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

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- Hydroxychloroquine
- Salazosulfapyridine
- Gold
- D-penicillamine
- Lobenzarit
- Actarit
- Bucillamine
- Iguratimod

10. 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

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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 (HBc) antibody, HBs antibody or HBV-DNA quantitation (However, patient with negative HBs antigen and HBV-DNA quantitation, and positive HBc 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

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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

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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

History of active tuberculosis	Chest X-ray for tuberculosis	Tuberculosis infection[b]	Exposure to patients with infective tuberculosis (interview)	Eligibility
Present	-	-	-	Not eligible
Absent	Abnormal (active)	-	-	Not eligible
	Abnormal (old)[a]	-	Either exposed or not exposed	Eligible if prophylaxis was given[c]
	Normal	Positive	Either exposed or not exposed	Eligible if prophylaxis was given[c]
		Negative	Exposed	Eligible if prophylaxis was given[c]
		Negative	Not exposed	Eligible

[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. When T-spot or Quantiferon Gold test was not feasible, tuberculin test was performed. Tuberculin was defined as

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positive with a red spot covering an area of ≥20 mm (10 mm for Korea, 5 mm for Taiwan), or induration. Tests conducted within 90 days prior to baseline could be used for diagnosis.

[c]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; lobenzarit; 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; leflunomide ≤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,

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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.

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- 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

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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.

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SUPPLEMENTARY TABLES

Supplementary Table 1. Sensitivity analysis of ACR20 response

	Number of responders, n (%)	Treatment difference versus placebo			
		Difference (%)*	Odds ratio†	95% CI (%)‡	P value§
ACR20 response at Week 12/ET (LOCF and non-responder imputation) (FAS)					
Placebo (N=101)	29 (28.7)				
Peficitinib 100 mg (N=104)	57 (54.8)	26.1	3.08	(1.72, 5.54)	<0.001
Peficitinib 150 mg (N=102)	71 (69.6)	40.9	5.68	(3.10, 10.39)	<0.001
Etanercept (open-label arm) (N=200)	163 (81.5)	52.8	-	-	-
ACR20 response at Week 12/ET (LOCF) (re-randomisation test‖) (FAS)					
Peficitinib 150 mg versus placebo					<0.001
Peficitinib 100 mg versus placebo					<0.001
ACR20 response at Week 12 (observed data) (FAS)					
Placebo (N=88)	29 (33.0)				
Peficitinib 100 mg (N=96)	57 (59.4)	26.4	2.98	(1.62, 5.46)	<0.001
Peficitinib 150 mg (N=92)	71 (77.2)	44.2	6.97	(3.59, 13.54)	<0.001
Etanercept (open-label arm) (N=191)	162 (84.8)	51.8	-	-	-
ACR20 response at Week 12/ET (LOCF) (PPS)					
Placebo (N=91)	30 (33.0)				
Peficitinib 100 mg (N=92)	55 (59.8)	26.8	3.05	(1.66, 5.60)	<0.001
Peficitinib 150 mg (N=95)	72 (75.8)	42.8	6.42	(3.37, 12.22)	<0.001
Etanercept (open-label arm) (N=188)	160 (85.1)	52.1	-	-	-

ACR20 response at Week 12 (multiple imputation assuming missing at random) (FAS)					
Placebo (N=101)	32.1%				
Peficitinib 100 mg (N=103)	58.7%	26.7	3.07	(1.70, 5.57)	<0.001
Peficitinib 150 mg (N=102)	75.8%	43.7	6.72	(3.52, 12.82)	<0.001
Etanercept (open-label arm) (N=200)	83.5%	51.4	-	-	-
ACR20 response at Week 12 (placebo multiple imputation) (FAS)					
Placebo (N=101)	31.2%				
Peficitinib 100 mg (N=103)	56.4%	25.2	2.91	(1.61, 5.25)	<0.001
Peficitinib 150 mg (N=102)	72.4%	41.2	5.80	(3.09, 10.87)	<0.001
Etanercept (open-label arm) (N=200)	82.3%	51.1	-	-	-

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)

	Placebo	Peficitinib 100 mg		Peficitinib 150 mg		Etanercept
	n/N (%)	n/N (%)	OR versus placebo (95% CI)	n/N (%)	OR versus placebo (95% CI)	
Number of prior biological DMARDs						
0	28/90 (31.1)	52/90 (57.8)	3.10 (1.67, 5.74)*	65/89 (73.0)	6.03 (3.15, 11.55)*	137/162 (84.6)
1	2/7 (28.6)	6/8 (75.0)	N/E	9/9 (100.0)	N/E	25/28 (89.3)
2	1/4 (25.0)	1/4 (25.0)	N/E	2/4 (50.0)	N/E	4/9 (44.4)
≥3	--	1/2 (50.0)	N/E	--	--	1/1 (100.0)
Prior biological DMARD-IR						
Yes	2/5 (40.0)	4/9 (44.4)	N/E	5/7 (71.4)	N/E	12/15 (80.0)
No	29/96 (30.2)	56/95 (58.9)	3.35 (1.84, 6.10)†	71/95 (74.7)	6.90 (3.64, 13.05)†	155/185 (83.8)
Concomitant DMARD use						
Yes	27/87 (31.0)	51/91 (56.0)	2.84 (1.54, 5.27)‡	67/89 (75.3)	6.92 (3.55, 13.51)‡	149/176 (84.7)
MTX	19/57 (33.3)	39/63 (61.9)	3.24 (1.52, 6.91)*	50/62 (80.6)	8.75 (3.74, 20.48)*	92/117 (78.6)
DMARDs other than MTX only	8/30 (26.7)	12/28 (42.9)	N/E	17/27 (63.0)	N/E	57/59 (96.6)
No	4/14 (28.6)	9/13 (69.2)	N/E	9/13 (69.2)	N/E	18/24 (75.0)

