACR20 response at Week 12 (observed data) (FAS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (N=88)</td>
<td>29 (33.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg (N=96)</td>
<td>57 (59.4)</td>
<td>26.4</td>
<td>2.98</td>
</tr>
<tr>
<td>Peficitinib 150 mg (N=92)</td>
<td>71 (77.2)</td>
<td>44.2</td>
<td>6.97</td>
</tr>
<tr>
<td>Etanercept (open-label arm) (N=191)</td>
<td>162 (84.8)</td>
<td>51.8</td>
<td>-</td>
</tr>
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<td><strong>ACR20 response at Week 12/ET (LOCF) (PPS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (N=91)</td>
<td>30 (33.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg (N=92)</td>
<td>55 (59.8)</td>
<td>26.8</td>
<td>3.05</td>
</tr>
<tr>
<td>Peficitinib 150 mg (N=95)</td>
<td>72 (75.8)</td>
<td>42.8</td>
<td>6.42</td>
</tr>
<tr>
<td>Etanercept (open-label arm) (N=188)</td>
<td>160 (85.1)</td>
<td>52.1</td>
<td>-</td>
</tr>
</tbody>
</table>
### ACR20 response at Week 12 (multiple imputation assuming missing at random) (FAS)

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate</th>
<th>Median Change</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=101)</td>
<td>32.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg (N=103)</td>
<td>58.7%</td>
<td>26.7</td>
<td>1.70</td>
<td>5.57</td>
<td>&lt;0.001</td>
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<tr>
<td>Peficitinib 150 mg (N=102)</td>
<td>75.8%</td>
<td>43.7</td>
<td>3.52</td>
<td>12.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etanercept (open-label arm)</td>
<td>83.5%</td>
<td>51.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ACR20 response at Week 12 (placebo multiple imputation) (FAS)

<table>
<thead>
<tr>
<th>Group</th>
<th>Response Rate</th>
<th>Median Change</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=101)</td>
<td>31.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg (N=103)</td>
<td>56.4%</td>
<td>25.2</td>
<td>1.61</td>
<td>5.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peficitinib 150 mg (N=102)</td>
<td>72.4%</td>
<td>41.2</td>
<td>3.09</td>
<td>10.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etanercept (open-label arm)</td>
<td>82.3%</td>
<td>51.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; LOCF, last observation carried forward; N, total number of responders and non-responders (percentages based on N); PPS, per protocol set. Patients with all baseline ACR components data missing were not included in percentages because ACR20 response cannot be calculated.

*Difference in proportion of responders (each group minus placebo)

†Based on logistic regression model: ACR20 response (responder, non-responder) = treatment + inadequate response to prior biological DMARD use (No, Yes) + concomitant DMARD use (No, Yes) + study region (Japan, Korea, and Taiwan). Odds ratio >1 favours peficitinib

‡CI was based on normal approximation to the binomial distribution

§Wald’s chi-squared test with no multiplicity adjustment. Etanercept was an open-label reference group and was not included in statistical comparisons with placebo

‖Re-randomisation test using the two-sided Monte Carlo p value. Based on logistic regression model: ACR20 response (responder, non-responder) = treatment + inadequate response to prior biological DMARD use (No, Yes) + concomitant DMARD use (No, Yes) + study region (Japan, Korea, or Taiwan)
**Supplementary Table 2.** Subgroup analysis of ACR20-CRP response at Week 12/ET (FAS)

