EXTENDED REPORT

Efficacy and safety of the oral Janus kinase inhibitor peficitinib (ASP015K) monotherapy in patients with moderate to severe rheumatoid arthritis in Japan: a 12-week, randomised, double-blind, placebo-controlled phase IIb study

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ABSTRACT

Objective To evaluate the efficacy, safety and dose response of a novel oral Janus kinase inhibitor, peficitinib (ASP015K), as monotherapy in Japanese patients with moderate to severe rheumatoid arthritis (RA).

Methods In a 12-week, double-blind study, 281 adult patients with RA with active disease not on concomitant disease-modifying antirheumatic drug therapy were randomised equally to once-daily placebo or peficitinib 25, 50, 100 and 150 mg. The primary endpoint was American College of Rheumatology (ACR) 20 response in the peficitinib treatment groups versus placebo at week 12.

Results Mean age was 53.0 years, 81.1% were female and 25.3% had previously used antitumour necrosis factor therapy. Peficitinib 50, 100 and 150 mg each showed statistically significantly higher ACR20 response rates compared with placebo, and response rates increased up to 150 mg with a statistically significant dose response. The total incidence of treatment-emergent adverse events (TEAEs) was similar between the placebo (64.3%) and peficitinib 25, 50, 100 and 150 mg groups (70.9%, 64.9%, 52.7% and 67.2%, respectively). TEAEs occurring more frequently in the peficitinib group compared with the placebo group included nasopharyngitis, increased blood creatine phosphokinase and diarrhoea. No cases of serious infections were reported. Herpes zoster occurred in four patients (two each in peficitinib 25 and 100 mg).

Conclusions Treatment with peficitinib as monotherapy for 12 weeks in Japanese patients with moderate to severe RA is efficacious and showed acceptable safety profile. These findings support further developments of peficitinib for RA treatment.

Trial registration number NCT01649999; Results.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that targets synovial tissues, and is associated with progressive disability, impairments in health-related quality of life, systemic complications, early death and higher socioeconomic costs.[1–3] Treatment of RA is based on disease-modifying antirheumatic drugs (DMARDs), typically starting with methotrexate (MTX).[4] Biologic agents such as tumour necrosis factor (TNF) inhibitors, which were developed later, have proven to be effective in patients not responding to conventional DMARDs; however, about 20%–40% of patients treated with a TNF inhibitor fail to achieve a 20% improvement in the American College of Rheumatology (ACR) criteria for RA, and more lose response over time or experience adverse events (AEs) following treatment.[5] Thus, there exists a need for new treatment options of RA with a different mechanism of action from currently used conventional DMARDs and biologic agents.

Molecules of the signal transduction pathway such as the Janus kinase (JAK) family are considered promising targets for RA treatment.[6 7] JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2) form the JAK family of non-receptor protein tyrosine kinases, and are critically important for immune cells and haematopoietic cells.[8] Tofacitinib is a clinically available JAK inhibitor for the treatment of RA with a dosage regimen of twice-daily oral administration.[9] It has been previously reported that the JAK inhibitor tofacitinib is an encouraging new option for RA treatment according to a review of its basic and clinical data,[10–13] and several randomised, controlled phase III trials have demonstrated its efficacy in the treatment of RA with an acceptable safety profile.[14–17]

Peficitinib (ASP015K) is a novel orally bioavailable JAK inhibitor in development for the treatment of RA. Peficitinib inhibits JAK1, JAK2, JAK3 and Tyk2 enzyme activities with inhibitory concentration 50% (IC50) values of 3.9, 5.0, 0.71 and 4.8 nmol/L, respectively, and has moderate selectivity for JAK3 inhibition. The other JAK inhibitor, tofacitinib or baricitinib, selectively suppresses JAK3 or JAK1/2, respectively. Milder inhibition of JAK2 by peficitinib may contribute to the mitigation of effects on red blood cells and platelets reported to be caused by JAK2 inhibition.[18] Moreover, peficitinib has shown an improvement in symptoms in RA animal models after once-daily oral administration,[19] and has demonstrated dose-dependent improvement in psoriatic disease activities in a 6-week phase IIa study.[20] The terminal mean half-life of peficitinib was estimated to be 7–13 h in pharmacological

studies with healthy subjects,[21] suggesting that peficitinib can be dosed once-daily in the next development stage.

Therefore, we conducted a randomised, double-blind, placebo-controlled phase IIb study to evaluate the efficacy, safety and dose response of peficitinib as monotherapy orally administered once daily for 12 weeks in Japanese patients with moderate to severe RA.