	Placebo	Peficitinib 100 mg		Peficitinib 150 mg		Etanercept
	n/N (%)	n/N (%)	OR versus placebo (95% CI)	n/N (%)	OR versus placebo (95% CI)	
MTX dose (mg/week) at baseline						
None	12/44 (27.3)	21/41 (51.2)	N/E	26/40 (65.0)	N/E	75/83 (90.4)
0–≤8	5/23 (21.7)	9/13 (69.2)	N/E	12/16 (75.0)	N/E	30/41 (73.2)
8–≤12	4/13 (30.8)	20/30 (66.7)	N/E	24/30 (80.0)	N/E	24/31 (77.4)
>12	10/21 (47.6)	10/20 (50.0)	1.14 (0.33, 4.00)*	14/16 (87.5)	N/E	38/45 (84.4)

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

		Week 0	Week 4	Week 8	Week 12	Week 52
ACR20, % (n/N)	Placebo	-	20.0 (19/95)	31.1 (28/90)	33.0 (29/88)	--
	100mg	-	43.9 (43/98)	51.0 (49/96)	59.4 (57/96)	73.2 (52/71)
	150mg	-	45.0 (45/100)	68.7 (68/99)	77.2 (71/92)	90.1 (73/81)
ACR50, % (n/N)	Placebo	-	3.2 (3/95)	5.6 (5/90)	10.2 (9/88)	--
	100mg	-	8.2 (8/98)	25.0 (24/96)	32.3 (31/96)	49.3 (35/71)
	150mg	-	14.0 (14/100)	35.4 (35/99)	45.7 (42/92)	75.3 (61/81)
ACR70, % (n/N)	Placebo	-	0.0 (0/95)	1.1 (1/90)	1.1 (1/88)	--
	100mg	-	1.0 (1/98)	11.5 (11/96)	14.6 (14/96)	35.2 (25/71)
	150mg	-	2.0 (2/100)	14.1 (14/99)	29.3 (27/92)	48.1 (39/81)
HAQ-DI, mean (SD)	Placebo	1.00 (0.66)	0.98 (0.65)	0.95 (0.65)	0.94 (0.63)	--

100mg	0.92 (0.69)	0.81 (0.62)	0.66 (0.57)	0.62 (0.59)	0.52 (0.59)
150mg	1.03 (0.67)	0.83 (0.59)	0.70 (0.54)	0.61 (0.53)	0.45 (0.45)

All values are observed data

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

n (%)	**Peficitinib 100 mg (N=96)**	**Peficitinib 150 mg (N=93)**	**Placebo to 100 mg at Week 12 (N=43)**	**Placebo to 150 mg at Week 12 (N=47)**	**Peficitinib 100 mg + 150 mg (N=189)**	**Etanercept (open-label arm) (N=191)**	**Total except for etanercept (N=279)**
Drug-related TEAEs*	50 (52.1)	47 (50.5)	27 (62.8)	26 (55.3)	97 (51.3)	93 (48.7)	150 (53.8)
SAE	5 (5.2)	6 (6.5)	4 (9.3)	5 (10.6)	11 (5.8)	14 (7.3)	20 (7.2)
Deaths	0	0	0	0	0	0	0
Drug-related SAEs*	2 (2.1)	2 (2.2)	2 (4.7)	2 (4.3)	4 (2.1)	5 (2.6)	8 (2.9)
≥Grade 3 TEAE†	9 (9.4)	16 (17.2)	2 (4.7)	12 (25.5)	25 (13.2)	23 (12.0)	39 (14.0)
TEAEs leading to permanent discontinuation of study drug or reference drug							
All	7 (7.3)	3 (3.2)	2 (4.7)	4 (8.5)	10 (5.3)	8 (4.2)	16 (5.7)
Drug-related*	3 (3.1)	2 (2.2)	2 (4.7)	4 (8.5)	5 (2.6)	6 (3.1)	11 (3.9)
SAEs	4 (4.2)	0	1 (2.3)	2 (4.3)	4 (2.1)	3 (1.6)	7 (2.5)
Drug-related SAEs*	2 (2.1)	0	1 (2.3)	2 (4.3)	2 (1.1)	2 (1.0)	5 (1.8)