<table>
<thead>
<tr>
<th>Number of prior biological DMARDs</th>
<th>Placebo n/N (%)</th>
<th>Peficitinib 100 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Peficitinib 150 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Etanercept n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28/90 (31.1)</td>
<td>52/90 (57.8)</td>
<td>3.10 (1.67, 5.74)*</td>
<td>65/89 (73.0)</td>
<td>6.03 (3.15, 11.55)*</td>
<td>137/162 (84.6)</td>
</tr>
<tr>
<td>1</td>
<td>2/7 (28.6)</td>
<td>6/8 (75.0)</td>
<td>N/E</td>
<td>9/9 (100.0)</td>
<td>N/E</td>
<td>25/28 (89.3)</td>
</tr>
<tr>
<td>2</td>
<td>1/4 (25.0)</td>
<td>1/4 (25.0)</td>
<td>N/E</td>
<td>2/4 (50.0)</td>
<td>N/E</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>--</td>
<td>1/2 (50.0)</td>
<td>N/E</td>
<td>--</td>
<td>--</td>
<td>1/1 (100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior biological DMARD-IR</th>
<th>Placebo n/N (%)</th>
<th>Peficitinib 100 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Peficitinib 150 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Etanercept n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2/5 (40.0)</td>
<td>4/9 (44.4)</td>
<td>N/E</td>
<td>5/7 (71.4)</td>
<td>N/E</td>
<td>12/15 (80.0)</td>
</tr>
<tr>
<td>No</td>
<td>29/96 (30.2)</td>
<td>56/95 (58.9)</td>
<td>3.35 (1.84, 6.10)†</td>
<td>71/95 (74.7)</td>
<td>6.90 (3.64, 13.05)†</td>
<td>155/185 (83.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant DMARD use</th>
<th>Placebo n/N (%)</th>
<th>Peficitinib 100 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Peficitinib 150 mg n/N (%)</th>
<th>OR versus placebo (95% CI)</th>
<th>Etanercept n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>27/87 (31.0)</td>
<td>51/91 (56.0)</td>
<td>2.84 (1.54, 5.27)‡</td>
<td>67/89 (75.3)</td>
<td>6.92 (3.55, 13.51)‡</td>
<td>149/176 (84.7)</td>
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<tr>
<td>MTX</td>
<td>19/57 (33.3)</td>
<td>39/63 (61.9)</td>
<td>3.24 (1.52, 6.91)†</td>
<td>50/62 (80.6)</td>
<td>8.75 (3.74, 20.48)*</td>
<td>92/117 (78.6)</td>
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<tr>
<td>DMARDs other than MTX only</td>
<td>8/30 (26.7)</td>
<td>12/28 (42.9)</td>
<td>N/E</td>
<td>17/27 (63.0)</td>
<td>N/E</td>
<td>57/59 (96.6)</td>
</tr>
<tr>
<td>No</td>
<td>4/14 (28.6)</td>
<td>9/13 (69.2)</td>
<td>N/E</td>
<td>9/13 (69.2)</td>
<td>N/E</td>
<td>18/24 (75.0)</td>
</tr>
<tr>
<td>MTX dose (mg/week) at baseline</td>
<td>Placebo</td>
<td>Peficitinib 100 mg</td>
<td>Peficitinib 150 mg</td>
<td>Etanercept</td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>n/N (%)</td>
<td>n/N (%) OR versus placebo (95% CI)</td>
<td>n/N (%) OR versus placebo (95% CI)</td>
<td>n/N (%) OR versus placebo (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/44 (27.3)</td>
<td>21/41 (51.2)</td>
<td>N/E</td>
<td>26/40 (65.0)</td>
<td>N/E</td>
<td>75/83 (90.4)</td>
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<tr>
<td>5/23 (21.7)</td>
<td>9/13 (69.2)</td>
<td>N/E</td>
<td>12/16 (75.0)</td>
<td>N/E</td>
<td>30/41 (73.2)</td>
<td></td>
</tr>
<tr>
<td>4/13 (30.8)</td>
<td>20/30 (66.7)</td>
<td>N/E</td>
<td>24/30 (80.0)</td>
<td>N/E</td>
<td>24/31 (77.4)</td>
<td></td>
</tr>
<tr>
<td>10/21 (47.6)</td>
<td>10/20 (50.0)</td>
<td>1.14 (0.33, 4.00)*</td>
<td>14/16 (87.5)</td>
<td>N/E</td>
<td>38/45 (84.4)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; DMARD, disease-modifying anti-rheumatic drug; IR, inadequate response; N, total number of responders and non-responders (percentages based on N); OR, odds ratio (calculated versus placebo). In the case of early termination, ACR components were analysed using the last observation carried forward method (LOCF) first, and then ACR20 response was calculated. CIs were based on a normal approximation to a binomial distribution.