METHODS
Study design
This was a phase IIb, randomised, double-blind, parallel-group, placebo-controlled, dose-finding, multicentre study with once-daily oral peficitinib or matching placebo as monotherapy in outpatients with moderate to severe RA (regardless of whether they had previously used or responded to another treatment drug). The study objective was to evaluate the efficacy, safety and dose response of a novel oral JAK inhibitor, peficitinib monotherapy. After a 4-week screening period, patients were equally assigned to a placebo or peficitinib 25, 50, 100, 150 mg group, and the study drug was orally administered once daily after breakfast for 12 weeks. After the 12-week treatment period, efficacy and safety assessments were performed, and a follow-up was also conducted 4 weeks after the end of treatment to confirm the incidence of AEs. This phase IIb study was performed at 43 sites in Japan between February 2012 and July 2013, and registered at ClinicalTrials.gov (NCT01649999).

Patients
Study subjects were adult outpatients (aged 20–75 years at the time of informed consent) with a diagnosis of RA according to the 1987 revised criteria of ACR[22] at least 6 months prior to screening, and who also had active RA defined as either a C-reactive protein (CRP) level >0.5 mg/dL or erythrocyte sedimentation rate (ESR) ≥28 mm/h, and ≥6 tender joints (using the 68-joint assessment) and ≥6 swollen joints (using the 66-joint assessment).

Patients treated with a stable dose of non-steroidal anti-inflammatory drugs (NSAIDs), oral morphine (≤30 mg/day or an equivalent amount of opioid analgesics), acetaminophen or an oral corticosteroid (≤10 mg/day of a prednisolone equivalent) were eligible. Changes in the dosage, dose regimen or route of administration were prohibited until completion of the study. Patients were excluded if they had taken biologic or non-biologic DMARDs within the following period prior to the first dose of study drug: within 28 days (etanercept and non-biologic DMARDs including MTX), 60 days (adalimumab, golimumab, infliximab and tocilizumab), 90 days (abatacept) and 180 days (rituximab). Administration of these DMARDs was also prohibited during the study.

Study assessments
Demographic and baseline characteristics and efficacy outcomes were assessed in the full analysis set, consisting of all randomised patients who received at least one dose of study drug. The primary efficacy variable was the percentage of patients achieving an ACR20 response[23] at week 12. The key secondary efficacy variables included percentages of patients achieving ACR50/70 responses,[23] mean change from baseline in the CRP level, mean change from baseline in the disease activity score (DAS) 28[24]-CRP, percentage of patients achieving DAS28-CRP <2.6, DAS28-CRP <3.2 or DAS28-ESR <2.6 and change from baseline in the health assessment questionnaire-disability index (HAQ-DI)[25] at week 12.

The safety analysis set (SAF) was defined as all patients who received at least one dose of the study drug. The safety in the SAF population was assessed by the incidence of AEs occurring in the period from the start of study drug administration to the end of the follow-up period, vital signs, 12-lead ECG and laboratory assessments.

Statistical analyses
Pairwise comparisons of the ACR20 response rate at week 12, the primary efficacy variable, to placebo were performed at each peficitinib dose level using Fisher's exact test. The Hochberg method was used for multiplicity adjustment. A dose response analysis of the primary efficacy variable was performed to explore the treatment-response relationship, and the analysis was based on a logistic regression model with the effect of dose as a continuous variable. For the secondary analyses, categorical variables were analysed using the Fisher's exact test, as described for the primary efficacy variable, but no multiplicity adjustment was performed in these analyses. Change from baseline variables at week 12 was analysed using the analysis of covariance model with fixed effects for treatment and baseline value as a covariate.

All statistical comparisons of peficitinib treatment groups were performed versus placebo, using two-sided tests at the 0.05 significance level. All data processing, summarisation and analyses were performed using SAS Drug Development (V.3.4) and PC-SAS (V.9.1.3, SAS Institute).

For these primary and secondary efficacy variables, missing data at the final evaluation point of week 12 were imputed using last observation carried forward (LOCF).

Sample size determination
It was assumed that the placebo response rate for ACR20 at week 12 was 25%, and 60% at a dose of peficitinib 150 mg, the highest dose, which was almost equivalent to the rate with tofacitinib.[14] Based on this assumption, 49 patients per group were needed to reach 80% power to detect a difference in the response rate for ACR20 at week 12 between placebo and peficitinib at a two-sided 0.0125 significance level by Fisher's exact test considering multiplicity adjustment. This study had to enrol 55 patients in each treatment group (total: 275 patients) to allow for a 10% dropout.

Ethics
The protocol and amendments of the study were reviewed and approved by an institutional review board (IRB) at each study site. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, and applicable laws and regulations. An IRB-approved written informed consent form was obtained from each patient or legal guardian prior to the initiation of any study-specific procedures.

RESULTS
Patients
Four hundred forty-nine patients were screened in this study, and 281 patients who fulfilled the entry criteria were randomised and treated with the study drug. The main reasons for not satisfying the criteria included positive hepatitis B antibody tests, did not meet the RA disease activity requirements and withdrawal of informed consent.

Two hundred and thirty-two (82.6%) patients completed the study, and 49 (17.4%) were discontinued. The most frequently

reported primary reasons for discontinuation were lack of efficacy (9.3%), AE (3.6%) and withdrawal of consent (2.8%). Two (3.6%), one (1.8%), two (3.5%), three (5.5%) and two (3.4%) patients in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively, reported discontinuation because of AEs (see online supplementary figure S1).