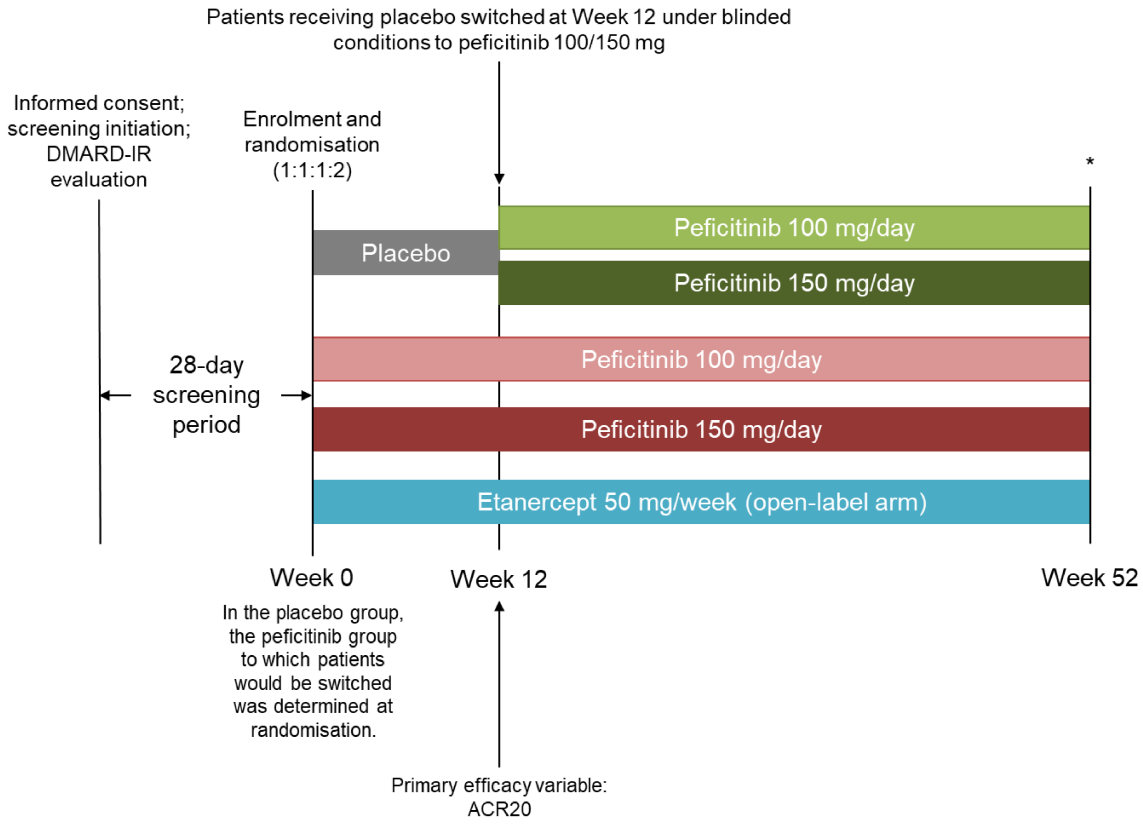
Treatment-emergent adverse events are defined as any adverse event that started or worsened in severity after initial dose of study drug or reference drug through the follow-up period. In this table, treatment-emergent adverse events from first dose after Week 12 visit through the follow-up period is 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



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.

