ONLINE SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS

Randomisation and blinding

All drug numbers were assigned randomly by the Case Registration Center under blind conditions, using an Interactive Web Response System. Treatment allocation to the placebo or peficitinib 100 mg or 150 mg groups was double-blinded. The peficitinib 100 mg or peficitinib 150 mg tablets and their corresponding placebo tablets were indistinguishable from each other. The packaging for each treatment group (peficitinib 100 mg or 150 mg and placebo) was also visually indistinguishable from that of other groups. The treatment code was only known to the person responsible for assigning study drugs, the person appointed at the institution performing measurements of plasma drug concentrations, persons in the safety control division (as necessary for suspected unexpected serious adverse reaction handling), and the independent data and safety monitoring board.

Patient inclusion criteria

A patient was eligible for study participation if all of the following applied:

1. Had received a full explanation of the study drug and this study in advance and provided written informed consent to participate in the study.
2. Male or female aged ≥20 years at the time of informed consent.
3. Had RA of <10 years duration at baseline, fulfilling 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 with a local action), oral morphine or equivalent opioid analgesics (≤30 mg/day), acetaminophen, or oral corticosteroids (≤ 10 mg/day in prednisolone equivalent).
5. At screening, patient 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 (latex agglutination test) of ≥1.00 mg/dL at screening.

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7. Met the ACR 1991 Revised Criteria for the Classification of Global Functional Status in RA Class I, II, or III at screening.
8. Had inadequate response to MTX that was continuously administered for at least 90 days prior to screening and MTX ≥8 mg/week for at least 28 days prior to baseline. However, an inadequate responder to MTX <8 mg/week was also eligible if intolerance precluded a dose increase.
9. Was able to continue a stable dose of MTX (a maximum of 16 mg/week) from at least 28 days prior to screening until the end of treatment (EOT).
10. Had bone erosion at the joint (as evidenced by X-rays of hands and feet within 90 days prior to baseline) assessed using mTSS, and either positive anti-cyclic citrullinated peptide (CCP) antibody ≥4.5 U/mL or positive rheumatoid factor >15 IU/mL at screening:
11. Willing and able to comply with the study requirements.

Patient exclusion criteria

A patient was excluded from participation if any of the following applied:

1. Had received a biological DMARD within the following specified periods:

- Etanercept: 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

2. Had an inadequate response to a biological DMARD as determined by the investigator/subinvestigator.

3. Had received 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.

- Salazosulfapyridine
- Lobenzarit

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- Gold
- Iguratimod
- D-penicillamine
- Bucillamine
- Actarit
- Leflunomide
- Tacrolimus
- Cyclosporine
- Cyclophosphamide
- Azathioprine
- Minocycline
- Mizoribine

4. Had received tofacitinib and other JAK inhibitors (including other investigational drugs).

5. Had received intra-articular, intravenous, intramuscular, or endorectal (excluding suppositories in patients with anal diseases) corticosteroid within 28 days prior to baseline.

6. Had participated in any study of peficitinib and had received peficitinib or placebo.

7. Had received other investigational drugs within 90 days or within five half-lives, whichever was longer, prior to baseline.

8. Had received 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. Had 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

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- 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 ≥11 pg/mL
- Positive hepatitis B surface (HBs) antigen, hepatitis B core (HBc) antibody, HBs Antibody, or HBV-DNA quantitation (however, a patient with negative HBs antigen and HBV-DNA quantitation, and positive HBc antibody, HBs antibody, or both was eligible if HBV-DNA was monitored by HBV-DNA quantitation at every scheduled visit after initiation of study drug administration.)
- Positive hepatitis C virus antibody

13. Had a history of or concurrent active tuberculosis. Eligibility criteria for tuberculosis are described below:

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

*Evidence of old tuberculosis was determined if chest X-ray revealed pleural thickening, band-like shadow and calcification ≥5 mm. Chest X-ray within 90 days prior to baseline could substitute for the screening test.

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†T-spot or Quantiferon Gold test was first priority. When the result was equivocal or invalid, retest including other test methods were allowed. If a retest was not performed, criteria for positive results were followed. 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 or more, or induration. Tests conducted within 90 days prior to baseline could be used for diagnosis.

‡Patient had to receive or had received prophylaxis with isoniazid or rifampicin. Prophylaxis was administered for 6 to 9 months, starting from at least 21 days prior to baseline.

14. Met 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 (prophylactic antibiotics were allowed).
- Had a high risk of infection (e.g., patient with urinary catheter) at the discretion of investigator/subinvestigator

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

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

17. Had received live or live attenuated virus vaccination within 56 days prior to baseline (inactivated vaccines including influenza and pneumococcal vaccines were allowed).

18. Had 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 that would make the patient unsuitable for the study as determined by the investigator/subinvestigator.

19. Had had a history of clinically significant allergy. Clinically significant allergy includes allergies such as systemic urticaria induced by specific antigens and drugs, anaphylaxis, and allergy associated with shock necessitating hospitalised treatment.

20. Had received medications that were cytochrome P450 (CYP) 3A substrates with narrow therapeutic range within 14 days prior to baseline. These medications included dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus and disopyramide.

21. Had (or had history of) concurrent cardiac failure, defined as New York Heart Association Classification Class III or higher.

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22. Had (or had history of) concurrent prolonged QT syndrome. Patient had prolonged QT interval (defined as QTc ≥500 msec; a patient with QTc ≥500 msec at retest was excluded) at screening.
23. Had (or had history of) congenital short QT syndrome. Patient had shortened QT interval (defined as QTc <330 msec; a patient with QTc <330 msec at retest was excluded) at screening.
24. Had a history of positive human immunodeficiency virus infection.
25. Female patient who was pregnant or might be pregnant, was nursing, wished to conceive for a period running from the time informed consent was given until 60 days after the EOT, or for whom the possibility of pregnancy could not be excluded as a result of the serum pregnancy test given at the time of screening.
26. Male patient who could not practice at least two types of contraception from the time of informed consent to 90 days after the EOT, or a female patient of childbearing potential who could not practice at least 2 types of contraception from the time of informed consent to 60 days after the EOT.
27. Male patient who did not agree not to donate sperm from the time of informed consent to 90 days after the EOT, or a female patient who did not agree not to donate ova from the time of informed consent to 60 days after the EOT.
28. Had been judged unsuitable to participate in the study for other reasons by the investigator/subinvestigator.
29. Had a history or complication of lymphatic diseases such as lymphoproliferative disorder, lymphoma, and leukaemia.

Closed testing procedure

The following closed testing procedure was used for multiplicity adjustment in the primary analysis:

- 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
- Step 3: mTSS change from baseline at Week 28/ET; peficitinib 150 mg vs placebo
- Step 4: mTSS change from baseline at Week 28/ET; peficitinib 100 mg vs placebo

The null hypothesis at Step 1 was tested at a significance level of 0.05. If this was statistically significant, the next step was initiated. The absence of statistical significance led to completion of the hypothesis test. These hypothesis tests continued up to Step 4 unless it was rejected.