*Based on logistic regression model: ACR20 response (responder, non-responder) = treatment + inadequate response to prior biological DMARD use (No, Yes) + concomitant DMARD use (No, Yes) + study region (Japan, Korea, and Taiwan). Odds ratio >1 favours peficitinib.

†Based on logistic regression model: ACR20 response (responder, non-responder) = treatment + concomitant DMARD use (No, Yes) + study region (Japan, Korea, and Taiwan). Odds ratio >1 favours peficitinib.

‡Based on logistic regression model: ACR20 response (responder, non-responder) = treatment + inadequate response to prior biological DMARD use (No, Yes) + study region (Japan, Korea, and Taiwan). Odds ratio >1 favours peficitinib.
**Supplementary Table 3.** ACR20, ACR50 and ACR70 response rates and HAQ-DI scores at Weeks 0, 4, 8, 12 and 52

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR20, % (n/N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td>20.0 (19/95)</td>
<td>31.1 (28/90)</td>
<td>33.0 (29/88)</td>
<td>--</td>
</tr>
<tr>
<td>100mg</td>
<td>-</td>
<td>43.9 (43/98)</td>
<td>51.0 (49/96)</td>
<td>59.4 (57/96)</td>
<td>73.2 (52/71)</td>
</tr>
<tr>
<td>150mg</td>
<td>-</td>
<td>45.0 (45/100)</td>
<td>68.7 (68/99)</td>
<td>77.2 (71/92)</td>
<td>90.1 (73/81)</td>
</tr>
<tr>
<td><strong>ACR50, % (n/N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-</td>
<td>3.2 (3/95)</td>
<td>5.6 (5/90)</td>
<td>10.2 (9/88)</td>
<td>--</td>
</tr>
<tr>
<td>100mg</td>
<td>-</td>
<td>8.2 (8/98)</td>
<td>25.0 (24/96)</td>
<td>32.3 (31/96)</td>
<td>49.3 (35/71)</td>
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<tr>
<td>150mg</td>
<td>-</td>
<td>14.0 (14/100)</td>
<td>35.4 (35/99)</td>
<td>45.7 (42/92)</td>
<td>75.3 (61/81)</td>
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<tr>
<td><strong>ACR70, % (n/N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo</td>
<td>-</td>
<td>0.0 (0/95)</td>
<td>1.1 (1/90)</td>
<td>1.1 (1/88)</td>
<td>--</td>
</tr>
<tr>
<td>100mg</td>
<td>-</td>
<td>1.0 (1/98)</td>
<td>11.5 (11/96)</td>
<td>14.6 (14/96)</td>
<td>35.2 (25/71)</td>
</tr>
<tr>
<td>150mg</td>
<td>-</td>
<td>2.0 (2/100)</td>
<td>14.1 (14/99)</td>
<td>29.3 (27/92)</td>
<td>48.1 (39/81)</td>
</tr>
<tr>
<td><strong>HAQ-DI, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00 (0.66)</td>
<td>0.98 (0.65)</td>
<td>0.95 (0.65)</td>
<td>0.94 (0.63)</td>
<td>--</td>
</tr>
<tr>
<td>Dose</td>
<td>Value 1 (SD)</td>
<td>Value 2 (SD)</td>
<td>Value 3 (SD)</td>
<td>Value 4 (SD)</td>
<td>Value 5 (SD)</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>100mg</td>
<td>0.92 (0.69)</td>
<td>0.81 (0.62)</td>
<td>0.66 (0.57)</td>
<td>0.62 (0.59)</td>
<td>0.52 (0.59)</td>
</tr>
<tr>
<td>150mg</td>
<td>1.03 (0.67)</td>
<td>0.83 (0.59)</td>
<td>0.70 (0.54)</td>
<td>0.61 (0.53)</td>
<td>0.45 (0.45)</td>
</tr>
</tbody>
</table>