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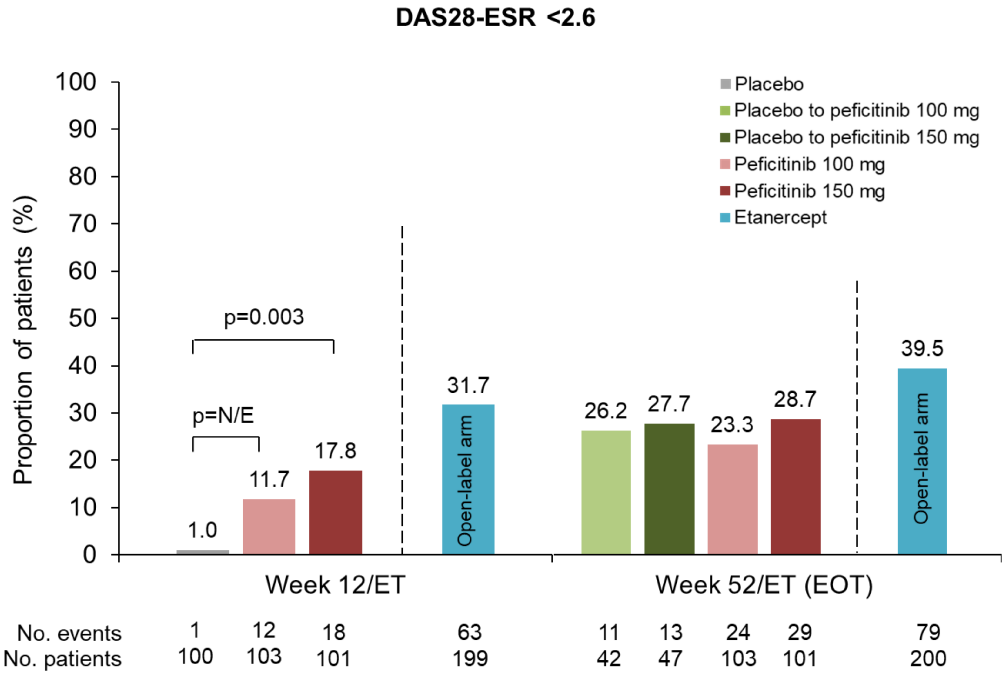
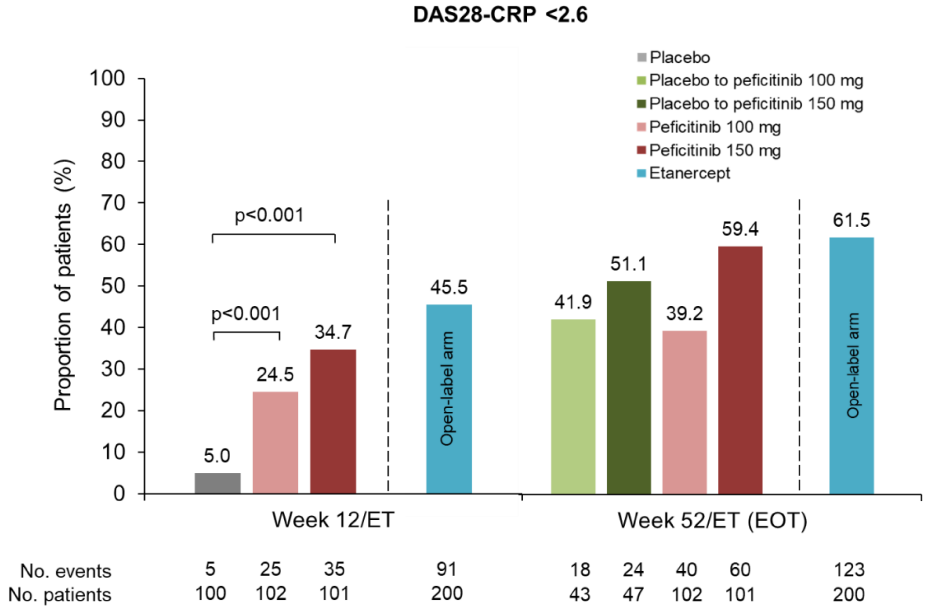
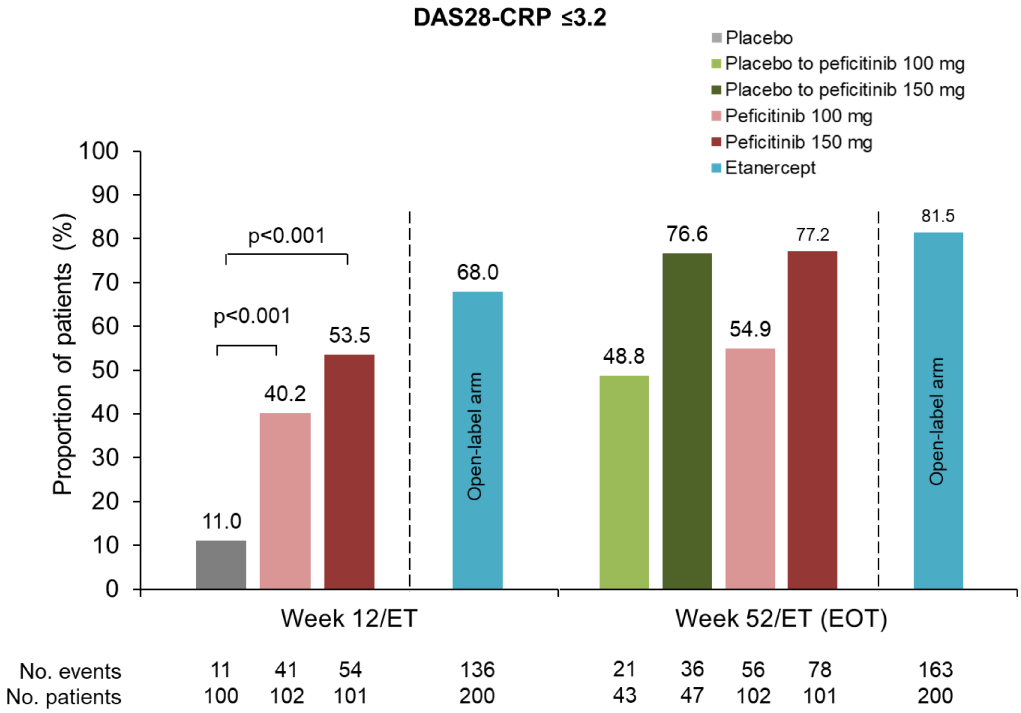
Supplementary Figure 2. Proportion of patients achieving DAS28-ESR <2.6, DAS28-CRP <2.6, and DAS28-CRP ≤3.2 at Week 12/ET and Week 52/ET (FAS)




DAS28-CRP <2.6
Placebo
Placebo to peficitinib 100 mg
Placebo to peficitinib 150 mg
Peficitinib 100 mg
Peficitinib 150 mg
Etanercept
Proportion of patients (%)
p<0.001
p<0.001
5.0
24.5
34.7
45.5
41.9
51.1
39.2
59.4
61.5
Open-label arm
Open-label arm
Week 12/ET
Week 52/ET (EOT)
No. events 5 25 35 91 18 24 40 60 123
No. patients 100 102 101 200 43 47 102 101 200


DAS28-CRP ≤3.2
Placebo
Placebo to peficitinib 100 mg
Placebo to peficitinib 150 mg
Peficitinib 100 mg
Peficitinib 150 mg
Etanercept
Proportion of patients (%)
p<0.001
p<0.001
11.0
40.2
53.5
68.0
48.8
76.6
54.9
77.2
81.5
Open-label arm
Open-label arm
Week 12/ET
Week 52/ET (EOT)
No. events 11 41 54 136 21 36 56 78 163
No. patients 100 102 101 200 43 47 102 101 200

[Footnote for all parts of Supplementary Figure 2]

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.