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178 **Assessments**

179 Individual van der Heijde-mTSS bone erosion scores were derived as follows: digital
180 radiographic images were stripped of electronic header information (e.g. subject identifiers,
181 time point of assessment) to ensure blinding and replaced with a unique site and subject
182 identifier. A visual QC review of the overall quality of digital images was performed prior to
183 each image being read. Two readers at a central facility read the images independently. The
184 mean mTSS was obtained from the scores given by the two primary readers if no
185 adjudication was necessary, or the mean of the scores given by all three readers
186 (adjudicator and the two primary readers) if adjudication was performed. If one reader's
187 mTSS was not available owing to an inadequate image at a given time point, the mean
188 mTSS at this time point was obtained from the mean of the two remaining readers' scores. If
189 an image for a patient was adjudicated and only two readers had adequate baseline images,
190 these two readers' scores were used to calculate the combined mTSS and change scores
191 for all time points, even though the third reader may have had adequate follow-up time point
192 images. If an image for a patient was adjudicated and only one reader had adequate
193 baseline images, all the time point images, mTSS and change scores, including baseline
194 and follow-up time points, were set as 'missing', even though follow-up time points may have
195 been adequate for all three readers. Overall, 31/519 (6%) radiographic readings required
196 input from an adjudicator. This was considered within the predefined quality threshold of
197 <15%, confirming agreement between the readers. The inter-reader SDC at Week 28 was
198 2.8.

199 **Statistical analyses**

200 For the assessment of joint destruction in patients who discontinued at or before Week 28
201 (after Day 48), or for patients treated initially with placebo and who switched due to lack of
202 efficacy to peficitinib at Week 12, mTSS at Week 28 (Day 197) was extrapolated using a
203 linear extrapolation method based on the mTSS at baseline and early termination (after Day
204 48) or Week 12 (Day 85) (before switching).

205 With regard to missing data for mTSS, erosion score and joint space narrowing score,
206 scores were imputed by linear extrapolation at Week 28/ET (Week 28 evaluation: Day 197).

207 1) For patients who discontinued at or before Week 28 (after Day 48) or for patients
208 initially treated with placebo and who switched to peficitinib at Week 12 owing to lack
209 of efficacy, mTSS at Week 28 (Day 197) was extrapolated using a linear

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extrapolation method based on the mTSS at baseline and early termination (after Day 48) or Week 12 (Day 85), i.e., before switching.

2) For patients who were initially treated with placebo, if measurement data were available at Week 28 (from Days 160 to 234) and patients had not yet been switched to peficitinib, then actual data were used (no imputation performed).
3) For the Week 52 (Day 365) evaluation, described as Week 52/ET, the score was extrapolated based on scores at baseline and early termination (after Day 48) or Week 12/Week 28, i.e., before switching for those patients initially on placebo.
4) If measurement data were available at Week 52 (from Days 328 to 402) and a patient was not initially randomised to placebo, then actual data were used (no imputation performed).

In the primary analysis of mean change from baseline of mTSS at Week 28/ET, 481 of 518 contributed radiographic scores at Week 28/ET. Of these 481 patients, 392 had observed data at Week 28 while the remaining 89 patients had imputed data by linear extrapolation.

SUPPLEMENTARY RESULTS

Narrative

The death by suicide of a 69-year-old male in the placebo group was reported 18 weeks after the Week-28 switch to peficitinib 100 mg. The patient received peficitinib concomitantly with oral MTX (at a dose of 10 mg/week) until his death. The patient's medical history reported the presence of osteoporosis, hyperlipidaemia, depression and insomnia. Other concomitant medications reported at the start of study treatment included folic acid, esomeprazole magnesium, isoniazid, alendronate sodium, fluvoxamine maleate, alprazolam, simvastatin, zopiclone, triazolam, amitriptyline hydrochloride, mirtazapine, pyridoxal phosphate and prednisolone. Adverse events experienced by the patient during the study included thermal burns to the right hand, constipation and lower back pain. The death was considered by the investigator to be unrelated to the study drug owing to the patient's diagnosis of depression.

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SUPPLEMENTARY TABLES

Supplementary Table 1 Sensitivity analysis of ACR20 response at Week 12/ET (LOCF and non-responder imputation, FAS)

	Responders, n (%)	Treatment difference versus placebo		
		Difference (%)*	95% CI (%)†	P value‡
ACR20 response at Week 12/ET (LOCF and non-responder imputation;§ FAS)				
Placebo (N=170)	37 (21.8)	-	-	-
Peficitinib 100 mg (N=174)	100 (57.5)	35.7	25.5, 45.9	<0.001
Peficitinib 150 mg (N=174)	110 (63.2)	41.5	31.4, 51.5	<0.001
ACR20 response at Week 12/ET (observed data;‖ FAS)				
Placebo (N=159)	37 (23.3)	-	-	-
Peficitinib 100 mg (N=168)	100 (59.5)	36.3	25.7, 46.8	<0.001
Peficitinib 150 mg (N=166)	110 (66.3)	43.0	32.6, 53.4	<0.001

CI, confidence interval; FAS, full analysis set; N, total number of responders and non-responders (percentages based on N). Patients with missing data for all baseline ACR components were not included in percentages because ACR20 response could not be calculated.
*Difference in proportion of responders (each active group minus placebo)
†CI based on normal approximation to the binomial distribution (continuity corrected)
‡Fisher's exact test. No multiplicity adjustment
§ACR components were LOCFed first and then ACR20 response was calculated. If ACR20 response was missing, then non-responder imputation was performed for missing ACR20 response
‖ACR20 response was calculated using data as reported in study database

Supplementary Table 2 Sensitivity analysis of change from baseline in van der Heijde-mTSS at Week 28 (observed data) and Week 28/ET (linear extrapolation [ANCOVA]), FAS

		Treatment difference versus placebo		
	Mean (SD)	**LS mean (SE)**	**95% CI (%)**	**P value***
Baseline, observed data†				
Placebo (N=169)	28.40 (36.28)	-	-	-
Peficitinib 100 mg (N=173)	25.23 (35.50)	-	-	-
Peficitinib 150 mg (N=174)	25.00 (32.38)	-	-	-
Week 28, observed data†				
Placebo (N=73)	35.29 (34.60)	-	-	-
Peficitinib 100 mg (N=159)	26.85 (36.80)	-	-	-
Peficitinib 150 mg (N=160)	26.42 (32.63)	-	-	-
Week 28 change, observed data†				
Placebo (N=73)	2.72 (4.78)	-	-	-
Peficitinib 100 mg (N=159)	1.59 (4.25)	-	-	0.082
Peficitinib 150 mg (N=160)	1.01 (2.88)	-	-	0.002
Week 28/ET, linear extrapolation‡				
Placebo (N=153)	33.14 (39.16)	-	-	-
Peficitinib 100 mg (N=164)	27.11 (36.84)	-	-	-
Peficitinib 150 mg (N=164)	26.01 (32.34)	-	-	-
Week 28/ET change, linear extrapolation‡				
Placebo (N=153)	3.37 (5.46)	-	-	-
Peficitinib 100 mg (N=164)	1.62 (4.23)	-1.69 (0.48)	-2.63, -0.75	<0.001
Peficitinib 150 mg (N=164)	1.03 (2.86)	-2.27 (0.48)	-3.22, -1.33	<0.001