All values are observed data
<table>
<thead>
<tr>
<th></th>
<th>Peficitinib 100 mg (N=96)</th>
<th>Peficitinib 150 mg (N=93)</th>
<th>Placebo to 100 mg at Week 12 (N=43)</th>
<th>Placebo to 150 mg at Week 12 (N=47)</th>
<th>Peficitinib 100 mg + 150 mg (N=189)</th>
<th>Etanercept (open-label arm) (N=191)</th>
<th>Total except for etanercept (N=279)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related TEAEs*</td>
<td>50 (52.1)</td>
<td>47 (50.5)</td>
<td>27 (62.8)</td>
<td>26 (55.3)</td>
<td>97 (51.3)</td>
<td>93 (48.7)</td>
<td>150 (53.8)</td>
</tr>
<tr>
<td>SAE</td>
<td>5 (5.2)</td>
<td>6 (6.5)</td>
<td>4 (9.3)</td>
<td>5 (10.6)</td>
<td>11 (5.8)</td>
<td>14 (7.3)</td>
<td>20 (7.2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related SAEs</td>
<td>2 (2.1)</td>
<td>2 (2.2)</td>
<td>2 (4.7)</td>
<td>2 (4.3)</td>
<td>4 (2.1)</td>
<td>5 (2.6)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>≥Grade 3 TEAE†</td>
<td>9 (9.4)</td>
<td>16 (17.2)</td>
<td>2 (4.7)</td>
<td>12 (25.5)</td>
<td>25 (13.2)</td>
<td>23 (12.0)</td>
<td>39 (14.0)</td>
</tr>
</tbody>
</table>

**Supplementary Table 4.** Overview of treatment-emergent adverse events from Week 12 to Week 52 or later

**Treatment-emergent adverse events are defined as any adverse event that started or worsened in severity after initial dose of study drug or reference drug through the follow-up period. In this table, treatment-emergent adverse events from first dose after Week 12 visit through the follow-up period is applicable. All values are n (%). SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event.**

*Possible or probable, as assessed by the investigator or records where relationship is missing.

†Based on National Cancer Institute Common Terminology Criteria for Adverse Events grading: grade 3 = severe or medically significant, grade 4 = life threatening, grade 5 = death related to AE.
SUPPLEMENTARY FIGURES

Supplementary Figure 1. Study design

Informed consent; screening initiation; DMARD-IR evaluation

Enrolment and randomisation (1:1:1:2)

28-day screening period

Patients receiving placebo switched at Week 12 under blinded conditions to peficitinib 100/150 mg

Placebo

Peficitinib 100 mg/day

Peficitinib 150 mg/day

Peficitinib 100 mg/day

Peficitinib 150 mg/day

Etanercept 50 mg/week (open-label arm)

Week 0

Week 12

Week 52

In the placebo group, the peficitinib group to which patients would be switched was determined at randomisation.

Primary efficacy variable: ACR20

IR, inadequate response

*Patients completing the study enrolled into an open-label extension study except for those in the etanercept group. Patients in the etanercept group or those who did not proceed to the extension study underwent follow-up observation 4 weeks after the end of the study treatment.
Supplementary Figure 2. Proportion of patients achieving DAS28-ESR <2.6, DAS28-CRP <2.6, and DAS28-CRP ≤3.2 at Week 12/ET and Week 52/ET (FAS)

DAS28-ESR <2.6

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Placebo to peficitinib 100 mg</th>
<th>Placebo to peficitinib 150 mg</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12/ET</td>
<td>1.0</td>
<td>11.7</td>
<td>17.8</td>
<td>31.7</td>
<td>26.2</td>
<td>27.7</td>
</tr>
<tr>
<td>Week 52/ET (EOT)</td>
<td>63</td>
<td>42</td>
<td>13</td>
<td>103</td>
<td>24</td>
<td>29</td>
</tr>
</tbody>
</table>

p=0.003
p=N/E

No patients: 100, 103, 101, 199, 42, 47, 103, 101, 200

CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; EOT, end of treatment; ET, early termination; N/E, not estimable. The percentage of patients with DAS28-CRP≤3.2 was not calculated for placebo/peficitinib 100 mg and placebo/peficitinib 150 mg. In the case of early termination, DAS components were analysed using the last observation carried forward method prior to calculation of DAS responses. P values were calculated using Wald’s Chi-square test with no multiplicity adjustment. Statistical comparisons were not conducted for Week 52/ET data. Etanercept was an open-label reference group and was not included in statistical comparisons with placebo.
Supplementary Figure 3. ACR20, ACR50 and ACR70 response rates from baseline to Week 12 and Week 12/ET

