Safety and efficacy of peficitinib in Asian patients with rheumatoid arthritis who had an inadequate response or intolerance to methotrexate: results of a multicenter, randomized, double-blind, placebo-controlled phase 3 study

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The Lancet Regional Health - Western Pacific 2024;42: 100925

Published Online 18 October 2023
https://doi.org/10.1016/j.lanwpc.2023.100925

Summary

Background The efficacy and safety of the oral Janus kinase inhibitor peficitinib were investigated in Asian patients with rheumatoid arthritis (RA).

Methods In this double-blind, phase 3 study, patients from mainland China, Korea, and Taiwan with RA and an inadequate response/intolerance to methotrexate were randomized (1:1:1) to once-daily placebo (N = 128), peficitinib 100 mg (N = 129), or 150 mg (N = 128) in combination with non-biologic DMARDs. At Week 24, patients receiving placebo switched to peficitinib 100 mg or 150 mg. American College of Rheumatology (ACR) 20 response at Week 24/early termination (ET) was the primary endpoint. Adverse events (AEs) were assessed. The study was registered at ClinicalTrials (NCT03660059).

Findings 385 patients were included in the analysis. ACR20 responses were statistically significantly higher in both peficitinib 100 mg (56.6%) and 150 mg (56.3%) groups versus placebo (24.2%); Odds Ratio (95% confidence interval, CI) 4.14 (2.42, 7.08) and 4.07 (2.38, 6.96), respectively (both $P < 0.001$) at Week 24/ET. The incidence rate of herpes zoster related disease (herpes zoster and varicella) was higher in patients who received peficitinib versus placebo, but no dose dependency was observed (incidence rate/100 patient-years (95% CI): peficitinib 6.7 (4.32, 10.37); placebo 3.7 (0.93, 14.88).

Abbreviations: ACR, American College of Rheumatology; AE, Adverse event; BMI, Body mass index; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; DAS, Disease activity score; DMARDs, Disease-modifying antirheumatic drugs; EOT, End of treatment; ESR, Erythrocyte sedimentation rate; ET, Early termination; EULAR, European League Against Rheumatism; FAS, Full analysis set; HAQ-DI, Health Assessment Questionnaire-Disability Index; IL, Interleukin; IR, Incidence rate; JAK, Janus kinase; LDA, Low disease activity; LOCF, Last observation carried forward; NRI, Non-responder imputation; MTX, Methotrexate; mTSS, van der Heijde-modified total Sharp score; PPS, Per protocol set; PY, Patient-year; RA, Rheumatoid arthritis; SAE, Serious adverse event; SAF, Safety analysis set; SE, Standard error; SD, Standard deviation; SF-36v2, Short Form Health Survey – 36-Item (version 2); STAT, Signal transducers and activators of transcription; TEAE, Treatment-emergent adverse event; TNF, Tumor necrosis factor; VAS, Visual analog scale

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Interpretation In Asian patients with RA and an inadequate response/intolerance to methotrexate, peficitinib 100 mg and 150 mg demonstrated superiority to placebo in the reduction of RA symptoms and was well tolerated. No additional benefit was observed with use of the higher peficitinib dose in this study population of predominantly Chinese patients.

Funding Astellas Pharma.

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Keywords: Peficitinib; Janus kinase inhibitor; Phase 3; Efficacy; Safety; Rheumatoid arthritis

Research in context

Evidence before this study

- Peficitinib (ASP015K), pan-Janus kinase inhibitor, has demonstrated efficacy and safety in several phase 2b/3 Asian and multinational studies of patients with rheumatoid arthritis (RA); furthermore, the efficacy and safety of peficitinib in patients with inadequate responses to conventional disease-modifying antirheumatic drugs (DMARDs) has also been established.
- To date peficitinib has been approved for use in Japan (2019) and Taiwan (2020) as a once-daily RA therapy at both 100 mg/day and 150 mg/day regimens; once daily 100 mg/day peficitinib has also been approved for RA therapy in Korea (2020).

Added value of this study

- This multiregional, randomized, double-blind, phase 3 study aimed to confirm the efficacy and safety of peficitinib in a predominantly Chinese patient population with RA. Patients with an inadequate response or intolerance to methotrexate at centers in mainland China, Taiwan, and in Korea were randomized to 52 weeks' treatment with peficitinib 100 mg/day or 150 mg/day, or placebo, in combination with conventional DMARDs.
- Peficitinib demonstrated statistically significant superiority over placebo for improvement in RA symptoms at Week 24 and showed further improvements from Week 24 through to study end (Week 52). Peficitinib was well tolerated, with an adverse event and laboratory profile consistent with the mechanism of action of peficitinib and previous clinical studies.

Implications of all the available evidence

- The study findings show that peficitinib is effective and well tolerated in Chinese patients with RA and may be a valuable addition to the treatment options available in mainland China and Taiwan, particularly for patients for whom conventional DMARDs are not an option.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that primarily targets synovial tissue in the joints of the body, leading to substantial pain and disability.[1] Changes in inflammatory and autoimmune processes are largely responsible for the synovial inflammation and local cartilage destruction observed in patients with RA.[1]

Treatment options targeting disease progression include conventional disease-modifying antirheumatic drugs (DMARDs [e.g., methotrexate (MTX)], biologic DMARDs [e.g., anti-tumor necrosis factor (TNF), anti-interleukin-6 (anti-IL-6) receptors] and targeted synthetic DMARDs [e.g., Janus kinase (JAK) inhibitors]).[2,3] Guidelines recommend first-line treatment with MTX together with close monitoring of disease activity, and using a combination of treatments when necessary to achieve low disease activity (LDA) or remission.[2,3] JAK inhibitors are one of the most recently developed types of DMARDs. JAKs are tyrosine kinases associated with the cytoplasmic domain of type I and II cytokine receptors; once activated, they phosphorylate signal transducers and activators of transcription (STATs), which then induce gene activation and promote inflammatory processes.[4] Many cytokines and interferons use the JAK-STAT pathway, making it an interesting therapeutic target for RA[5] and other immune-mediated inflammatory diseases.[6]