ANCOVA, analysis of covariance; CI, confidence interval; ET, early termination; FAS, full analysis set; LS, least squares; SD, standard deviation; SE, standard error.
Higher mTSS indicates greater disease activity.
*For observed data, p values were based on rank analysis of covariance model: rank of mTSS change = treatment + baseline rank of mTSS. For data derived by linear extrapolation, p values were based on analysis of covariance model for Week 28/ET change: change from baseline at Week 28/ET = treatment + baseline value
†Patients who discontinued at or before Week 28 or who switched to receive peficitinib instead of placebo at Week 12 due to lack of efficacy were not included in the observed data sensitivity analysis
‡For patients who discontinued at or before Week 28 or who were switched to receive peficitinib

instead of placebo at Week 12 due to lack of efficacy, mTSS at Week 28/ET was extrapolated using a linear extrapolation method based on the mTSS at baseline and early termination or Week 12 (Day 85) (before switching)

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Supplementary Table 3 Number of patients with ACR20, ACR50 and ACR70 responses, and HAQ-DI scores over time (FAS)

Outcome	Treatment group	Week				
		0 (baseline)	4	8	12	52
ACR20, n/N (%)	Placebo	-	27/164 (16.5)	33/161 (20.5)	37/159 (23.3)	-
	Peficitinib 100 mg	-	65/170 (38.2)	86/168 (51.2)	100/168 (59.5)	123/145 (84.8)
	Peficitinib 150 mg	-	82/170 (48.2)	103/166 (62.0)	110/166 (66.3)	128/147 (87.1)
ACR50, n/N (%)	Placebo	-	5/164 (3.0)	9/161 (5.6)	13/159 (8.2)	-
	Peficitinib 100 mg	-	17/170 (10.0)	33/168 (19.6)	50/168 (29.8)	97/145 (66.9)13
	Peficitinib 150 mg	-	27/170 (15.9)	55/166 (33.1)	80/166 (48.2)	100/147 (68.0)
ACR70, n/N (%)	Placebo	-	1/164 (0.6)	1/161 (0.6)	4/159 (2.5)	-
	Peficitinib 100 mg	-	2/170 (1.2)	13/168 (7.7)	21/168 (12.5)	57/145 (39.3)
	Peficitinib 150 mg	-	7/170 (4.1)	23/166 (13.9)	41/166 (24.7)	77/147 (52.4)
HAQ-DI, mean (SD)	Placebo	1.05 (0.66)	1.06 (0.70)	1.03 (0.70)	1.03 (0.71)	-
	Peficitinib 100 mg	0.91 (0.65)	0.82 (0.63)	0.72 (0.60)	0.68 (0.60)	0.49 (0.53)
	Peficitinib 150 mg	1.02 (0.62)	0.81 (0.62)	0.70 (0.57)	0.63 (0.56)	0.47 (0.51)

HAQ DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation

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Supplementary Table 4 Overview of TEAEs from Week 12 to Week 28 (SAF)

	Placebo (N=82)	**Peficitinib 100 mg (N=167)**	**Peficitinib 150 mg (N=165)**	**Placebo to 100 mg at Week 12 (N=37)**	**Placebo to 150 mg at Week 12 (N=38)**	**Peficitinib 100 mg + 150 mg (N=332)**
All TEAEs	50 (61.0)	95 (56.9)	104 (63.0)	21 (56.8)	25 (65.8)	199 (59.9)
Drug-related TEAEs*	27 (32.9)	63 (37.7)	72 (43.6)	16 (43.2)	11 (28.9)	135 (40.7)
Deaths	0	0	0	0	0	0
SAEs	2 (2.4)	5 (3.0)	3 (1.8)	0	0	8 (2.4)
Drug-related SAEs*	2 (2.4)	3 (1.8)	1 (0.6)	0	0	4 (1.2)
≥Grade 3 TEAEs†	5 (6.1)	7 (4.2)	6 (3.6)	1 (2.7)	1 (2.6)	13 (3.9)
TEAE leading to permanent discontinuation of study drug						
All	4 (4.9)	4 (2.4)	1 (0.6)	0	0	5 (1.5)
Drug-related*	3 (3.7)	3 (1.8)	1 (0.6)	0	0	4 (1.2)
SAEs	2 (2.4)	2 (1.2)	0	0	0	2 (0.6)
Drug-related SAEs*	2 (2.4)	2 (1.2)	0	0	0	2 (0.6)

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

Supplementary Table 5 Overview of TEAEs from Week 28 to Week 52 or later (SAF)

	Peficitinib 100 mg (N=158)	**Peficitinib 150 mg (N=158)**	**Placebo to 100 mg at Week 12 (N=36)**	**Placebo to 150 mg at Week 12 (N=36)**	**Placebo to 100 mg at Week 28 (N=39)**	**Placebo to 150 mg at Week 28 (N=34)**	**Peficitinib 100 mg + 150 mg (N=316)**
All TEAEs	114 (72.2)	112 (70.9)	22 (61.1)	27 (75.0)	25 (64.1)	26 (76.5)	226 (71.5)
Drug-related TEAEs*	72 (45.6)	74 (46.8)	14 (38.9)	18 (50.0)	17 (43.6)	17 (50.0)	146 (46.2)
Deaths	0	0	0	0	1 (2.6)‡	0	0
SAEs	10 (6.3)	8 (5.1)	2 (5.6)	1 (2.8)	1 (2.6)	1 (2.9)	18 (5.7)
Drug-related SAEs*	4 (2.5)	5 (3.2)	2 (5.6)	1 (2.8)	0	1 (2.9)	9 (2.8)
≥Grade 3 TEAEs†	15 (9.5)	15 (9.5)	2 (5.6)	2 (5.6)	2 (5.1)	2 (5.9)	30 (9.5)
TEAE leading to permanent discontinuation of study drug							
All	4 (2.5)	6 (3.8)	3 (8.3)	2 (5.6)	2 (5.1)	0	10 (3.2)
Drug-related*	1 (0.6)	5 (3.2)	2 (5.6)	2 (5.6)	1 (2.6)	0	6 (1.9)
SAEs	3 (1.9)	4 (2.5)	1 (2.8)	0	1 (2.6)	0	7 (2.2)
Drug-related SAEs*	1 (0.6)	3 (1.9)	1 (2.8)	0	0	0	4 (1.3)

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. SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event. All values are n (%).

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

†Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade: grade 3 = severe or medically significant, grade 4 = life threatening, grade 5 = death related to AE.