**No. with response, n/N**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>N</th>
<th>n</th>
<th>N</th>
<th>n</th>
<th>N</th>
<th>n</th>
<th>N</th>
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<tr>
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<td>29/88</td>
<td>31/101</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg</td>
<td>43/98</td>
<td>49/96</td>
<td>57/96</td>
<td>60/104</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 150 mg</td>
<td>45/100</td>
<td>68/99</td>
<td>71/92</td>
<td>76/102</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>122/200</td>
<td>157/195</td>
<td>162/191</td>
<td>167/200</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Proportion of patients, %**

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20.0</td>
<td>43.9</td>
<td>45.0</td>
<td>61.0</td>
</tr>
<tr>
<td></td>
<td>31.1</td>
<td>51.0</td>
<td>68.7</td>
<td>80.5</td>
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<td></td>
<td>33.0</td>
<td>59.4</td>
<td>77.2</td>
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<td></td>
<td>30.7</td>
<td>57.7</td>
<td>74.5</td>
<td>83.5</td>
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</table>
### No. with response, n/N

<table>
<thead>
<tr>
<th>Group</th>
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<th>4</th>
<th>8</th>
<th>12</th>
<th>12/ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3/595</td>
<td>5/90</td>
<td>9/88</td>
<td>9/101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg</td>
<td>8/98</td>
<td>24/98</td>
<td>31/96</td>
<td>32/104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 150 mg</td>
<td>14/100</td>
<td>35/99</td>
<td>42/92</td>
<td>43/102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>59/200</td>
<td>92/195</td>
<td>105/191</td>
<td>105/200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Proportion of patients, %

<table>
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<tr>
<th>Group</th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.2</td>
<td>5.6</td>
<td>10.2</td>
<td>8.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 100 mg</td>
<td>8.2</td>
<td>25.0</td>
<td>32.3</td>
<td>30.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peficitinib 150 mg</td>
<td>14.0</td>
<td>35.4</td>
<td>45.7</td>
<td>42.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>29.5</td>
<td>47.2</td>
<td>55.0</td>
<td>52.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplementary material

ET, early termination. For ACR50 and ACR70, results of ad-hoc analysis using a logistic regression model, "ACR50 or ACR70 response (responder, non-responder) = treatment", are shown. For all timepoints except for Week 12/ET and EOT, observed data are plotted. For Week 12/ET and EOT, in the case of early termination, ACR components were analysed using the last observation carried forward method (LOCF) first, and then ACR20/50/70 responses were calculated. P values for ACR70 differences from placebo were not estimable for peficitinib 100 mg and 150 mg at Week 4. P values were calculated using Wald’s Chi-square test with no multiplicity adjustment, except for ACR20 response rates at Week 12/ET for which a closed testing procedure was used for multiplicity adjustment. Etanercept was an open-label reference group and was not included in statistical comparisons with placebo.

*p<0.05; **p<0.01; ***p<0.001
**Supplementary Figure 4.** Rates of remission and low disease activity at Week 12/ET and Week 52/ET (EOT): proportion of patients with (A) CDAI score ≤2.8; (B) CDAI score ≤10 (low disease activity); (C) SDAI score ≤3.3 and (D) SDAI score ≤11 (low disease activity)

A

![Bar chart showing CDAI score ≤2.8](image)

- **Placebo**
- **Peficitinib 100 mg**
- **Peficitinib 150 mg**
- **Etanercept**

<table>
<thead>
<tr>
<th>No. events</th>
<th>0</th>
<th>9</th>
<th>10</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>100</td>
<td>103</td>
<td>101</td>
<td>200</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 12/ET</th>
<th>Placebo</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=N/E</td>
<td>p=N/E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>8.7</td>
<td>9.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 52/ET (EOT)</th>
<th>Placebo</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.4</td>
<td>23.8</td>
<td>32.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. events | 19 | 24 | 65 |
| No. patients | 103 | 101 | 200 |
Supplementary material