The JAK inhibitors tofacitinib, baricitinib, and upadacitinib are widely available, and licensed in up to 80 countries worldwide.[5] Peficitinib (ASP015K) is a pan-JAK inhibitor that is currently approved for clinical use in patients with RA in Japan, Korea, and Taiwan,[5,7] and is in late-stage development in China.[8] However, despite the wide range of treatments for RA,[9,10] several medical needs such as pain, impaired physical

functionality, and fatigue can lead to a substantially reduced quality of life and also impact social activity. These unmet needs have yet to be fully addressed.[9,11]

In the 52-week phase 3 RAJ3 trial, conducted in Japan, Korea, and Taiwan, peficitinib (100 mg and 150 mg once daily), as monotherapy or combined with DMARDs, was evaluated against placebo or open label etanercept (50 mg once weekly for safety comparison) in patients with active RA who had an inadequate response/intolerance to prior DMARDs.[12] Statistically significant clinical improvements were demonstrated with both doses of peficitinib, compared with placebo. In the 52-week, randomized, double-blind, placebo-controlled RAJ4 trial conducted in Japan, patients received peficitinib or placebo in combination with MTX.[13] The RAJ4 trial showed statistically significantly greater American College of Rheumatology (ACR)20 response rates for peficitinib (58.6% and 64.4% at 100 mg and 150 mg once-daily doses, respectively) compared with placebo (21.8%; $P < 0.001$) at Week 12.[13] A statistically significant reduction in radiographic progression, determined by change from baseline in van der Heijde-modified total Sharp score (mTSS), was also observed for both peficitinib doses versus placebo ($P < 0.001$).[13,14] In both of the RAJ3 and RAJ4 trials, peficitinib was well tolerated for up to 1 year, with no new safety signals compared to other JAK inhibitors.[12,13] Additionally, by Week 12, there were clinically meaningful improvements in patient-reported outcomes, including pain, physical function, and work productivity.[15]

To further characterize the efficacy and safety of peficitinib in Asian patients, the current placebo-controlled study assessed peficitinib treatment in combination with non-biologic DMARDs in mainland Chinese, Taiwanese, and Korean patients with RA who had an inadequate response or intolerance to MTX.

Methods

Study design and patients

This was a multinational, randomized, placebo-controlled, double-blind, parallel-group, confirmatory study (NCT03660059). The efficacy and safety of peficitinib at once-daily doses of 100 mg and 150 mg, in combination with MTX or other non-biologic DMARDs was evaluated in patients with RA who had an inadequate response or intolerance to MTX. Patients were enrolled at 42 centers in mainland China, Korea, and Taiwan, and the study was conducted from September 27, 2018, to November 2, 2021. The full list of study investigators at each location has been provided in the Supplementary Methods.

Randomization and masking

Following screening, participants were randomized in a 1:1:1 ratio to peficitinib 100 mg or peficitinib 150 mg or placebo. Biased-coin minimization randomization process was used, with study center, concomitant MTX use at baseline, and prior biologic DMARD response as factors. The randomization list and study medication blind were provided and maintained by a web-based randomization system provided by an independent vendor (Cenduit). The treatment code could only be known to the person responsible for assigning study drugs, person appointed at the central laboratory performing measurements of plasma drug concentrations and persons in the pharmacovigilance department when necessary for suspected unexpected serious adverse reaction handling. Unblinded data was shared with specified users via a secure file transfer protocol. Peficitinib and placebo were administered orally once daily after breakfast for a total of 52 weeks. At Week 24, subjects in the placebo group were switched to receive either peficitinib 100 mg or 150 mg under blinded conditions determined randomly at baseline. Patients made a follow-up visit around 28 days after the Week 52 visit. The study design is summarized in Supplementary Figure S1.

Clinical data management

All clinical data were entered by each study center into an electronic database provided by the sponsor. To ensure the collection of accurate, consistent data, periodic monitoring site visits were conducted by sponsor personnel, or a sponsor delegated clinical research organization. Data were reviewed for accuracy and computer logic checks were performed to identify potential errors. Audits performed by an independent contractor were conducted as part of the independent sponsor quality assessment. Coding of medical terms was performed using MedDRA v23.0.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation—Good Clinical Practice, including the archiving of essential documents guidelines and the applicable laws/regulations. All participants provided written informed consent. The protocol, amendments, and consent documentation were reviewed and approved by the institutional review board/independent ethics committees at each study center. There were four amendments to the original protocol (three non-substantial and one substantial), including an update to the planned study period, an increase in the number of planned study centers, and clarification of missing data processing related to the Coronavirus disease 2019 (COVID-19) outbreak (see Supplementary Methods).