Demographic characteristics and baseline disease activities were similar across the treatment groups (table 1).

Efficacy
ACR response rates
The primary efficacy variable of ACR20 response rates at week 12 were 10.7%, 23.6%, 31.6%, 54.5% and 65.5% in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively (figure 1). Differences from the placebo group were 12.9%, 20.9%, 43.8% and 54.8% in the peficitinib 25, 50, 100 and 150 mg groups, respectively, and were statistically significant in the peficitinib 50 mg ($p=0.021$), 100 mg ($p<0.001$) and 150 mg ($p<0.001$) groups. Based on a logistic regression model, there was a statistically significant dose response in the ACR20 response rates at week 12 ($p<0.001$).

The secondary efficacy variable of ACR50 response rates were 5.4%, 7.3%, 8.8%, 30.9% and 29.3% in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively, and were statistically significant in the peficitinib 100 mg ($p<0.001$) and 150 mg ($p=0.001$) groups. The ACR70 response rates were 1.8%, 0.0%, 1.8%, 16.4% and 12.1% in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively, and were statistically significant in the peficitinib 100 mg group ($p=0.008$) (figure 1).

Other efficacy variables
Mean changes from baseline in the CRP level at week 12 are shown in figure 2A, and were statistically significant in the peficitinib 25 mg ($p=0.005$), 50 mg ($p<0.001$), 100 mg ($p<0.001$) and 150 mg ($p<0.001$) groups. Mean changes from baseline in DAS28-CRP were statistically significant in the peficitinib 50 mg ($p<0.001$), 100 mg ($p<0.001$) and 150 mg ($p<0.001$) groups (figure 2B). DAS28-CRP <2.6 rates (figure 2C), DAS28-CRP <3.2 rates (figure 2D) and mean changes from baseline in HAQ-DI (figure 2F) were statistically significantly different in peficitinib 100 and 150 mg groups. DAS28-ESR <2.6 rates (figure 2E) were higher in peficitinib 100 and 150 mg groups compared with other groups, but were not statistically significantly different from placebo.

Statistically significant differences from baseline values were first observed at week 2 for the ACR20 response in the dose range of 50–150 mg ($p<0.05$) (figure 3A). Earlier changes were seen in the DAS28-CRP, HAQ-DI and CRP variables, and statistically significant differences were first observed at week 1 in the dose of 150 mg ($p<0.05$), 100–150 mg ($p<0.05$) and 50–150 mg ($p<0.01$), respectively (figure 3B–D).

Safety
Adverse events
Treatment-emergent AEs (TEAEs) are summarised in table 2. TEAEs were reported in 36 (64.3%) and 144 (64.0%) patients in the placebo and combined peficitinib groups, respectively. Serious TEAEs were reported in 1 (1.8%), 1 (1.8%), 2 (3.5%), 3 (5.5%) and 0 patients in the placebo and peficitinib 25, 50, 100 and 150 mg groups, respectively (see online supplementary table S1). One death (cerebral haemorrhage) was reported in the peficitinib 50 mg group in a patient with hypertension and type 2 diabetes mellitus. Malignancy was not observed in any of the peficitinib groups. No cases of serious infections were reported. Herpes zoster occurred in four patients (two each in the

Table 1 Demographic and baseline characteristics (FAS population)

|	Placebo (N=56)	Peficitinib 25 mg (N=55)	Peficitinib 50 mg (N=57)	Peficitinib 100 mg (N=55)	Peficitinib 150 mg (N=58)	p Value
Age (years)	54.2±12.1	52.9±9.5	54.2±11.6	52.1±12.1	51.6±12.1	0.655*
<65 years, n (%)	45 (80.4)	50 (90.9)	45 (78.9)	45 (81.8)	51 (87.9)	NT
Female, n (%)	43 (76.8)	46 (83.6)	46 (80.7)	42 (76.4)	51 (87.9)	0.663†
BW (kg)	58.31±10.92	58.85±12.10	55.13±11.61	55.89±13.08	55.29±9.54	0.268*
RA duration (years)	6.92±5.39	8.03±8.12	6.69±5.52	7.58±7.12	6.95±5.17	0.789*
TJC (68 count)	12.4±8.0	15.8±9.6	15.8±9.4	16.1±9.9	16.0±9.3	0.174*
SJC (66 count)	10.9±4.5	12.1±5.5	11.2±5.3	13.7±8.4	12.9±6.5	0.099*
PGA (mm)	54.01±20.30	57.15±18.88	56.74±20.96	59.45±21.73	59.36±21.41	0.622*
PtGA (mm)	52.29±27.76	58.09±22.61	59.46±26.42	58.19±24.64	61.15±24.73	0.416*
Pain VAS (mm)	53.05±27.10	55.82±22.95	59.16±26.38	57.14±25.32	60.57±24.22	0.550*
DAS28-CRP	5.10±1.01	5.30±0.86	5.26±0.98	5.34±1.07	5.41±1.12	0.541*
DAS28-ESR‡	5.77±0.91	5.99±0.89	5.98±0.92	6.07±1.02	6.08±1.07	0.438*
HAQ-DI	0.88±0.68	0.93±0.65	0.94±0.66	1.02±0.64	0.95±0.69	0.858*
CRP (mg/dL)	2.54±2.36	2.40±2.69	2.14±2.32	2.59±2.84	2.41±2.05	0.888*
ESR (mm/hr)	47.14±23.49	47.35±23.79	47.11±26.61	48.98±23.67	49.43±26.82	0.978*
Prior anti-TNF use, n (%)	16 (28.6)	11 (20.0)	14 (24.6)	14 (25.5)	16 (27.6)	0.940†
Prior MTX use, n (%)	50 (89.3)	49 (89.1)	51 (89.5)	47 (85.5)	54 (93.1)	0.906†