[Figure for all parts of Supplementary Figure 4]

EOT, end of treatment; ET, early termination; N/E, not estimable. In the case of early termination, CDAI/SDAI components were analysed using the last observation carried forward method (LOCF) first, and then CDAI/SDAI scores were calculated. P values were calculated using Wald’s Chi-square test with no multiplicity adjustment. Etanercept was an open-label reference arm and was not included in statistical comparisons with placebo.
Supplementary Figure 5. Changes from baseline to Week 12/ET in (A) CDAI and (B) SDAI

A

CDAI

No. of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>100</td>
<td>95</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>Peficitinib 100 mg</td>
<td>103</td>
<td>98</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>Peficitinib 150 mg</td>
<td>102</td>
<td>100</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Etanercept</td>
<td>200</td>
<td>200</td>
<td>195</td>
<td>191</td>
</tr>
</tbody>
</table>

Mean change

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Peficitinib 100 mg</th>
<th>Peficitinib 150 mg</th>
<th>Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5.62</td>
<td>-7.67</td>
<td>-8.87</td>
<td>-7.25</td>
</tr>
<tr>
<td>Peficitinib 100 mg</td>
<td>-11.01</td>
<td>-13.74</td>
<td>-15.55</td>
<td>-14.91</td>
</tr>
<tr>
<td>Peficitinib 150 mg</td>
<td>-11.42</td>
<td>-17.06</td>
<td>-19.91</td>
<td>-19.20</td>
</tr>
<tr>
<td>Etanercept</td>
<td>-15.73</td>
<td>-19.31</td>
<td>-21.21</td>
<td>-20.74</td>
</tr>
</tbody>
</table>
B

SDAI

Mean change from baseline

Baseline Week 4 Week 8 Week 12 Week 12/ET

Placebo 100 95 90 88 99
Peficitinib 100 mg 103 98 96 96 101
Peficitinib 150 mg 102 100 98 92 101
Etanercept 200 200 195 191 200

Mean change
Placebo -5.54 -7.61 -8.92 -7.22
Peficitinib 100 mg -11.83 -14.71 -16.59 -16.08
Peficitinib 150 mg -12.78 -18.66 -21.62 -20.93
Etanercept -17.08 -20.64 -22.54 -21.84

[Footnote for both parts of Supplementary Figure 5]

CDAI, clinical disease activity index; ET, early termination; SDAI, simplified disease activity index. For all timepoints except for Week 12/ET, observed data are plotted. For Week 12/ET, in the case of early termination, CDAI/SDAI components were analysed using the last observation carried forward method (LOCF) first, and then CDAI/SDAI were calculated. Data are plotted as mean. P values were calculated with no multiplicity adjustment. Etanercept was an open-label reference arm and was not included in statistical comparisons with placebo.

*p<0.05; **p<0.01; ***p<0.001
LIST OF STUDY SITES

Japan

Medical Corporation Association Osaki Internal Clinic
Medical Corporation Association Sagawa Akira Rheumatology Clinic
Sapporo City General Hospital
General Incorporated Foundation Hikarigaoka-Aiseikai Hikarigaoka Spellman Hospital
Medical Corporation Heizenkai Ohno Clinic
Medical Corporation Association Kojokai, Hirose Clinic
Honjo Rheumatism Clinic
Medical Corporation Kojunikai Osaka Rehabilitation Hospital
Hiroshima Red Cross Hospital & Atomic-bomb Survivors Hospital
Medical Corporation Hiroshima Rheumatology Clinic
Medical Corporation SORR Shigenobu Orthopedic Rheumatism and Rehabilitation Clinic
Medical Corporation Association Aiaikai Ishioka Clinic
Medical Corporation Koyukai Oribe Rheumachika Naika Clinic
Shono Rheumatism Clinic
National Hospital Organization Kyushu Medical Center
Social Medical Corporation Association Kumamoto-Marutakai Kumamoto Orthopaedic Hospital
Medical Corporation Jyukai Yu-Family Clinic
National University Corporation Tokyo Medical And Dental University Medical Hospital
Nagaoka Red Cross Hospital
Medical Corporation Association Katayama Seikeigeka Rheumatism Clinic
Medical Corporation Izumiyamakai East Sendai Rheumatism and Internal Medicine Clinic
National University Corporation Hokkaido University Hospital
Institute of Rheumatology, Tokyo Women’s Medical University
Medical Corporation Inoue Hospital
Medical Corporation Koseikai Kuroda Orthopedic Hospital
Medical Corporation Association Aoi Kai Sendai Taihaku Hospital
Nagoya University Hospital