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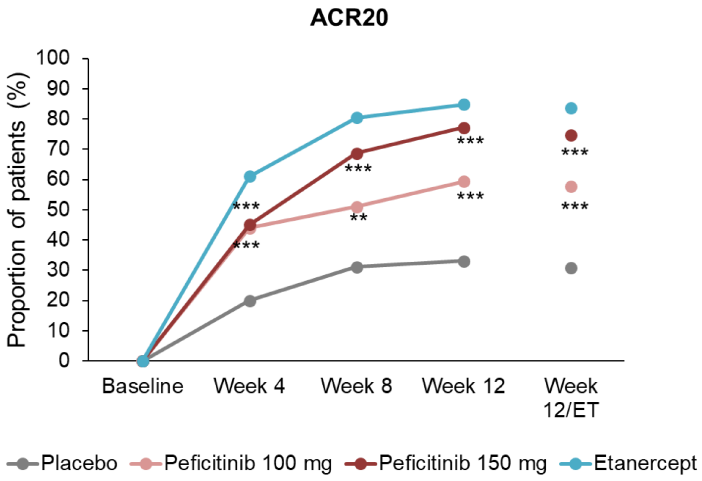
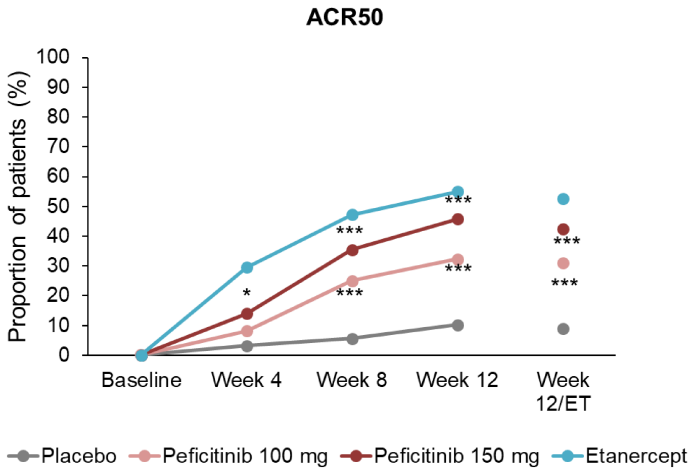
Supplementary Figure 3. ACR20, ACR50 and ACR70 response rates from baseline to Week 12 and Week 12/ET



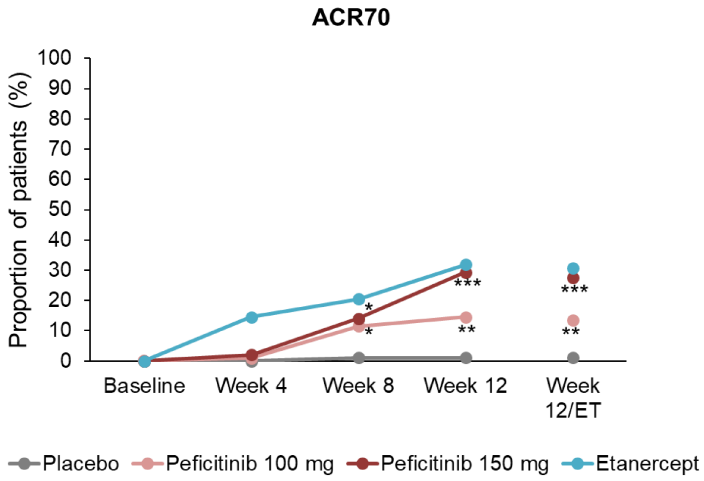
No. with response, n/N				
Placebo	19/95	28/90	29/88	31/101
Peficitinib 100 mg	43/98	49/96	57/96	60/104
Peficitinib 150 mg	45/100	68/99	71/92	76/102
Etanercept	122/200	157/195	162/191	167/200
Proportion of patients, %				
Placebo	20.0	31.1	33.0	30.7
Peficitinib 100 mg	43.9	51.0	59.4	57.7
Peficitinib 150 mg	45.0	68.7	77.2	74.5
Etanercept	61.0	80.5	84.8	83.5

Tanaka Y, *et al. Ann Rheum Dis* 2019; 0:1320–1332. doi: 10.1136/annrheumdis-2019-215163