Data are expressed as mean±SD unless otherwise noted.
*One way analysis of variance.
†χ^2 test (continuity corrected).
‡N=56, 55, 57, 54 and 58 in the placebo, peficitinib 25 mg, 50 mg, 100 mg and 150 mg groups, respectively.
BW, body weight; CRP, C-reactive protein; DAS28-CRP, disease activity score using C-reactive protein; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, health assessment questionnaire-disability index; MTX, methotrexate; NT, not tested; PGA, physician's global assessment of arthritis; PtGA, patient's global assessment of arthritis; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor; VAS, visual analogue scale.

Figure 1 American College of Rheumatology (ACR) response rates at week 12 (full analysis set population). In case of early termination, ACR components were analysed using last observation carried forward method first, and then ACR20/50/70 responses were calculated. *p<0.05, **p<0.01, ***p<0.001 (Fisher's exact test; the Hochberg method was used for multiplicity adjustment, and adjusted p values were indicated for the ACR20.)
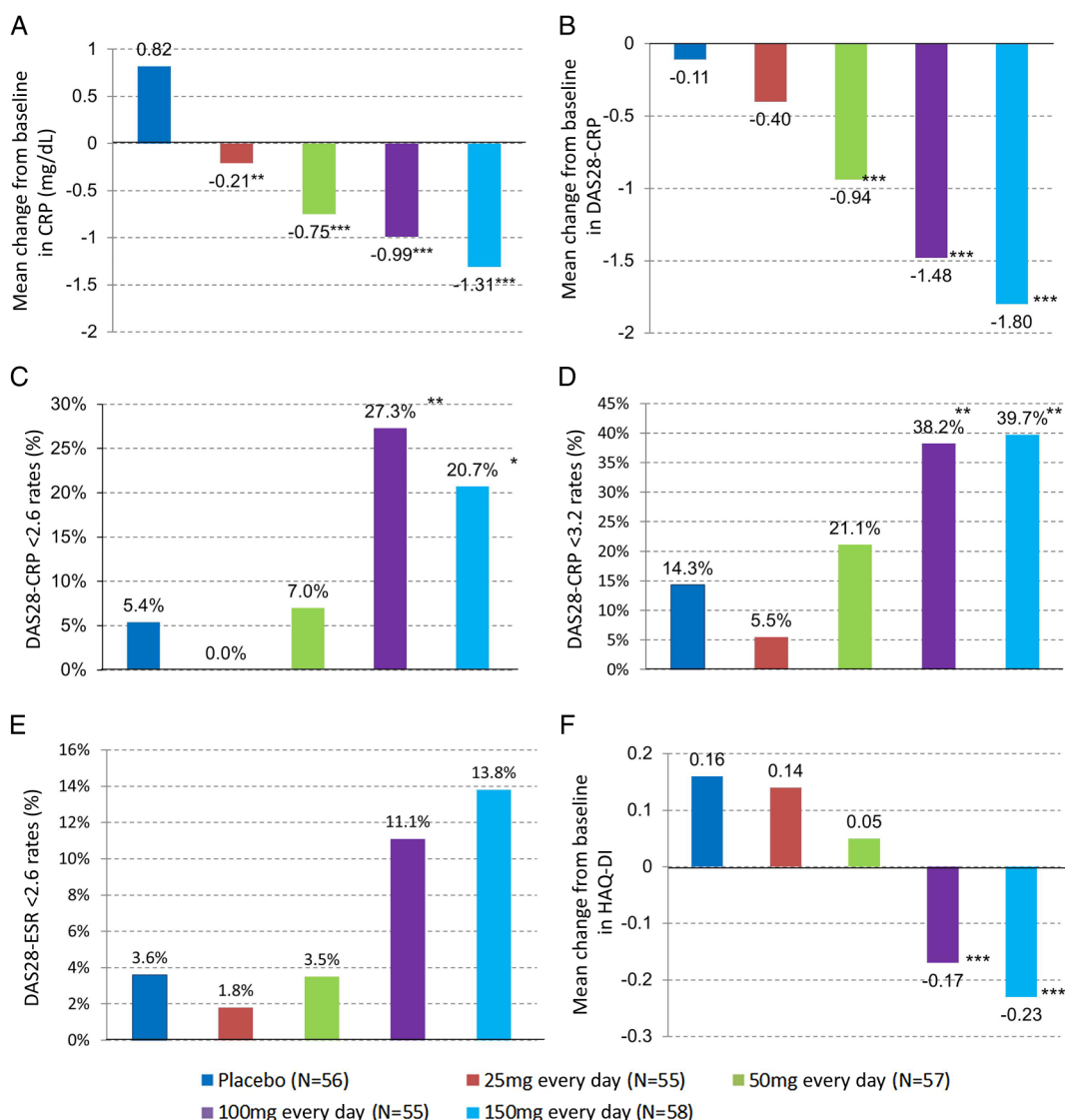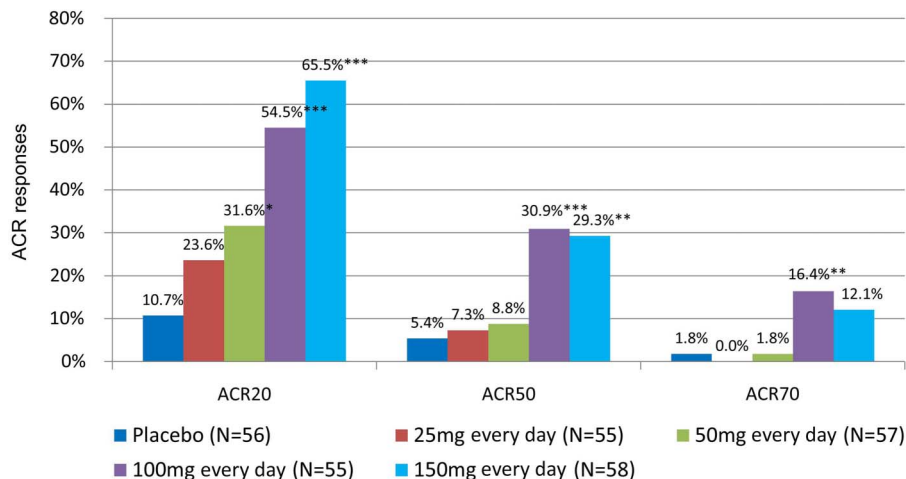