Patients

Adult patients with an RA diagnosis consistent with the 1987 ACR revised criteria[16] or ACR/European League Against Rheumatism (EULAR) 2010 criteria[17] for classification of RA were eligible to participate. Active RA was evidenced by six or more tender/painful joints (68-joint

assessment), six or more swollen joints (66-joint assessment), and C-reactive protein (CRP) >0.50 mg/dL at screening. Eligible patients must have had an inadequate response/intolerance to MTX (7.5–20.0 mg/week) used ≥90 days prior to screening and at a stable oral dose for ≥28 days prior to baseline visit. Patients intolerant to MTX must have had regular use of other conventional DMARDs. Patients were excluded if they had used any JAK inhibitors or previous biologic DMARDs within a specified period, or if they had malignant tumor, lymphatic diseases, infection, or selected laboratory abnormalities or other ongoing illness that would make the individual unsuitable for the study (see Supplementary Methods for full list of inclusion/exclusion criteria). Patients who were unable to attend on-site visits due to COVID-19 had data collected by local hospitals or a remote visit. If remote visits for 3 or more consecutive months occurred without any laboratory test results to support the safety evaluation, the investigator was required to provide written evaluation of the suitability of the patient to continue the study.

Endpoints

The primary efficacy endpoint was the response rate according to ACR20 improvement criteria[18] at Week 24/early termination (ET). Key secondary efficacy endpoints assessed throughout the overall study period (randomization to Week 52/end of treatment [EOT]) included response rates according to ACR20/50/70 criteria,[19] and mean (standard deviation [SD]) change from baseline in disease activity score (DAS)28-CRP. Other endpoints included; rates of disease remission (defined as DAS28-CRP scores of <2.6), percentage of participants with good/good or moderate EULAR response; LDA (defined as DAS28-CRP scores of ≤3.2), change from baseline in patient-reported outcomes (including the Health Assessment Questionnaire-Disability Index [HAQ-DI] and 36-item Short Form Health Survey version 2 [SF-36v2]), Tender Joint Count (TJC) (68 joints), Swollen Joint Count (SJC) (66 joints), SDAI score, Physician's Global Assessment of Arthritis (PGA), and ACR/EULAR remission (TJC 68 joints ≤1, SJC 66 joints ≤1, CRP ≤1 mg/dL, and subject's global assessment of arthritis (SGA) ≤1 cm).

Safety

Key safety variables included treatment-emergent adverse events (TEAEs) from the initial dose of placebo or study drug through Week 52, or follow-up period, including the incidence of cardiovascular and cerebrovascular adverse events (AEs), thromboembolic events, gastrointestinal perforation, and malignancy. TEAEs of special interest, which included serious infections, herpes zoster and herpes zoster-related disease, infections that required intravenous anti-infectious therapy, and venous thromboembolism (including arteriovenous thromboembolism and pulmonary embolism) were assessed per 100 patient-years (PYs) for the overall study period. Mean (SD) change from baseline in hematological and biochemical parameters after initial dose of study drug through Week 52 or EOT were assessed.

Sample size

Based on ACR 20% response rates at Week 24 in previous peficitinib studies[12,13,20] and placebo responses in other RA studies in Chinese patient populations,[21] the assumed response rates were 30%, 55% and 75% for placebo, peficitinib 100 mg and peficitinib 150 mg, respectively. It was estimated that 85 patients per group would provide 90% power at a two-sided 0.05 significance level. Chinese regulations state that at least 100 evaluable patients per arm are required; considering possible early termination or drop-outs, target enrollment was set to 115 patients per group in China. With the target sample size for the other 2 regions set to 30 patients, a total sample size of 375 patients (125 subjects per treatment group) was set across all 3 regions.

Statistical analysis

The primary analysis was conducted in the full analysis set (FAS), which comprised all randomized subjects who received at least one dose of the study drug. For the ACR20 response at Week 24/ET, pairwise comparisons to placebo were performed at each peficitinib dose level using logistic regression model with treatment group (placebo, peficitinib 100 mg, or peficitinib 150 mg) as the factor, and the prior biologic DMARD response and concomitant MTX use at baseline as the covariates. Statistical significance was determined via Wald's chi-squared test and a closed testing procedure was used for multiplicity adjustment in the primary analysis. A series of sensitivity analyses were conducted to assess the robustness of findings from the primary efficacy analyses; the null hypotheses were tested at a two-sided significance level of 0.05. As part of the sensitivity analyses, the validity of dynamic allocation was also assessed by re-randomization testing using Monte Carlo sampling method.

Secondary efficacy binary variables used the same logistic regression model as the primary analysis. To evaluate homogeneity of treatment effects across patients with different demographic and baseline characteristics, logistic regression modelling was also performed for subgroup categories. Continuous variables were analyzed using analysis of covariance (ANCOVA) with treatment group as the factor, and the prior biologic DMARD response, concomitant MTX use at baseline, and baseline value as covariates. Each peficitinib group was compared with placebo (to Week 24/ET); multiplicity for the secondary efficacy variables were not adjusted. Safety analyses were conducted on the safety analysis set (SAF), which included randomized patients who received at least one dose of study

drug. To adjust for differences in subjects' durations in the study and the potential differential dropout rates between the treatment groups, events per 100PYs with 95% CI were calculated for each treatment group for TEAEs of special interest. For consistency with previous peficitinib phase 3 studies,[12,13] last observation carried forward (LOCF) methodology was used for missing data in the primary analysis. Multiple imputation methods, including non-responder imputation, were applied in sensitivity analyses for the primary endpoint (described in Supplementary Methods). Statistical analyses were performed using SAS version 9.4.

Role of the funding source

The study was funded by Astellas Pharma, who provided the financial and medical writing support and the investigational drug supplies for the study.

Results

Efficacy

Patient disposition and baseline characteristics

Patient disposition throughout the study is shown in Fig. 1. Of 649 patients screened, 385 were randomized and treated with the study drug: 345 patients from mainland China, 15 from Korea, and 25 from Taiwan. Demographic characteristics, RA history, and baseline disease activity were well balanced, with no statistically significant differences among treatment groups (Table 1). The mean age of patients ranged from 48.9 to 50.9 years, and the mean treatment compliance rate was >97.5% in all treatment groups. The FAS and SAF included all 385 randomized patients. The percentages of participants who discontinued the study were 17.7% up to Week 24 and 26.2% for the overall study period; the number of patient discontinuations were generally comparable across treatment groups.