‡A 69-year-old male patient who was switched from placebo to peficitinib 100 mg at Week 28 committed suicide at Day 323 (Week 46). The patient had a history of depression and the death was considered unrelated to study drug.

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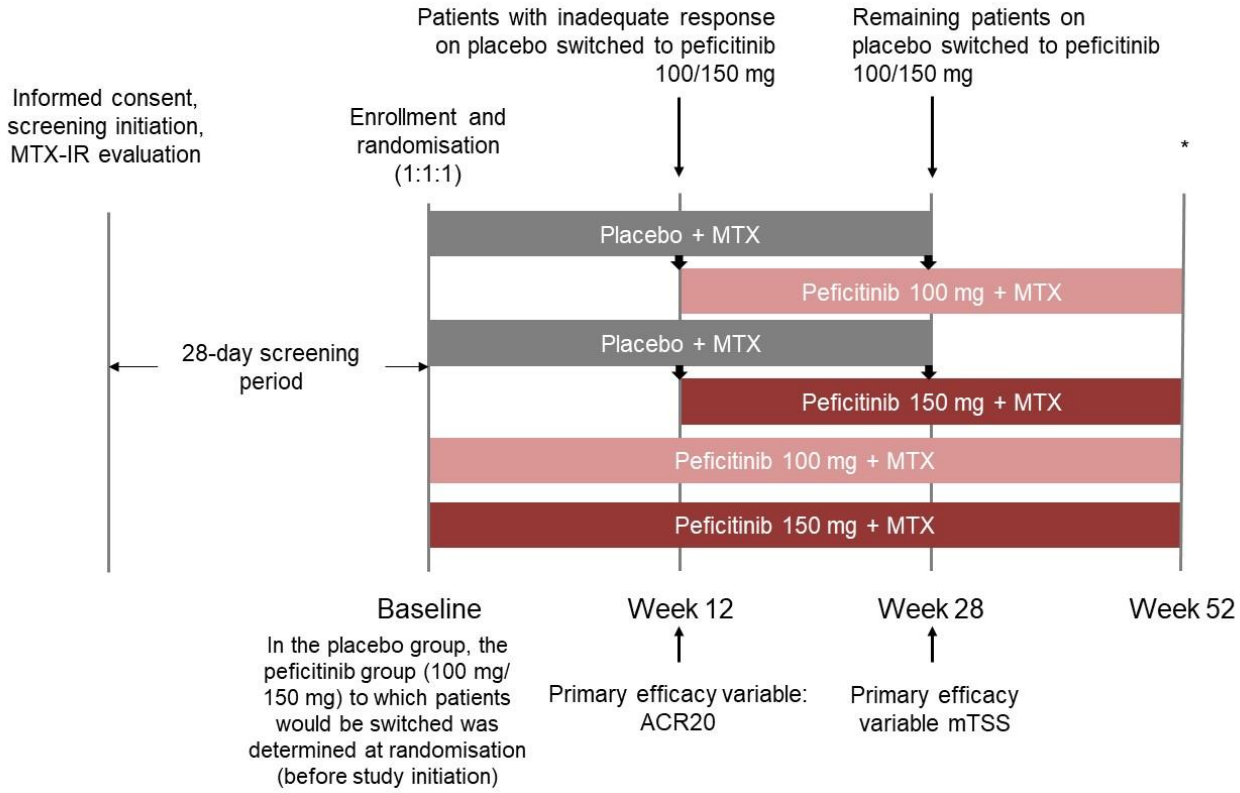
SUPPLEMENTARY FIGURES

Supplementary Figure 1 Study design



[Footnote for Supplementary Figure 1]