Figure 2 Efficacy variables of (A) mean changes from baseline in CRP, (B) mean changes from baseline in DAS28-CRP, (C) DAS28-CRP <2.6 rates, (D) DAS28-CRP <3.2 rates, (E) DAS28-ESR <2.6 rates and (F) mean changes from baseline in HAQ-DI at week 12. In case of early termination, missing data were imputed using the LOCF method. Changes from baseline variables ((A), (B) and (F)) were analysed using the analysis of covariance model with fixed effects for treatment and baseline value as a covariate. The categorical variables ((C), (D) and (E)) were analysed using the Fisher's exact test. *p<0.05, **p<0.01, ***p<0.001. CRP, C-reactive protein; DAS, disease activity score; HAQ-DI, health assessment questionnaire-disability index; LOCF, last observation carried forward.
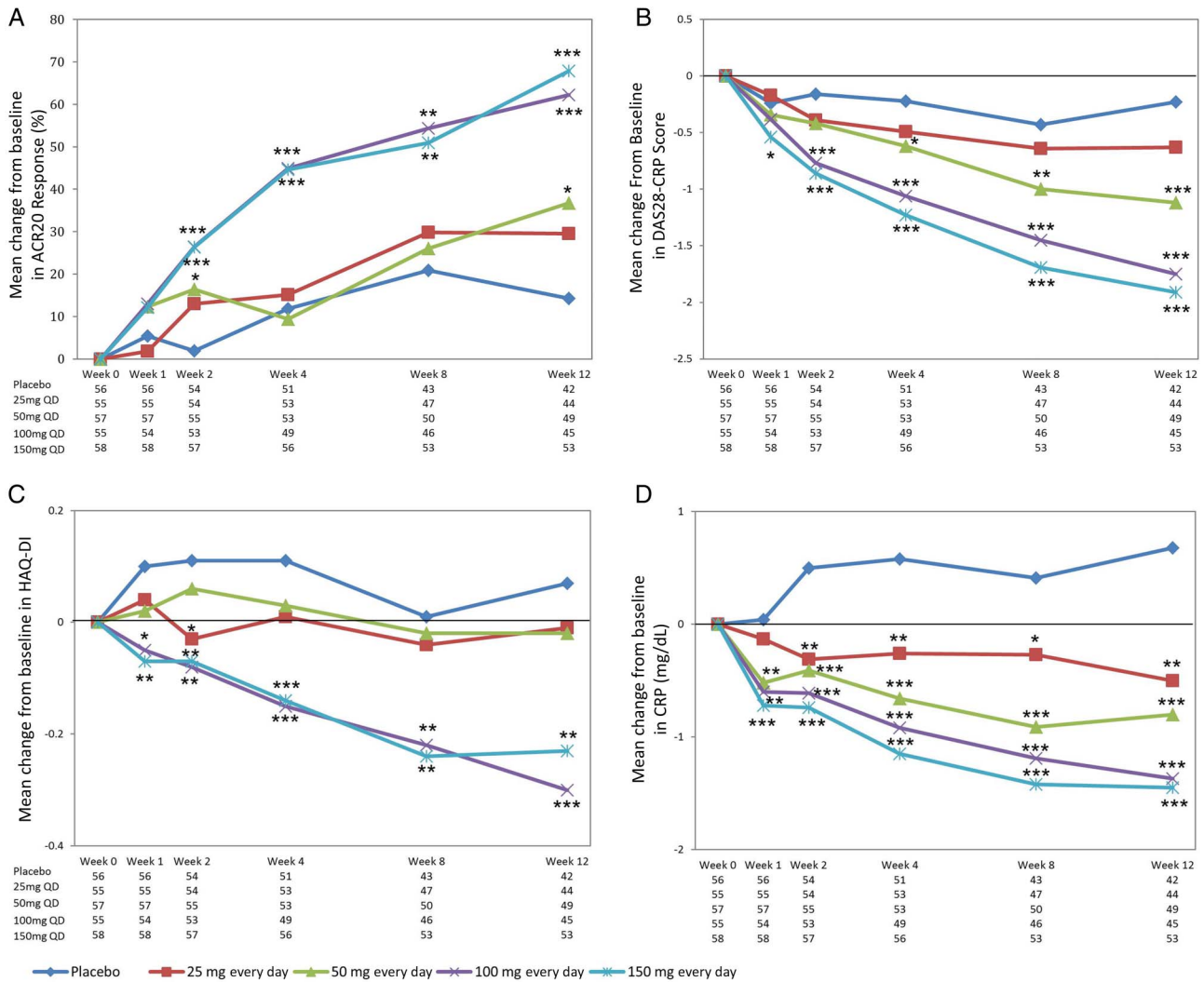
Figure 3 Efficacy variables of mean changes from baseline in the (A) ACR20, (B) DAS28-CRP, (C) HAQ-DI and (D) CRP over time. Changes from baseline variables were analysed using the analysis of covariance model with fixed effects for treatment and baseline value as a covariate. *p<0.05, **p<0.01, ***p<0.001. CRP, C-reactive protein; DAS, disease activity score; HAQ-DI, health assessment questionnaire-disability index.