Impact of COVID-19

The study included the period during which the COVID-19 pandemic occurred. No patients enrolled in the study tested positive for COVID-19. During the overall study period 40.6% (52/128), 44.2% (57/129), and 41.4% (53/128) in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively had at least one visit affected by the COVID-19 pandemic. From Week 0 to Week 24, 23.4% (30/128), 22.5% (29/129), and 25.0% (32/128) of patients in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively, had at least one visit affected by COVID-19. Up to week 24, one patient in each of the peficitinib 100 mg and 150 mg groups had treatment interruption due to COVID-19, and there were no treatment suspensions. During the overall period, treatment interruption due to COVID-19 ranged from 1.8% to 2.3% across the treatment groups and treatment suspension due to COVID-19 ranged from 2.2% to 9.1%.

Primary efficacy endpoint

Peficitinib demonstrated statistically significant superiority over placebo for improvement in RA symptoms at Week 24 (Table 2). ACR20 response rates at Week 24/ET (LOCF) were statistically significant in both the peficitinib 100 mg and 150 mg groups compared to placebo (Table 2). Sensitivity analyses confirmed the robustness of the results from the primary efficacy analysis (Supplementary Table S1), and that the randomization process did not impact the primary analysis results. Subgroup analyses confirmed higher primary efficacy response rates with peficitinib versus placebo in all subgroups except for two with a limited number of participants, the Korean subgroup (data not shown) and patients who received ≥3 prior biologic DMARDs (Supplementary Figure S5a–l). In total, at Week 24/ET, 29.4% (113/385) subjects had missing data for ACR20 evaluation and subsequently required data imputation; the main reasons leading to missing data included participants' discontinuation (16.8%, 65/385) and the COVID-19 pandemic (8.8%, 34/385). The extent of missing data was also generally balanced across each treatment group.

Key secondary efficacy endpoints

ACR50 and ACR70 response rates, and the proportion of patients who achieved DAS28-CRP remission (score <2.6) and LDA (score ≤3.2) were statistically significantly higher in the peficitinib 100 mg and 150 mg groups compared to placebo at Week 24/ET (Supplementary Figures S2 and S3). Further improvements in ACR20/50/70 response rates were observed from Week 24 through Week 52/EOT (Supplementary Figure S4a–c). The mean (SD) changes from baseline in DAS28-CRP score at Week 24/ET (LOCF) were −0.706 (1.118), −1.866 (1.227), and −1.716 (1.236) in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively; the differences from placebo were statistically significant in both 100 mg and 150 mg peficitinib groups (LS mean treatment difference [95% CI]: −1.147 [−1.432–0.861] and −1.007 [−1.292, −0.723], respectively; $P < 0.001$ for both). Improvements in the mean change from baseline in DAS28-CRP score continued from Week 24 through Week 52/EOT (Supplementary Figure S4d). Consistent benefits with peficitinib were also observed for other secondary endpoints at Week 24/ET and Week 52/EOT (Supplementary Tables S2–S4).

Regarding patient-reported outcomes, the mean (SD) changes from baseline in HAQ-DI score at Week 24/ET (LOCF) were −0.10 (0.43), −0.42 (0.54), and −0.41 (0.58) in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively; differences from placebo were statistically significant in both peficitinib groups (LS mean difference [95%CI]: −0.32 (−0.43, −0.21) and −0.29 [−0.40, −0.18], respectively, $P < 0.001$ for both) (Supplementary Table S5). Additionally, HAQ-DI improvement rates (defined as ≥0.22 reduction in HAQ-DI score) at Week 24/ET (LOCF) were 39.1%,