IR, inadequate responder
*Patients completing the study enrolled into the open-label extension study. Patients 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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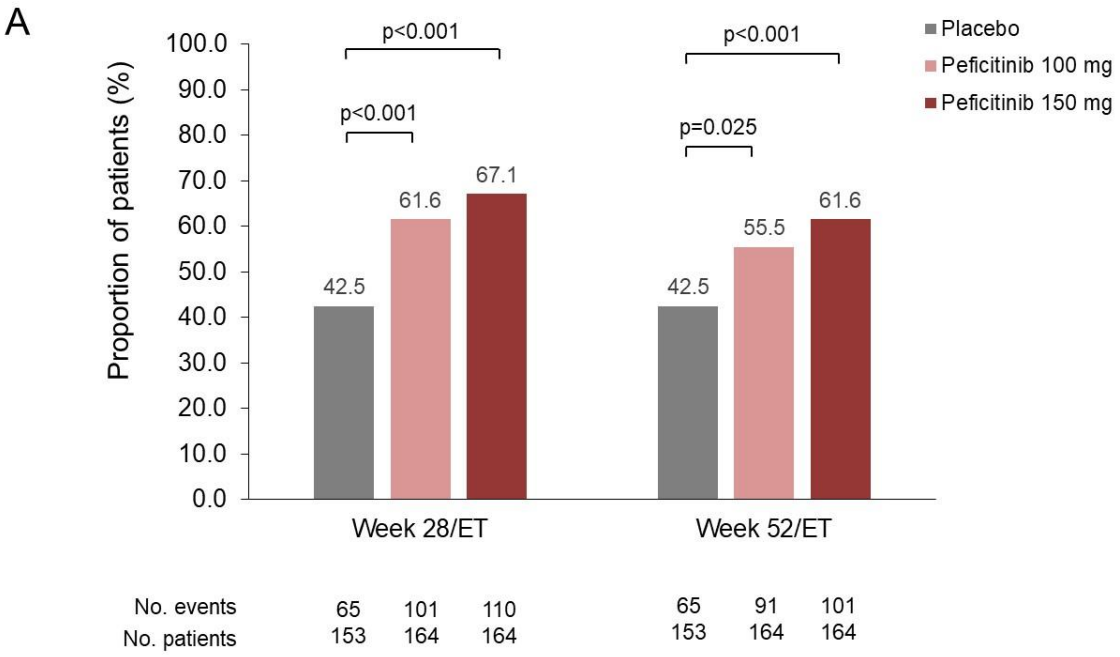
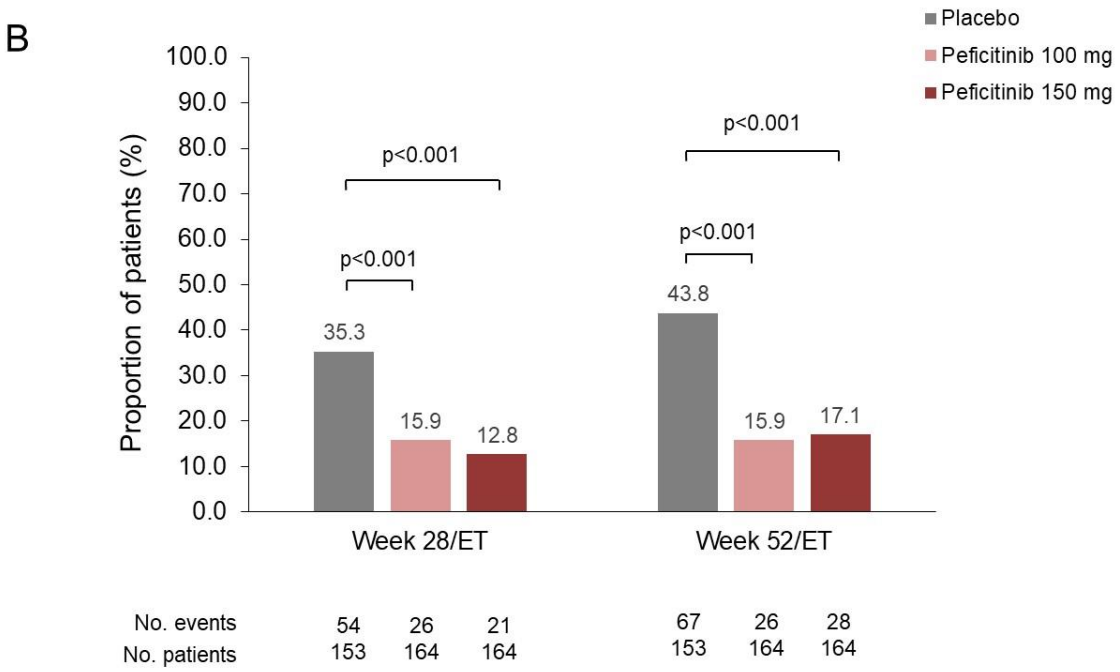
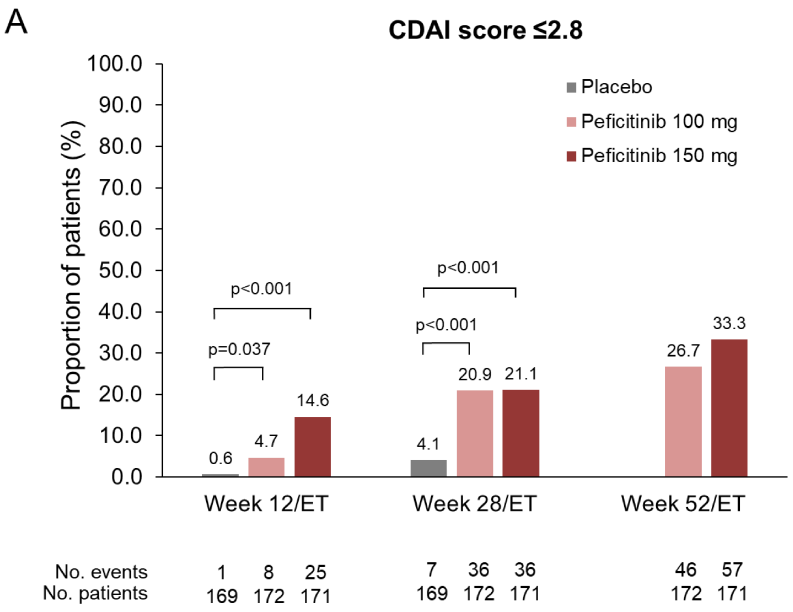
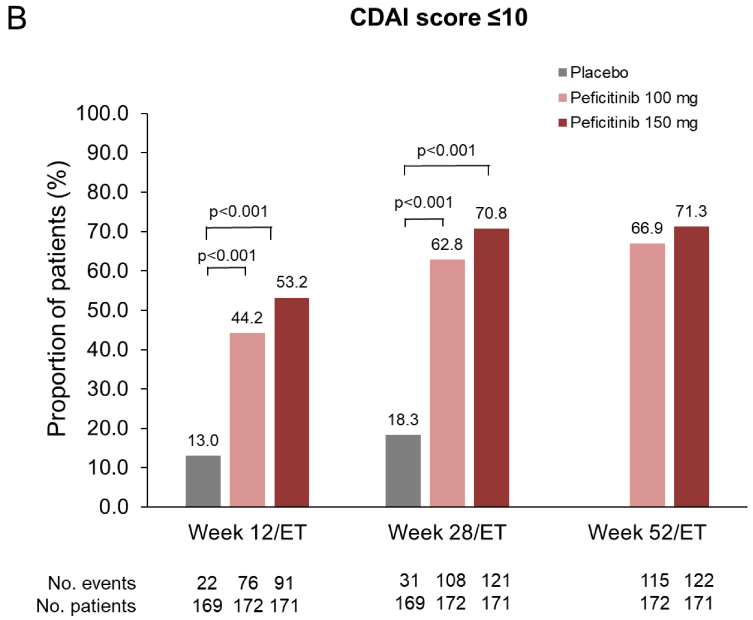
Supplementary Figure 2 Proportions of patients showing a change from baseline in mTSS **A)** ≤0 and **B)** ≥3 at Week 28/ET and Week 52/ET (linear extrapolation) (FAS)




B
Placebo
Peficitinib 100 mg
Peficitinib 150 mg
Proportion of patients (%)
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
p<0.001
p<0.001
p<0.001
p<0.001
35.3
15.9
12.8
43.8
15.9
17.1
Week 28/ET
Week 52/ET
No. events 54 26 21 67 26 28
No. patients 153 164 164 153 164 164

Supplementary Figure 3 Proportions of patients achieving **a)** CDAI score ≤2.8, **B)** CDAI score ≤10, **C)** SDAI score ≤3.3 and **D)** SDAI score ≤11 at Week 12/ET, Week 28/ET and Week 52/ET (linear extrapolation) (FAS)





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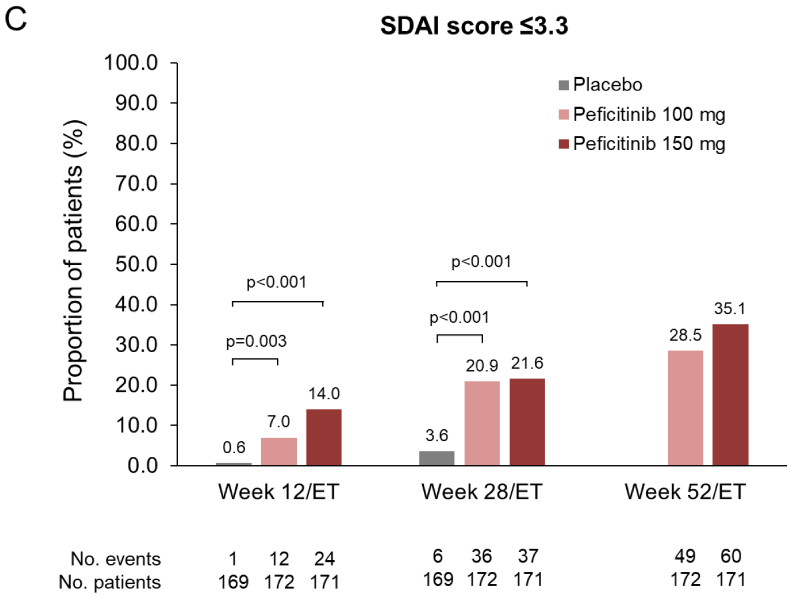