peficitinib 25 and 100 mg groups); all of these events were assessed as grade 2.

The TEAE leading to discontinuation was mainly RA aggravation (21 out of a total 32 patients), and this TEAE was observed in 7 (12.5%), 6 (10.9%), 4 (7.0%), 3 (5.5%) and 1 (1.7%) patient in the placebo and peficitinib 25, 50, 100 and 150 mg

groups, respectively. TEAEs occurring in ≥5% of patients in any treatment group included RA aggravation, nasopharyngitis, blood creatine phosphokinase (CPK) increase, diarrhoea, constipation, blood triglycerides increase, cystitis, stomatitis, dyspepsia and lipids increase (see online supplementary table S2). TEAEs occurring more frequently in the combined peficitinib group

Table 2 Overview of TEAEs

	Placebo (N=56)	Peficitinib 25 mg (N=55)	Peficitinib 50 mg (N=57)	Peficitinib 100 mg (N=55)	Peficitinib 150 mg (N=58)	Peficitinib total (N=225)
Any TEAEs	36 (64.3%)	39 (70.9%)	37 (64.9%)	29 (52.7%)	39 (67.2%)	144 (64.0%)
≥Grade 3 TEAEs*	3 (5.4%)	4 (7.3%)	3 (5.3%)	6 (10.9%)	2 (3.4%)	15 (6.7%)
Serious TEAEs	1 (1.8%)	1 (1.8%)	2 (3.5%)	3 (5.5%)	0	6 (2.7%)
Deaths	0	0	1 (1.8%)	0	0	1 (0.4%)
TEAEs leading to discontinuation	10 (17.9%)	7 (12.7%)	5 (8.8%)	6 (10.9%)	4 (6.9%)	22 (9.8%)
Infections and infestations	12 (21.4%)	18 (32.7%)	14 (24.6%)	7 (12.7%)	17 (29.3%)	56 (24.9%)
GI disorders	3 (5.4%)	8 (14.5%)	11 (19.3%)	6 (10.9%)	10 (17.2%)	35 (15.6%)

Data are expressed as number of patients (%).
*Based on NCI-CTCAE grade; grade 3=severe or medically significant, grade 4=life threatening, grade 5=death related to adverse event.
GI disorders, gastrointestinal disorders; TEAE, treatment-emergent adverse event.

compared with the placebo group included nasopharyngitis (13.3% vs 5.4%), blood CPK increase (4.9% vs 0%) and diarrhoea (3.6% vs 1.8%). The incidence of blood CPK increase was higher in the peficitinib 150 mg group (12.1%). Most blood CPK increases were grade 1 or 2 in severity. The CPK increase tended to be recovered to baseline levels even with continuous treatment of peficitinib.