No. with response, n/N				
Placebo	3/95	5/90	9/88	9/101
Peficitinib 100 mg	8/98	24/96	31/96	32/104
Peficitinib 150 mg	14/100	35/99	42/92	43/102
Etanercept	59/200	92/195	105/191	105/200
Proportion of patients, %				
Placebo	3.2	5.6	10.2	8.9
Peficitinib 100 mg	8.2	25.0	32.3	30.8
Peficitinib 150 mg	14.0	35.4	45.7	42.2
Etanercept	29.5	47.2	55.0	52.5

Tanaka Y, *et al. Ann Rheum Dis* 2019; 0:1320–1332. doi: 10.1136/annrheumdis-2019-215163



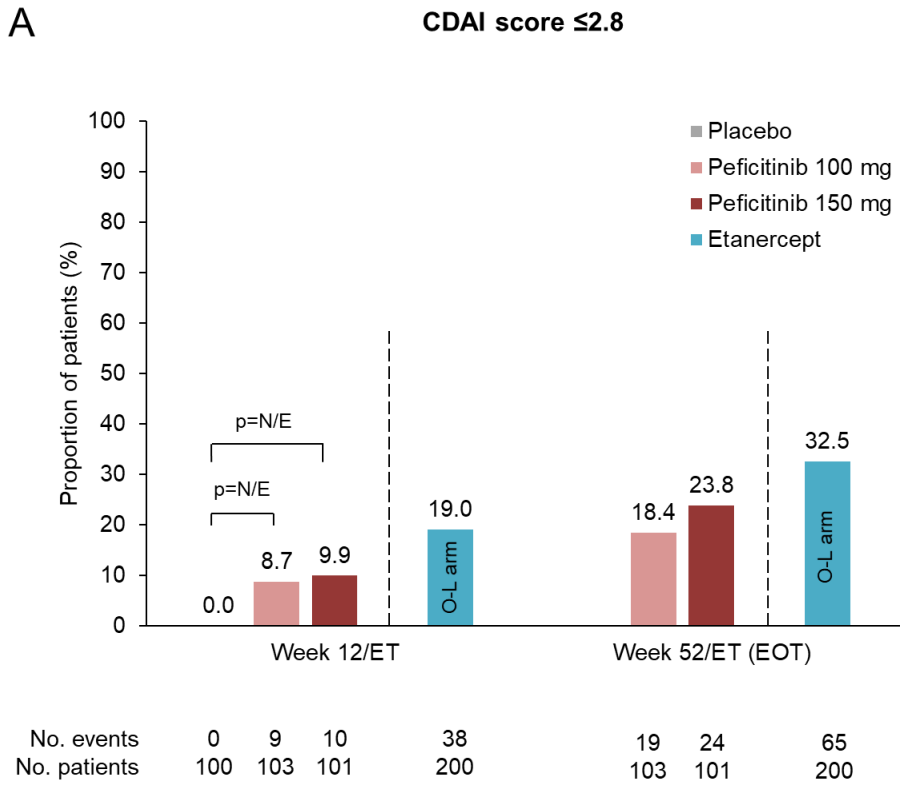
No. with response, n/N				
Placebo	0/95	1/90	1/88	1/101
Peficitinib 100 mg	1/98	11/96	14/96	14/104
Peficitinib 150 mg	2/100	14/99	27/92	28/102
Etanercept	29/200	40/195	61/191	61/200
Proportion of patients, %				
Placebo	0.0	1.1	1.1	1.0
Peficitinib 100 mg	1.0	11.5	14.6	13.5
Peficitinib 150 mg	2.0	14.1	29.3	27.5
Etanercept	14.5	20.5	31.9	30.5

[Footnote for all parts of Supplementary Figure 3]

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)