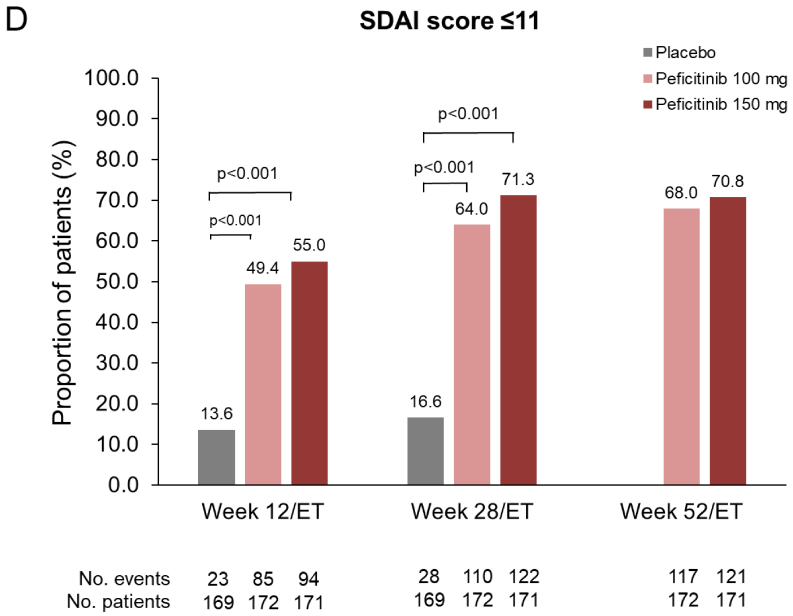

[Footnote applies to all parts of Supplementary Figure 3]

P values were determined using Fisher's exact test with no multiplicity adjustment.

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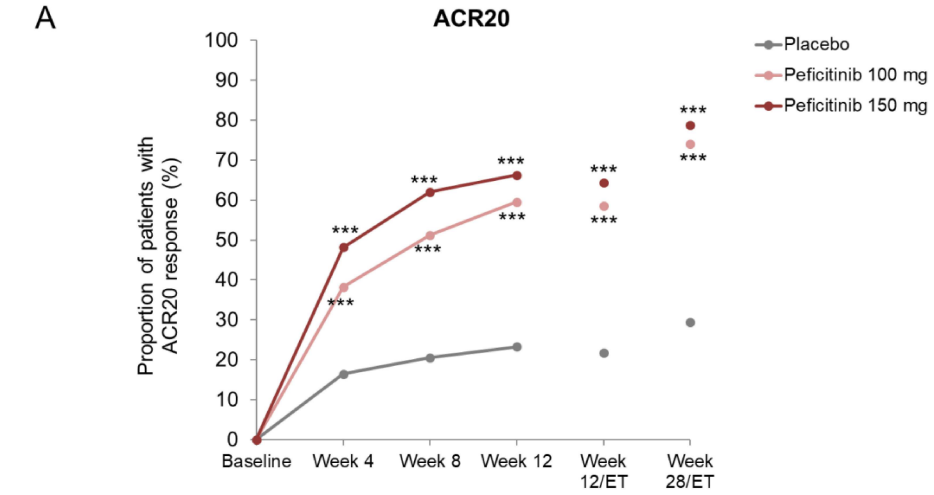
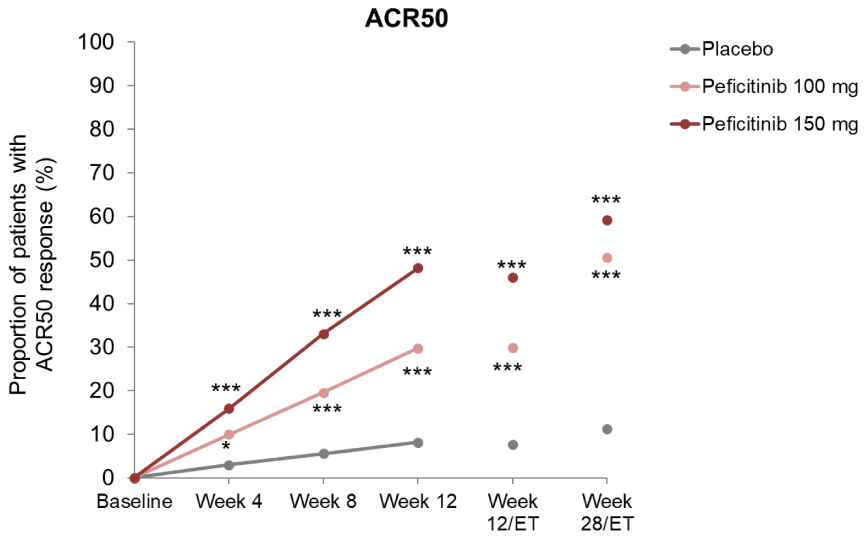
Supplementary Figure 4 A) ACR20, **B)** ACR50, and **C)** ACR70 responses over time (FAS)



No. with response (n/N)					
Placebo	27/164	33/161	37/159	37/170	50/170
100 mg	65/170	86/168	100/168	102/174	129/174
150 mg	82//170	103/166	110/166	112/174	137/174
Proportion of patients (%)					
Placebo	16.5	20.5	23.3	21.8	29.4
100 mg	38.2	51.2	59.5	58.6	74.1
150 mg	48.2	62.0	66.3	64.4	78.7

B



No. with response (n/N)					
Placebo	5/164	9/161	13/159	13/170	19/170
100 mg	17/170	33/168	50/168	52/174	88/174
150 mg	27/170	55/166	80/166	80/174	103/174
Proportion of patients (%)					
Placebo	3.0	5.6	8.2	7.6	11.2
100 mg	10.0	19.6	29.8	29.9	50.6
150 mg	15.9	33.1	48.2	46.0	59.2

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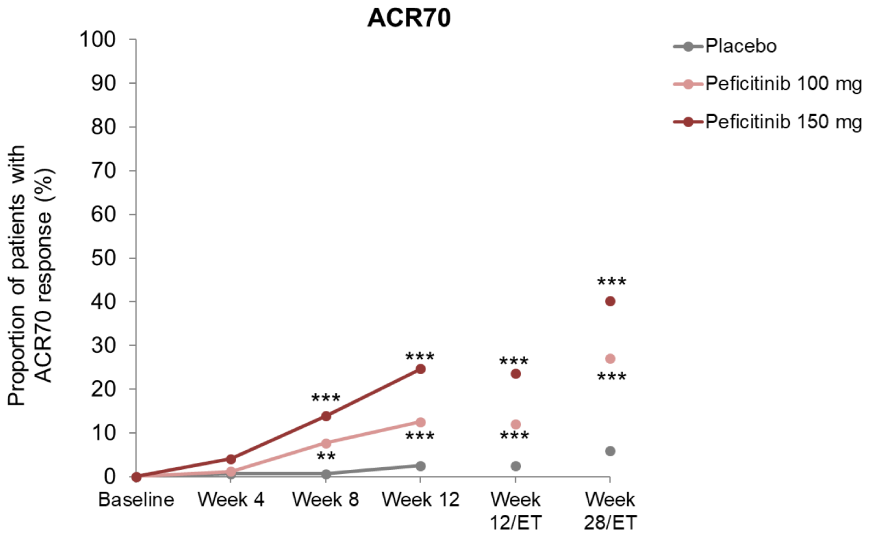
C