Laboratory assessments

Decreases in the absolute neutrophil count and increases in the CPK level were observed in the peficitinib groups compared with the placebo group. Increases in haemoglobin, lymphocytes, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, and decreases in platelets were also observed in the

peficitinib groups compared with the placebo group (table 3A). No major differences in the LDL/HDL ratio were observed between treatment groups. There were more patients who experienced the decreased neutrophils categorised as mild or moderate to severe in the peficitinib 100 and 150 mg groups compared with the placebo group (table 3B). Elevated alanine aminotransferase and LDL (≥130 mg/dL) were also more frequently observed in the peficitinib groups (table 3B). On the other hand, decreased haemoglobin was more frequently observed in the placebo group and did not show dose dependency in peficitinib groups.

Vital signs and 12-lead ECG

No notable trend was observed in vital signs or ECG findings.

Table 3 Laboratory parameters at week 12 ((A) changes from baseline and (B) shifts from baseline)

	Placebo (N=56)	Peficitinib 25 mg (N=55)	Peficitinib 50 mg (N=57)	Peficitinib 100 mg (N=55)	Peficitinib 150 mg (N=58)
(A) Changes from baseline					
Absolute neutrophil count (10^6/L)	146.4±1105.0	20.0±1308.3	66.7±1297.2	−532.7±1449.3	−444.8±1729.6
Lymphocytes (10^6/L)	57.1±375.6	−150.9±403.6	−77.2±420.0	56.4±435.4	48.3±481.3
Haemoglobin (g/L)	−5.2±8.5	−0.8±7.3	−1.6±6.4	1.5±8.2	2.0±7.9
Platelets (10^9/L)	26.9±54.0	0.4±48.8	−6.7±56.5	−21.1±55.4	−26.1±47.6
Creatinine (μmol/L)	−0.1±5.5	1.8±4.7	2.6±4.9	3.6±5.8	5.4±4.3
CPK (U/L)	−5.6±26.1	13.8±25.0	7.6±101.9	33.7±30.1	63.7±117.7
Total cholesterol (mmol/L)	−0.259±0.641	0.051±0.567	0.133±0.585	0.315±0.647	0.559±0.704
LDL cholesterol (mmol/L)	−0.162±0.479	−0.028±0.423	0.035±0.479	0.080±0.507	0.208±0.605
HDL cholesterol (mmol/L)	−0.091±0.234	0.080±0.205	0.128±0.222	0.269±0.265	0.338±0.284
Triglycerides (mmol/L)	0.003±0.230	0.035±0.332	0.073±0.373	0.133±0.484	0.187±0.472
(B) Shifts from baseline					
Decreased neutrophils					
Mild	1 (1.8%)	0	0	2 (3.6%)	0
Moderate to severe	0	0	0	2 (3.6%)	1 (1.7%)
Life threatening	0	0	0	0	0
Decreased lymphocytes					
Mild	19 (33.9%)	13 (23.6%)	15 (26.3%)	13 (23.6%)	16 (27.6%)
Moderate to severe	32 (57.1%)	36 (65.5%)	34 (59.6%)	32 (58.2%)	36 (62.1%)
Life threatening	0	0	0	0	1 (1.7%)
Decreased haemoglobin					
Mild to moderate	23 (41.1%)	4 (7.3%)	10 (17.5%)	9 (16.4%)	9 (15.5%)
Severe	3 (5.4%)	1 (1.8%)	0	1 (1.8%)	0
Potentially life threatening	0	0	0	0	0
Elevated ALT					
≥1× ULN	0	1 (1.8%)	1 (1.8%)	3 (5.5%)	0
≥2× ULN	0	0	0	1 (1.8%)	1 (1.7%)
≥3× ULN	1 (1.8%)	0	0	0	0
Maximum LDL (mg/dL)					
<100	17 (30.4%)	12 (21.8%)	11 (19.3%)	14 (25.5%)	11 (19.0%)
100 to <130	23 (41.1%)	22 (40.0%)	21 (36.8%)	21 (38.2%)	21 (36.2%)
130 to <160	11 (19.6%)	16 (29.1%)	13 (22.8%)	9 (16.4%)	15 (25.9%)
160 to <190	4 (7.1%)	5 (9.1%)	8 (14.0%)	7 (12.7%)	6 (10.3%)
≥190	1 (1.8%)	0	4 (7.0%)	4 (7.3%)	5 (8.6%)