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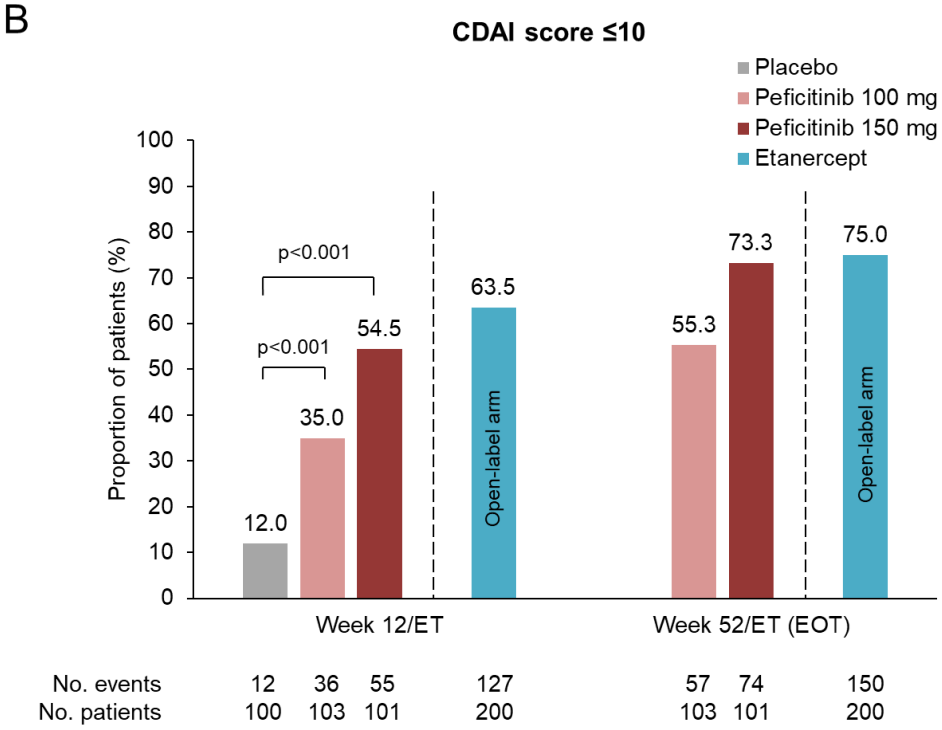
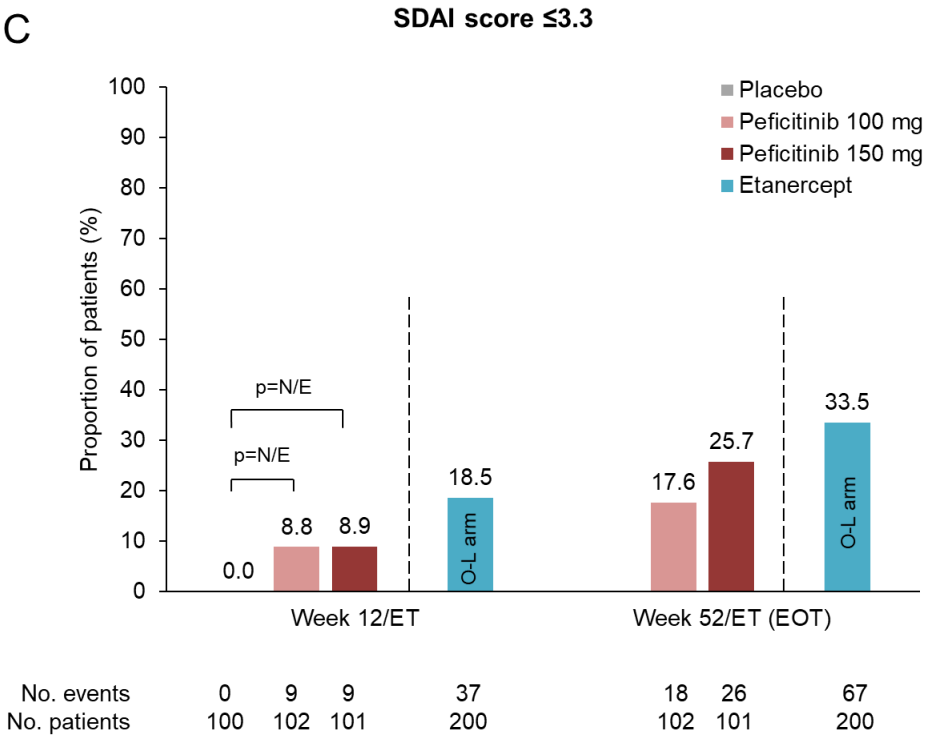
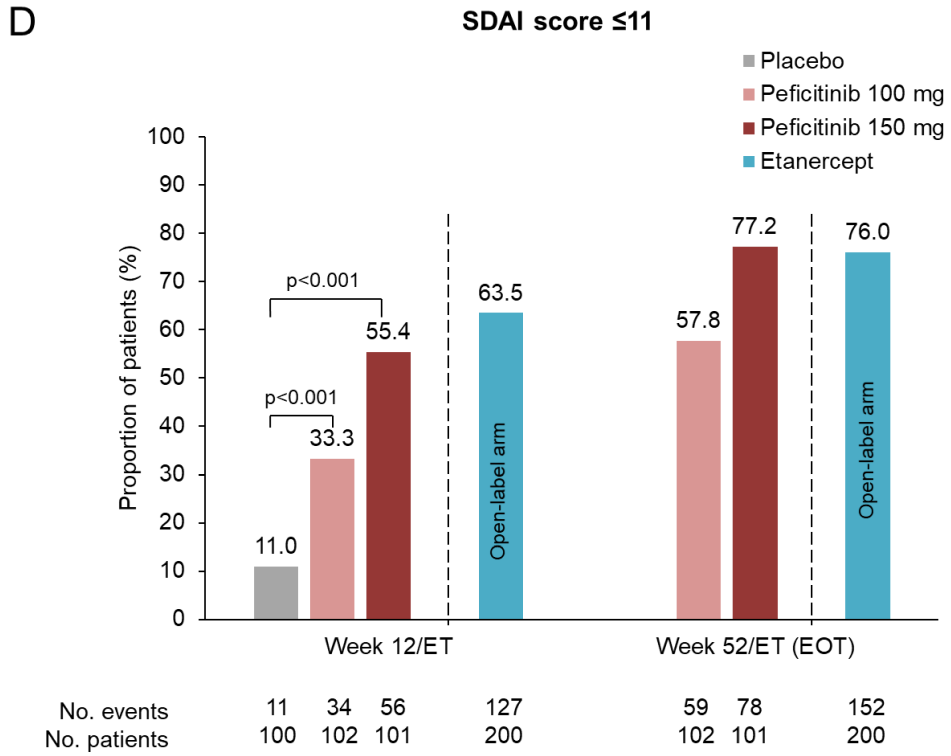