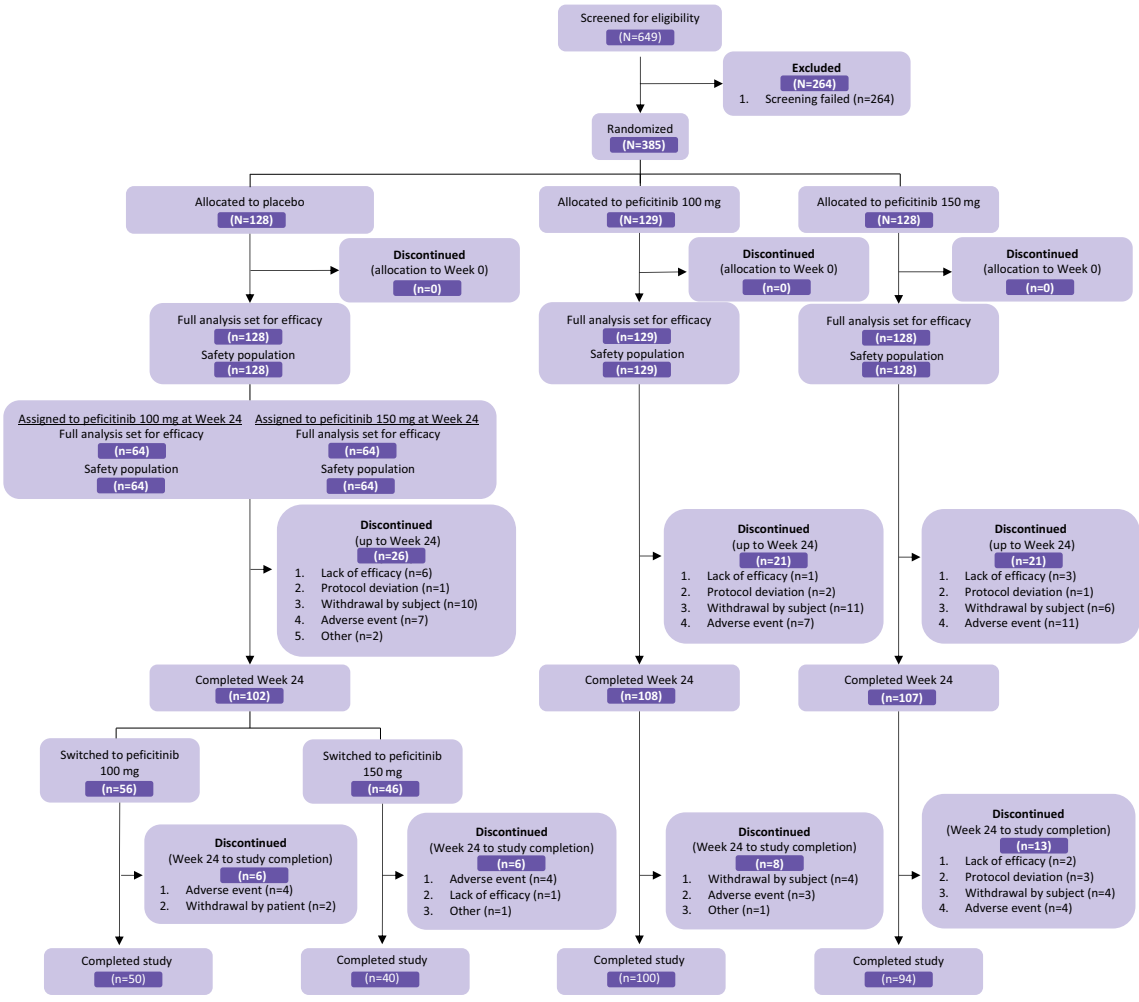

Fig. 1: Patient disposition.

62.8%, and 56.3% in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively. Mean (SD) changes from baseline in SF-36v2 physical component summary scores at Week 24/ET (LOCF) were 1.49 (6.42), 4.44 (7.14), and 4.44 (7.14) in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively (Supplementary Table S5). Mean (SD) changes from baseline in SF-36v2 mental component summary scores at Week 24/ET (LOCF) were –0.80 (9.22), 2.55 (10.46), and 3.38 (9.84) in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively (Supplementary Table S5). Differences from placebo in SF-36v2 mental and physical component summary scores were statistically significant in both peficitinib groups (Supplementary Table S5).

Safety

Treatment-emergent adverse events

From Week 0 through Week 24, TEAEs were reported in 75.8% (97/128), 79.8% (103/129), and 83.6% (107/128) of patients in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively (Table 3). The majority of TEAEs were mild in severity in all treatment groups, and no deaths were reported during the study period. Through Week 24, TEAEs leading to permanent discontinuation occurred in 6.3% (8/128), 3.9% (5/129), and 3.9% (5/128) of patients in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively (Table 3). Through Week 24, treatment-emergent serious adverse events (SAEs) were reported in 8.6% (11/128), 5.4% (7/129), and 7.8% (10/128) of participants in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively. Treatment-emergent SAEs led to permanent discontinuation in 3.9% (5/128), 1.6% (2/129), and 1.6% (2/128) of patients in the placebo, peficitinib 100 mg, and peficitinib 150 mg groups, respectively.

In the overall period, incidence rates (IRs) of herpes zoster-related disease were numerically higher in the peficitinib groups versus placebo, including