No. with response (n/N)					
Placebo	1/164	1/161	4/159	4/170	10/170
100 mg	2/170	13/168	21/168	21/174	47/174
150 mg	7/170	23/166	41/166	41/174	70/174
Proportion of patients (%)					
Placebo	0.6	0.6	2.5	2.4	5.9
100 mg	1.2	7.7	12.5	12.1	27.0
150 mg	4.1	13.9	24.7	23.6	40.2

[Footnote applies to all parts of Supplementary Figure 4]

*p<0.05; **p<0.01; **p<0.001

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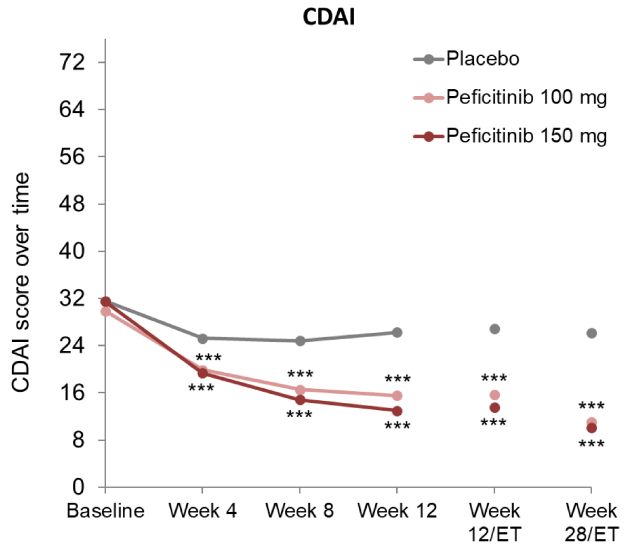
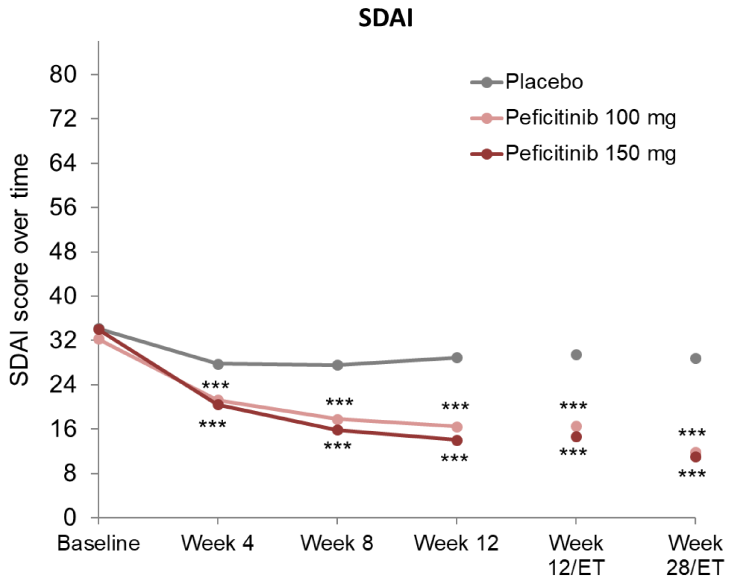
Supplementary Figure 5 Change from baseline over time in **A)** CDAI score and **B)** SDAI score (FAS)

A



No. of patients						
Placebo	169	165	162	159	169	169
100 mg	174	170	168	168	172	172
150 mg	174	170	166	166	171	171
Mean CDAI score						
Placebo	31.56	25.21	24.81	26.23	26.87	26.17
100 mg	29.88	19.88	16.57	15.56	15.65	11.03
150 mg	31.51	19.33	14.85	12.99	13.54	10.11

B



No. of patients						
Placebo	169	165	162	158	169	169
100 mg	174	170	168	168	172	172
150 mg	174	170	166	166	171	171
Mean SDAI score						
Placebo	34.18	27.79	27.54	28.90	29.55	28.81
100 mg	32.31	21.23	17.78	16.44	16.57	11.80
150 mg	34.03	20.46	15.83	14.04	14.66	11.03

[Footnote applies to both parts of Supplementary Figure 5]

*p<0.05, **p<0.01, ***p<0.001

Figures show observed data for Weeks 0 to 12 and LOCF for Week 12/ET and 28/ET. P values derived from Fisher's exact test with no multiplicity adjustment, except for ACR20 response rates at Week12/ET, for which a closed testing procedure was used for multiplicity adjustment.