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Medical Corporation Seijinkai Hokkaido Medical Center for Rheumatic Diseases
Hospital of the University of Occupational and Environmental Health, Japan
Matsubara Mayflower Hospital
Medical Corporation Association Matsubara Clinic
National University Corporation The University of Tokyo Hospital
Kumamoto Rheumatology Clinic
Medical Corporation Daimyokai Miyasato Clinic
Kawasaki Municipal Hospital
Komagamine Rheumatoid Orthopaedic Clinic
Medical Corporation Association Koshinkai Ohira Orthopaedic Hospital
Osafune Clinic
Medical Corporation Rheumatology Kenkeikai Azuma Rheumatology Clinic
Sugimoto Clinic
Social Welfare Organization Saiseikai Imperial Gift Foundation, Inc. Mito Saiseikai General Hospital
Medical Corporation Seiwakai Hiroshima Clinic
Specific Medical Corporation Seijinkai Okubo Hospital
Medical Corporation Kakuseikai Tsurukami Orthopedic Rheumatism Clinic
Medical Corporation Association Kawasaki Rheumatism & Internal Medicine Clinic
National Hospital Organization Kyushu Medical Center
Ogawa Internal Medicine Clinic
National Hospital Organization Toneyama National Hospital
Medical Corporation Ishinkai Kaneko Internal and Rheumatoid Clinic
Medical Corporation Association Seisenkai Fujimori Clinic
National Hospital Organization Beppu Medical Center
Medical Corporation Seiryukai Eiraku Clinic
Suzuki Clinic
National Hospital Organization Fukuoka Hospital
Aichi Koseiren Kainan Hospital
National Hospital Organization Himeji Medical Center
Social Welfare Organization Saiseikai Imperial Gift Foundation, Inc. Osaka Saiseikai Suita Hospital
Social Medical Corporation Yukinoseibokai St. Mary's Hospital
National Hospital Organization Tokyo Medical Center
Japanese Red Cross Koga Hospital
Japanese Red Cross Kagoshima Hospital
National Hospital Organization Ureshino Medical Center
Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers
Kamituga Koseiren Kamituga General Hospital
National Hospital Organization Osaka Minami Medical Center
Local Incorporated Administrative Agency Nagano Municipal Hospital
Saitama Medical University Hospital
Toho University Ohashi Medical Center
Tokai University Hospital
University Hospital Kyoto Prefectural University of Medicine
National University Corporation Osaka University Hospital
Okayama University Hospital
Kagawa University Hospital
Medical Corporation Association R&O Shizuoka Rheumatism Orthopedic Rehabilitation Hospital
Social Welfare Corporation Hakodate Koseiin Hakodate Goryokaku Hospital
Soshigaya Okura Clinic
National University Corporation Kobe University Hospital
Medical Corporation Ryokufukai Misato Marine Hospital
Medical Corporation Hinouekai Higami Hospital
Social Welfare Corporation Mitsui Memorial Hospital
Yokohama City Minato Red Cross Hospital
Medical Corporation Hidaka Orthopedic Hospital
Medical Corporation Gotokai Nagasaki Medical Hospital of Rheumatology
Public interest incorporated foundation Sasaki Institute Kyoundo Hospital
Medical Corporation Association Hoyokai Matsuta Internal Clinic
National Hospital Organization Nagasaki Medical Center
Social Medical Corporation Association Kinoshitakai Kamagaya General Hospital
Miyashita Rheumatology Clinic
Medical Corporation Tokito Clinic Rheumatology & Orthopaedic Surgery
Medical Corporation Soshikai Munakata Yasuhiko Clinic
Medical Corporation Inokuchi Clinic
Medical Corporation Shureikai Oasis Clinic
National Hospital Organization Toyohashi Medical Center
National Hospital Organization Nagoya Medical Center
Medical Corporation Tokushukai Fukuoka Tokushukai Medical Center
Japanese Red Cross Nagasaki Genbaku Hospital
General Incorporated Foundation Konankai Konan Kakogawa Hospital
Federation of National Public Service Personnel Mutual Aid Associations Tonan Hospital
Social Welfare Corporation Saiseikai Imperial Gift Foundation, Inc. Chibaken Saiseikai Narashino Hospital
Hyogo College of Medicine Hospital
Japanese Red Cross Okayama Hospital
Federation of National Public Service Personnel Mutual Aid Associations Shinkokura Hospital
Aso Iizuka Hospital
Social Medical Corporation Zenjinkai Shiminnomori Hospital
Japanese Red Cross Kyoto Daiichi Hospital
Kushiro Red Cross Hospital
Social Medical Corporation Sokokai Gyoda General Hospital Gyoda Clinic
Matsudo City General Hospital
Social Welfare Corporation St. Teresa’s Society St. Joseph’s Hospital
Independent Administrative Agency Japan Organization of Occupational Health and Safety Chubu Rosai Hospital
Federation of National Public Service Personnel Mutual Aid Associations Hamanomachi Hospital
Kakegawa City and Fukuroi Hospital Companies Orchestra Middle East Far-General Medical Center
Local Incorporated Administrative Agency Higashiosaka City Medical Center
Japanese Red Cross Shizuoka Hospital
Japan Mutual Aid Association of Public School Teachers Kinki Central Hospital
Kindai University Sakai Hospital