	Placebo (N = 128)	Peficitinib 100 mg (N = 129)	Peficitinib 150 mg (N = 128)
Female, n (%)	95 (74.2)	99 (76.7)	106 (82.8)
Age in years, mean (SD)	50.2 (10.9)	50.9 (11.7)	48.9 (11.2)
≥65 years, n (%)	9 (7.0)	14 (10.9)	9 (7.0)
Study region, n (%)			
Mainland China	117 (91.4)	116 (89.9)	112 (87.5)
Korea	2 (1.6)	5 (3.9)	8 (6.3)
Taiwan	9 (7.0)	8 (6.2)	8 (6.3)
Height (cm), mean (SD)	160.7 (7.9)	160.5 (7.4)	159.4 (6.5)
Body weight (kg), mean (SD)	58.5 (10.5)	57.6 (9.4)	58.5 (10.6)
BMI (kg/m^2), mean (SD)	22.6 (3.4)	22.4 (3.5)	23.0 (4.1)
Previous medication, (yes), n (%)	113 (88.3)	108 (83.7)	112 (87.5)
Complications, n (%)[a]	87 (68.0)	91 (70.5)	89 (69.5)
Concomitant DMARD category at baseline, n (%)			
MTX	117 (91.4)	118 (91.5)	116 (90.6)
DMARD except for MTX only	11 (8.6)	11 (8.5)	12 (9.4)
Prednisolone dose at baseline, n (%)	39 (30.5)	44 (34.1)	41 (32.0)
Mean (SD), mg/day	6.1 (2.4)	6.2 (2.6)	5.7 (2.6)
Median, mg/day	5.0	5.0	5.0
Q1–Q3, mg/day	5.0–7.5	5.0–8.8	5.0–7.5
Duration of RA, years			
Mean (SD)	5.9 (7.0)	5.7 (6.2)	6.2 (6.5)
Median	3.8	4.2	4.5
Q1–Q3	0.8–8.2	0.7–8.7	1.1–7.9
Prior treatment, n (%)			
MTX	117 (91.4)	118 (91.5)	116 (90.6)
Non-biologic DMARDs[b]	98 (76.6)	86 (66.7)	93 (72.7)
Biologic DMARDS	62 (48.4)	57 (44.2)	59 (46.1)
MTX dose at baseline, mean (SD), mg/week	11.7 (2.7)	11.2 (2.5)	11.8 (2.5)
COVID impact (yes), n (%)[c]	52 (40.6)	57 (44.2)	53 (41.4)
Week 0–24	30 (23.4)	29 (22.5)	32 (25.0)
Week 24–52 or later	29 (22.7)	37 (28.7)	27 (21.1)
Subject's Global Assessment of Arthritis Pain (100 mm VAS), mean (SD)[d]	63.0 (21.8)	62.3 (22.3)	63.5 (21.5)
Subject's Global Assessment of Arthritis (100 mm VAS), mean (SD)[d]	64.6 (22.0)	64.2 (22.7)	66.0 (21.2)
Physician's Global Assessment of Arthritis (100 mm VAS), mean (SD)[d]	61.8 (17.8)	62.6 (17.43)	63.7 (16.8)
CRP (mg/dL)[f]			
Mean (SD)	3.0 (2.9)	3.3 (3.4)	2.7 (2.6)
Median	1.6	1.8	1.4
Q1–Q3	1.0–4.0	1.0–4.7	0.8–4.1
ESR (mm/h)[f]			
Mean (SD)	47.2 (26.4)	45.0 (26.9)	47.4 (28.3)
Median	42.0	39.5	42.0
Q1–Q3	27.5–68.0	24.0–64.0	25.0–66.5
DAS28-CRP, mean (SD)[g]	5.7 (0.9)	5.8 (1.0)	5.7 (1.0)
DAS28-ESR, mean (SD)[g]	6.3 (1.0)	6.2 (1.0)	6.3 (1.1)
TJC-68[g]			
Mean (SD)	18.7 (12.1)	18.2 (11.0)	19.6 (11.4)
Median	15.0	15.0	17.0
Q1–Q3	10.0–24.0	10.0–24.0	11.0–25.0
TJC-28[g]			
Mean (SD)	13.1 (7.0)	13.3 (6.9)	13.2 (6.3)
Median	11.0	12.0	12.0
Q1–Q3	8.0–18.0	7.0–18.0	8.0–16.5

(Table 1 continues on next page)

	Placebo (N = 128)	Peficitinib 100 mg (N = 129)	Peficitinib 150 mg (N = 128)
(Continued from previous page)			
SJC-66[g]			
Mean (SD)	11.3 (6.1)	12.0 (7.6)	12.1 (7.8)
Median	10.0	9.0	9.0
Q1–Q3	7.0–14.0	7.0–15.0	7.0–15.0
SJC-28[g]			
Mean (SD)	9.4 (4.9)	9.7 (5.4)	9.4 (5.0)
Median	8.0	8.0	8.0
Q1–Q3	6.0–11.0	6.0–13.0	6.0–12.5
SGAP, (100 mm VAS), mean (SD)[d]	63.0 (21.8)	62.3 (22.3)	63 5 (21.5)
SDAI score, mean (SD)[g]	38.2 (13.4)	39.0 (14.0)	38.1 (12.8)
WPAI score, mean (SD)			
% Work time missed	7.8 (15.5)	11.6 (22.6)	9.2 (16.1)
% Impairment while working	49.0 (24.2)	49.1 (27.1)	47.7 (25.0)
% Overall work impairment	51.7 (25.6)	52.5 (28.5)	51.1 (26.2)
% Activity impairment	64.9 (21.1)	65.3 (24.0)	65.8 (22.6)
HAQ-DI score, mean (SD)[e]	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)
SF36-v2: physical component summary score, mean (SD)[h]	34.8 (7.5)	35.4 (8.5)	34.6 (7.8)
SF36-v2: mental component summary score, mean (SD)[h]	39.5 (11.2)	40.3 (11.8)	39.8 (12.4)

BMI, body mass index; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease modifying anti-rheumatoid arthritis drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, health assessment questionnaire-disease index; MTX, methotrexate; RA, rheumatoid arthritis; SF36-v2, Short Form Health Survey – 36-Item (version 2); SD, standard deviation; SGAP, Subject's Global Assessment of Arthritis Pain; SJC swollen joint count; TJC, tender joint count; VAS, visual analog scale, WPAI, Work Productivity and Activity Impairment Questionnaire. [a]Diseases that remain uncured at the time of the first dose of study intervention. [b]Except for MTX. [c]Covid-19 Impact is defined as patients' at least one affected visit due to COVID-19. [d]Possible VAS scores range 0–100, with higher scores indicating higher disease activity. [e]Possible HAQ-DI scores range 0–3, with higher scores indicating greater disability. [f]Higher CRP and ESR values indicate greater inflammation. [g]Higher values indicate higher levels of disease activity. [h]Higher scores indicate better health state.

Table 1: **Patient demographics and baseline characteristics (FAS).**

peficitinib-treated patients who were switched from placebo at Week 24 (Table 4). The IRs of other TEAEs of special interest (including serious infections and infections that required intravenous anti-infective therapy) were numerically lower among patients who received peficitinib compared to the placebo group (Table 4). In the overall period, no venous thromboembolism or pulmonary embolism was reported in the peficitinib groups; however, one patient in the placebo group reported arterial thromboembolism after switching to peficitinib 150 mg (Table 4). One patient in each treatment group experienced a cardiovascular/cerebrovascular event through Week 24 (cerebral infarction in the placebo group and transient ischemic attack/myocardial ischemia in the peficitinib 100 mg/150 mg groups, respectively). Cardiovascular and cerebrovascular findings for the overall study period are summarized in Supplementary Table S6. In addition, no gastrointestinal perforation or malignancy was reported during the overall study period.