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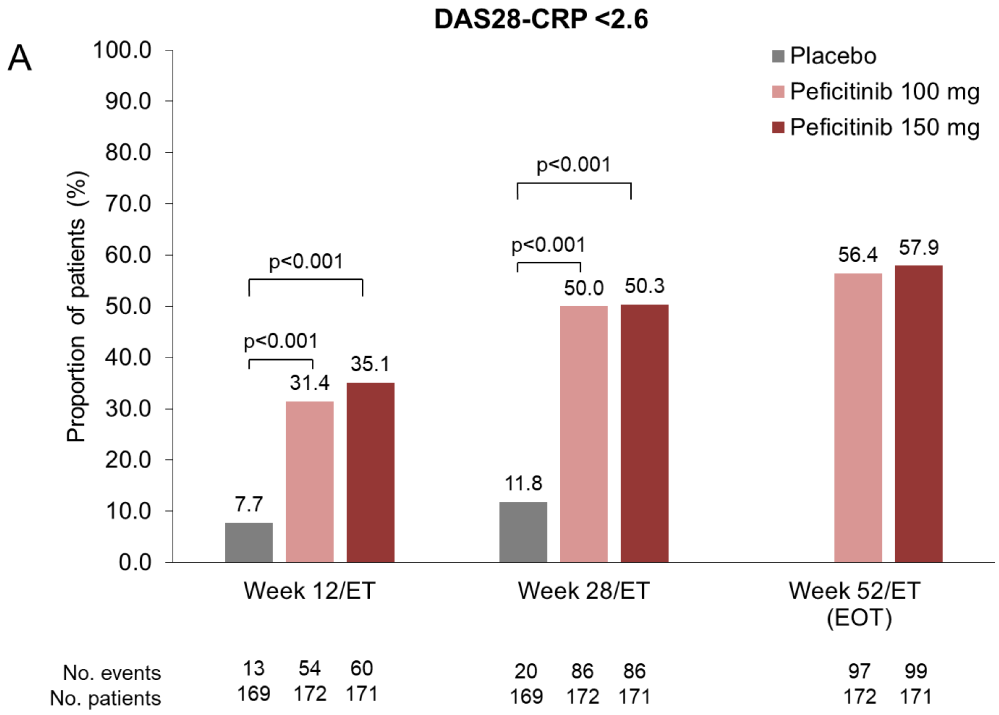
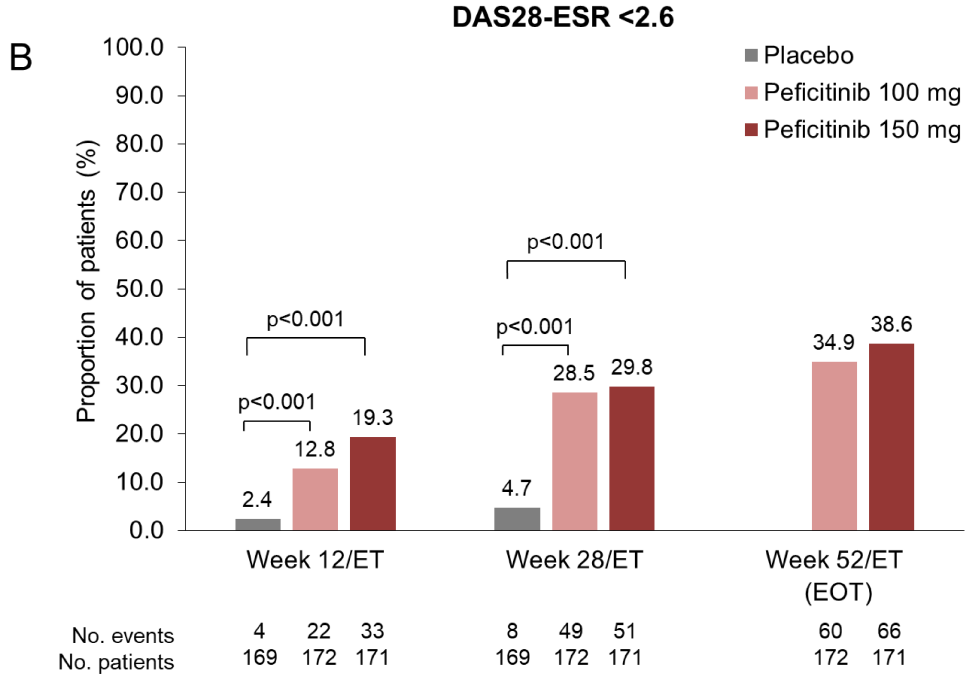
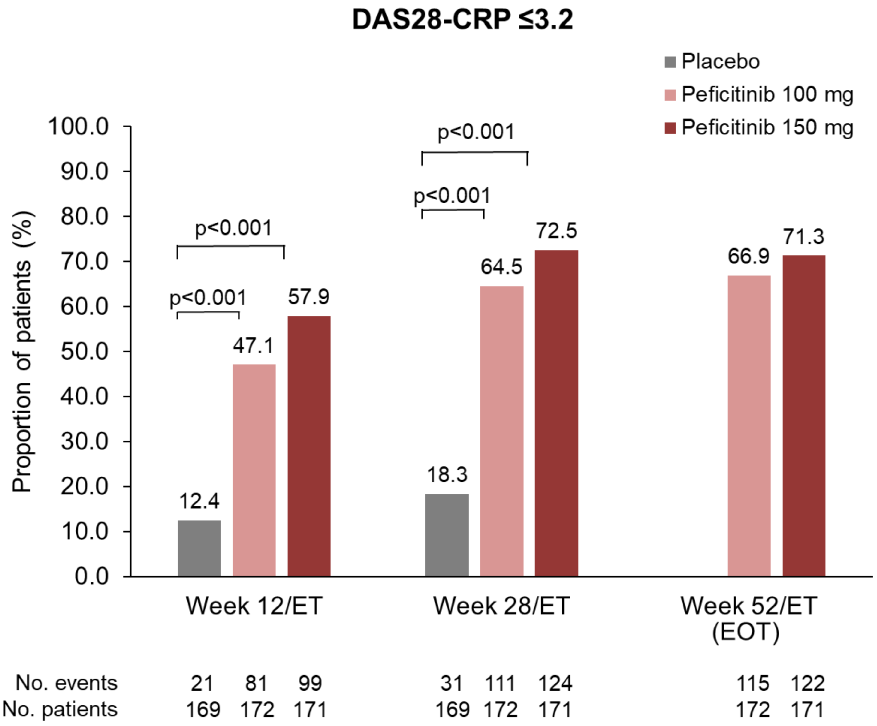
Supplementary Figure 6 Proportion of patients achieving **A)** DAS28-CRP <2.6, **B)** DAS28-ESR <2.6 and **C)** DAS28-CRP ≤3.2, at Week 12/ET, Week 28/ET and Week 52/ET (EOT) (FAS)





C



[Footnote applies to all parts of Supplementary Figure 6]

Figures show data for last observation carried forward derived from an imputation method. Statistical comparisons were not conducted for Week 52/ET data. P values were derived from Fisher's exact test with no multiplicity adjustment.

LIST OF STUDY CENTRES

Please note that all the sites are located in 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 Kumamoto Saishunso National Hospital
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 Orthopedic Rheumatology 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
University of Tsukuba Hospital
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
Medical Corporation Association Shizuoka Miyake Orthopedic Clinic
Medical Corporation Association Katokukai Kang Rheumatism and Orthopedic Clinic
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

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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
Japanese Red Cross 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 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
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
Medical Corporation Association Hoseikai Oki Medical Clinic
Kushiro Red Cross Hospital
Social Medical Corporation Sokokai Gyoda General Hospital Gyoda Clinic
Social Welfare Corporation St. Teresa's Society St. Joseph's Hospital
Social Medical Corporation Hoseikai Marunouchi 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
Social Medical Corporation Fukushima Koseikai Fukushima Daiichi Hospital
Funabashi Municipal Medical Center
Medical Corporation Nagamine Orthopedic Clinic
Independent Administrative Agency Japan Community Health care Organization Yokkaichi Hazu Medical Center

Osaki Citizen Hospital
Toyohashi Municipal Hospital
Social Medical Corporation Shinkokinenkai, Shinko Hospital
Japanese Red Cross Kitami Hospital
Medical Corporation Fukumankai Morita Internal Medicine Clinic
Japanese Red Cross Society Nagano Hospital
Social Medical Corporation Koujunkai Daido Clinic
Sugimoto Rheumatology and Internal Medicine Clinic
Independent Administrative Agency Japan Community Health Care Organization Osaka Hospital
Medical Corporation Seiryukai Miyashima RA & Orthopaedic Clinic
Medical Corporation Association Sakurakai Morita Hospital
Asahi General Hospital
Hitachi, Ltd. Hitachinaka General Hospital