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National Hospital Organization Shimoshizu Hospital
National University Corporation Toyama University Hospital
Fujita Health University Hospital
National Hospital Organization Sagamihara National Hospital
Incorporated Educational Institution, St. Luke’s International University, St. Luke’s International Hospital
National University Corporation The University of Tokyo Hospital
Niigata Rheumatic Center
Jichi Medical University Hospital
National University Corporation Osaka University Hospital
Nagasaki University Hospital
Toho University Omori Medical Center
Juntendo University Hospital
Osaka City University Hospital
National University Corporation Tohoku University Hospital
Nippon Medical School Hospital
Social Medical Corporation Foundation Hakujujikai Sasebo Chuo Hospital
National University Corporation Kobe University Hospital
Shirahama Foundation for Health and Welfare Shirahama Hamayu Hospital
JA Aichi Koseiren Toyota Kosei Hospital
Osaka Rheumatology Clinic
NTT-East Sapporo Hospital
Kyoto University Hospital
Saitama Medical Center
Independent Administrative Agency Japan Community Health care Organization Isahaya General Hospital
Medical Corporation Association Yamanakai Higashi-Hiroshima Memorial Hospital
Kyushu University Hospital

Korea
Seoul National University Hospital
Hanyang University Seoul Hospital
Severance Hospital
Daegu Catholic University Medical Center
Chonnam National University Hospital
Inha University Hospital
Ajou University Hospital
Chonbuk National University Hospital
KonKuk University Hospital
Keimyung University Dongsan Medical Center
KyungHee University Hospital

Taiwan
National Taiwan University Hospital
Taipei Veteran General Hospital
Chang Gung Memorial Hospital-LinKou
Taichung Veterans General Hospital
China Medical University Hospital
Dalin Branch of Buddhist Tzu Chi General Hospital
Chang Gung Memorial Hospital-Kaohsiung
Kaohsiung Medical University Chung-Ho Memorial Hospital
Kaohsiung Veterans General Hospital
Chung Shan Medical University Hospital
Cathay General Hospital
National Cheng Kung University Hospital