Data are expressed as mean±SD, and baseline is the last non-missing measurement prior to initial dosing of study drug.
Data are expressed as patient number and the percentage.
The following categorisations defined using Outcome Measures in Rheumatology (OMERACT) criteria: Decreased neutrophils were categorised as mild (≥1500 to <2000 cells/mm³), moderate to severe (<1500 to ≥500 cells/mm³) and life threatening (<500 cells/mm³). Decreased lymphocytes were categorised as mild (≥1500 to <2000 cells/mm³), moderate to severe (<1500 to ≥500 cells/mm³) and life threatening (<500 cells/mm³). Decreased haemoglobin were categorised as mild to moderate (decrease from baseline: ≥1 to ≤2 g/dL), severe (decrease from baseline: >2 to <3 g/dL or absolute value: >7 and <8 g/dL) and potentially life threatening (decrease from baseline: ≥3 or absolute value: ≤7 g/dL).
ALT, alanine aminotransferase; CPK, creatine phosphokinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ULN, upper limit of normal.

DISCUSSION

This was a phase IIb, dose-finding study in patients with moderate to severe RA to evaluate the efficacy and safety of a newly developed JAK inhibitor, peficitinib monotherapy, in Japan. We designed this study to treat the patients with a peficitinib monotherapy, which usually demonstrates clear efficacy dose responses compared with DMARD background therapy. Once-daily oral administration of peficitinib for 12 weeks reduced RA symptoms statistically, according to the measured efficacy variables in this study, including the ACR response and DAS28-CRP score. A statistically significant dose response was observed in the primary efficacy variable of the ACR20 response rate at week 12 (or at early termination), and the differences from the placebo group were 12.9%, 20.9%, 43.8% and 54.8% in the peficitinib 25, 50, 100 and 150 mg groups, respectively.

Results of the secondary efficacy variables, such as ACR50/70 response rates and DAS28-CRP supported the results for the primary efficacy variable to some extent. In general, the peficitinib 100 and 150 mg groups showed a statistically significant improvement in the secondary efficacy variables compared with the placebo group. Peficitinib was also suggested to improve RA patients' activities of daily life in HAQ-DI. Serum matrix metalloproteinase-3, known as a predictor of joint destruction in RA,[26] showed clear dose-dependent change up to the 150 mg group (see online supplementary figure S2).

Sensitivity analysis using the non-responder imputation method was also performed for the efficacy variables of ACR20, 50 and 70 response rates, and the results were similar to the primary results of ACR response rates using LOCF method (data are not shown). ACR response rates in the peficitinib 100 and 150 mg groups were comparable with past clinical trials of anti-TNF monotherapies conducted in Japan. On the other hand, efficacy of peficitinib in combination with MTX has not been demonstrated in Japan. The efficacies of peficitinib are now confirmed in more detail by ongoing phase III studies designed with a combination with DMARDs including MTX, larger number of study patients and longer treatment period (ClinicalTrials.gov: NCT02308163 and NCT02305849).

Peficitinib showed acceptable safety profile in short-term treatment of 12 weeks. No apparent dose dependency was observed in the incidence of ≥grade 3 TEAEs or serious TEAEs across the placebo and peficitinib groups. The most frequently reported AEs were nasopharyngitis, aggravation of RA due to lack of efficacy, gastrointestinal events and CPK elevation, but no serious infection was observed in this study. However, it is very important to carefully evaluate the safety of peficitinib in future studies, especially adverse effects related to the suppression of immune functions such as infections, because it has been demonstrated that the JAK inhibitor tofacitinib reduced the T cell stimulatory capacity of human monocyte-derived dendritic cells,[27] and inhibited human B cell activation in in vitro study.[28] Herpes zoster occurred in total four patients (6.3/100 patient-year) in peficitinib groups with no dose dependency, and the incidence rate is comparable with the tofacitinib treated Asian patient (7.6/100).[29] However, we think that more cautious consideration and measurement for this event are needed, after considering the safety results of ongoing phase III studies of peficitinib. Laboratory changes related to lipids (HDL and LDL), CPK, serum creatinine, platelet counts and neutrophil counts were observed, consistent with observations with the other JAK inhibitor, tofacitinib.[30] Decreases in the platelet and neutrophil counts were thought to be related to the inhibition of the JAK signal pathway.[31] However, a mean decrease in haemoglobin, which may attribute to JAK2 inhibition, was not observed even in the highest dose groups and mean haemoglobin levels were dose-dependently increased up to the highest dose in this 12-week treatment study.

In conclusion, peficitinib reduced RA symptoms statistically, and a dose response was observed in the ACR20 response rate. Peficitinib showed acceptable safety profile in short-term treatment of 12 weeks. The findings of this phase IIb study support the two ongoing phase III studies of peficitinib for RA treatment option.

Ethics approval IRB at each participating site.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Abstract has been presented at EULAR and JCR annual conferences, however, this is the first manuscript.

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