Clinical laboratory evaluations

At Week 24, decreases in neutrophils, lymphocytes, and platelets, were observed in the peficitinib groups

	Responder		Treatment difference versus placebo			
	N	n (%)	Difference (%)[a]	Odds ratio[b]	95% CI (%)[c]	P-value[d]
Placebo	128	31 (24.2)				
100 mg	129	73 (56.6)	32.4	4.14	(2.42, 7.08)	<0.001
150 mg	128	72 (56.3)	32.0	4.07	(2.38, 6.96)	<0.001

ACR, American College of Rheumatology; CI, Confidence interval; COVID-19, Coronavirus disease 2019; CRP: C-reactive protein; DMARD: Disease-modifying antirheumatic drug; ET: early termination; FAS: Full Analysis Set; LOCF: Last Observation Carried Forward for missing ACR components; MTX: Methotrexate. All intercurrent events including COVID-19 were handled in the same way. Allocation factors including prior biologic-DMARD response (No, Yes) and Concomitant MTX Use at baseline were from treatment history form. [a]Difference in percentage of responders; peficitinib minus placebo. [b]Based on logistic regression model: ACR20 response (responder, non-responder) = Treatment + the prior biologic-DMARD response (No, Yes) + Concomitant MTX Use at baseline (No, Yes). Odds ratio >1 favored peficitinib. [c]CI was based on normal approximation to the binomial distribution. [d]Wald's chi-squared test. Closed testing procedure was used for multiplicity adjustment.

Table 2: **Primary analysis: ACR20-CRP response at week 24/ET (LOCF) (FAS).**

	Week 0–24			
	Placebo (N = 128)[a]	Peficitinib 100 mg (N = 129)[b]	Peficitinib 150 mg (N = 128)[c]	Total (N = 385)
AEs, n (%)	97 (75.8)	103 (79.8)	107 (83.6)	307 (79.7)
Drug-related AEs[c], n (%)	74 (57.8)	82 (63.6)	84 (65.6)	240 (62.3)
Deaths, n (%)	0	0	0	0
SAEs, n (%)	11 (8.6)	7 (5.4)	10 (7.8)	28 (7.3)
Drug-related SAEs[c], n (%)	4 (3.1)	3 (2.3)	4 (3.1)	11 (2.9)
AEs leading to permanent discontinuation of study intervention, n (%)	8 (6.3)	5 (3.9)	5 (3.9)	18 (4.7)
Drug-related AEs leading to permanent discontinuation of study intervention[c], n (%)	4 (3.1)	3 (2.3)	2 (1.6)	9 (2.3)
SAEs leading to permanent discontinuation of study intervention, n (%)	5 (3.9)	2 (1.6)	2 (1.6)	9 (2.3)
Drug-related SAEs leading to permanent discontinuation of study intervention[c], n (%)	1 (0.8)	0	1 (0.8)	2 (0.5)
Serious infections				
Patient-year period	53.8	57.8	56.8	168.4
No. participants who had at least 1 incidence	4	1	2	7
Incidence rate/100 patient-years (95% CI)	7.4 (2.79, 19.83)	1.7 (0.24, 12.28)	3.5 (0.88, 14.08)	4.2 (1.98, 8.72)
Herpes-zoster related disease				
Patient-year period	53.7	57.1	56.1	167.0
No. participants who had at least 1 incidence	2	5	3	10
Incidence rate/100 patient-years (95% CI)	3.7 (0.93, 14.88)	8.8 (3.64, 21.04)	5.3 (1.72, 16.57)	6.0 (3.22, 11.13)
Herpes-zoster				
Patient-year period	53.7	57.1	56.3	167.1
Number of participants who had at least 1 incidence	2	5	2	9
Incidence rate/100 patient-years (95% CI)	3.7 (0.93, 14.88)	8.8 (3.64, 21.04)	3.6 (0.89, 14.21)	5.4 (2.8, 10.35)
Infections requiring intravenous anti-infectious therapy				
Patient-year period	53.1	56.0	56.4	165.5
No. participants who had at least 1 incidence	7	4	2	13
Incidence rate/100 patient-years (95% CI)	13.2 (6.29, 27.68)	7.1 (2.68, 19.02)	3.5 (0.89, 14.19)	7.9 (4.56, 13.53)
Venous thromboembolism[d]				
Patient-year period	54.5	57.9	56.9	169.3
No. participants who had at least 1 incidence	0	0	0	0
Incidence rate/100 patient- years (95% CI)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)

n (%) represents number and percent of participants with events.AE, adverse event; NC, not calculable; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event. [a]Including adverse events which occurred in participants initially randomized to receive peficitinib 100 mg from study Day 1. [b]Including adverse events which occurred in participants initially randomized to receive peficitinib 150 mg from study Day 1. [c]Possible or probable, as assessed by the investigator or records where relationship was missing. [d]Also includes cases of arteriovenous thromboembolism and pulmonary embolism.

Table 3: **Safety summary: adverse events and selected TEAEs of special interest through week 24.**

compared to the placebo group (Supplementary Table S7). Increases in hemoglobin, serum creatinine, creatine kinase, and low-density and high-density lipoprotein cholesterol were also observed in the peficitinib groups compared to the placebo group at Week 24. No notable differences were observed in mean changes from baseline in laboratory parameters at Week 52/EOT compared with Week 24/ET (Supplementary Table S7).