CDAI score ≤10
Placebo
Peficitinib 100 mg
Peficitinib 150 mg
Etanercept
Proportion of patients (%)
p<0.001
p<0.001
12.0
35.0
54.5
63.5
55.3
73.3
75.0
Open-label arm
Open-label arm
Week 12/ET
Week 52/ET (EOT)
No. events 12 36 55 127 57 74 150
No. patients 100 103 101 200 103 101 200

C

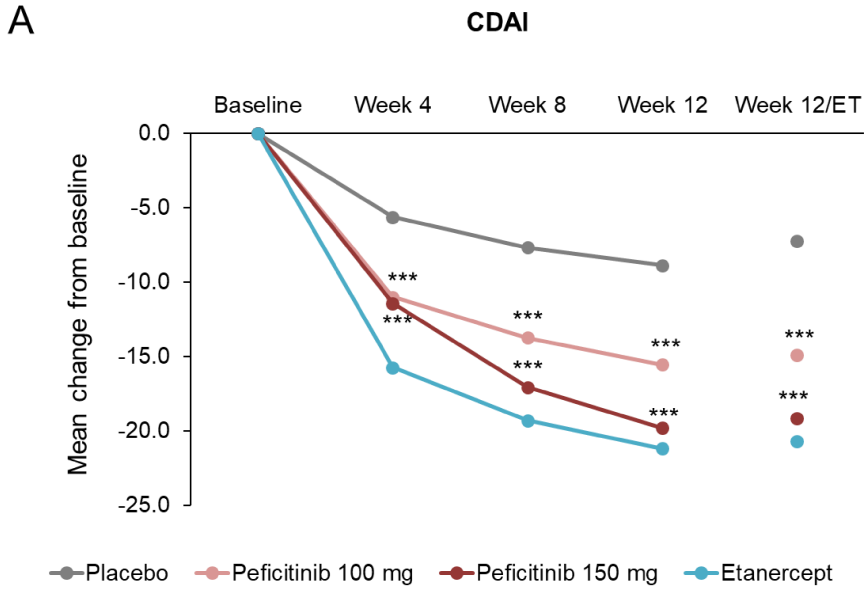

SDAI score ≤3.3
Placebo
Peficitinib 100 mg
Peficitinib 150 mg
Etanercept
Proportion of patients (%)
p=N/E
p=N/E
0.0
8.8
8.9
18.5
17.6
25.7
33.5
O-L arm
O-L arm
Week 12/ET
Week 52/ET (EOT)
No. events 0 9 9 37 18 26 67
No. patients 100 102 101 200 102 101 200



[Footnote 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.

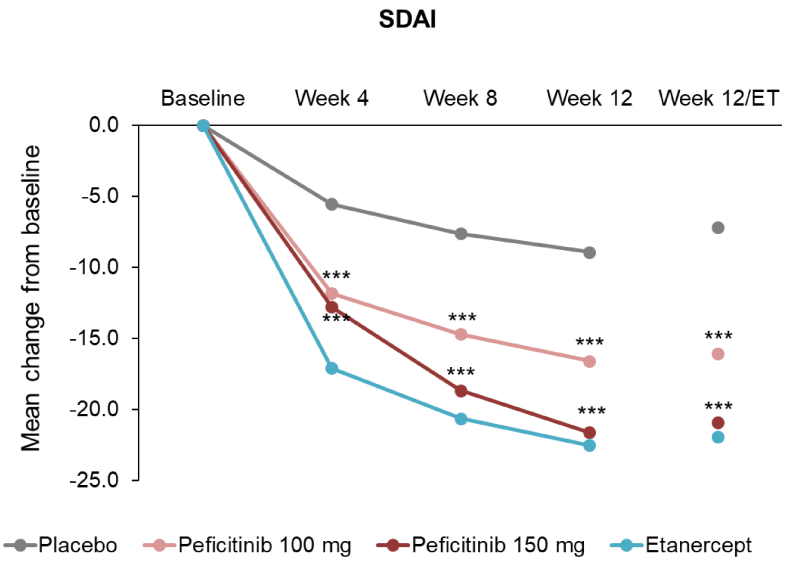
Supplementary Figure 5. Changes from baseline to Week 12/ET in **(A)** CDAI and **(B)** SDAI



No. of patients					
Placebo	100	95	90	88	99
Peficitinib 100 mg	103	98	96	96	102
Peficitinib 150 mg	102	100	99	92	101
Etanercept	200	200	195	191	200

Mean change				
Placebo	-5.62	-7.67	-8.87	-7.25
Peficitinib 100 mg	-11.01	-13.74	-15.55	-14.91
Peficitinib 150 mg	-11.42	-17.06	-19.81	-19.20
Etanercept	-15.73	-19.31	-21.21	-20.74

B



No. of patients					
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	-17.09	-20.64	-22.54	-21.94

[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 Jiyukai 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 Aoikai Sendai Taihaku Hospital

Nagoya University Hospital

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

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