Discussion

A number of clinical studies conducted globally[22,23] and within Asia (Japan, Korea, and Taiwan)[12,13,20] have demonstrated the efficacy and safety of peficitinib for the treatment of RA, based on multiple efficacy indicators, including ACR response rates or DAS28 score. However, while the efficacy and safety of other JAK inhibitors have been demonstrated in Chinese patients with RA and an inadequate response/intolerance to DMARDs,[24,25] this has not been demonstrated for peficitinib. Thus, the aim of this confirmatory study was to characterize the efficacy and safety of peficitinib across in a predominantly Chinese patient population.

The study results demonstrated the superiority of peficitinib over placebo for improvement in RA symptoms in patients with RA and an inadequate response or intolerance to MTX. The use of 100 mg and 150 mg daily doses of peficitinib in this and other phase 3 trials was based on Phase IIb study results (RAJ1 study) in Japanese patients; findings from the RAJ1 study showed statistically significant dose-dependent improvements in ACR20 and DAS-28-CRP responses with peficitinib monotherapy from 50 mg up to 150 mg, with no dose-dependent safety concerns.[20] Consistent with previous

	Placebo (N = 128)[a]	Peficitinib 100 mg (N = 129)[b]	Peficitinib 150 mg (N = 128)[c]	Peficitinib 100 mg + 150 mg (N = 257)[d]	Peficitinib total (N = 357)[e]	Total (N = 385)
AEs, n (%)	97 (75.8)	119 (92.2)	119 (93.0)	238 (92.6)	322 (90.2)	351 (91.2)
Drug-related AEs[c], n (%)	74 (57.8)	100 (77.5)	101 (78.9)	201 (78.2)	280 (78.4)	301 (78.2)
Deaths, n (%)	0	0	0	0	0	0
SAEs, n (%)	11 (8.6)	14 (10.9)	18 (14.1)	32 (12.5)	39 (10.9)	50 (13.0)
Drug-related SAEs[c], n (%)	4 (3.1)	10 (7.8)	8 (6.3)	18 (7.0)	25 (7.0)	29 (7.5)
AEs leading to permanent discontinuation of study intervention, n (%)	8 (6.3)	6 (4.7)	8 (6.3)	14 (5.4)	16 (4.5)	24 (6.2)
Drug-related AEs leading to permanent discontinuation of study intervention[c], n (%)	4 (3.1)	4 (3.1)	3 (2.3)	7 (2.7)	9 (2.5)	13 (3.4)
SAEs leading to permanent discontinuation of study intervention, n (%)	5 (3.9)	3 (2.3)	4 (3.1)	7 (2.7)	8 (2.2)	13 (3.4)
Drug-related SAEs leading to permanent discontinuation of study intervention[c], n (%)	1 (0.8)	1 (0.8)	2 (1.6)	3 (1.2)	4 (1.1)	5 (1.3)
Serious infections						
Patient-year period	53.8	123.6	120.5	244.1	305.1	358.9
No. participants who had at least 1 incidence	4	4	6	10	13	17
Incidence rate/100 patient-years (95% CI)	7.4 (2.79, 19.83)	3.2 (1.21, 8.62)	5.0 (2.24, 11.09)	4.1 (2.20, 7.62)	4.3 (2.47, 7.34)	4.7 (2.94, 7.62)
Herpes-zoster related disease						
Patient-year period	53.7	121.5	116.4	237.9	299.0	352.3
No. participants who had at least 1 incidence	2	7	11	18	20	22
Incidence rate/100 patient-years (95% CI)	3.7 (0.93, 14.88)	5.8 (2.75, 12.09)	9.5 (5.23, 17.07)	7.6 (4.77, 12.01)	6.7 (4.32, 10.37)	6.2 (4.11, 9.48)
Herpes-zoster						
Patient-year period	53.7	121.5	117.1	238.6	299.7	353.1
No. participants who had at least 1 incidence	2	7	10	17	19	21
Incidence rate/100 patient-years (95% CI)	3.7 (0.93, 14.88)	5.8 (2.75, 12.09)	8.5 (4.60, 15.87)	7.1 (4.43, 11.46)	6.3 (4.04, 9.94)	5.9 (3.88, 9.12)
Infections requiring intravenous anti-infectious therapy						
Patient-year period	53.1	119.6	118.8	238.4	298.6	349.7
No. participants who had at least 1 incidence	7	7	9	16	21	28
Incidence rate/100 patient-years (95% CI)	13.2 (6.29, 27.68)	5.9 (2.79, 12.28)	7.6 (3.94, 14.56)	6.7 (4.11, 10.95)	7.0 (4.59, 10.79)	8.0 (5.53, 11.60)
Venous thromboembolism[f]						
Patient-year period	54.5	125.5	122.1	247.6	309.3	363.8
No. participants who had at least 1 incidence	0	0	0	0	1	1
Incidence rate/100 patient-years (95% CI)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	0.3 (0.05, 2.30)	0.3 (0.04, 1.95)

n (%) represents number and percent of participants with events.AE, adverse event; NC, not calculable; CI, confidence interval; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event. Incidence rate = calculated as (100 × number of participants who had at least 1 incidence/total patient-year). [a]Including adverse events which occurred in placebo exposure duration in initially assigned placebo participants. [b]Including adverse events which occurred in participants initially randomized to receive peficitinib 100 mg from study Day 1. [c]Including adverse events which occurred in participants initially randomized to receive peficitinib 150 mg from study Day 1. [d]Including adverse events which occurred in initially assigned 100 mg or 150 mg participants. [e]Including adverse events which occurred after initial peficitinib dosing. Adverse events which occurred after switching from placebo to peficitinib 100 mg or 150 mg (Week 24) group were included in peficitinib Total column. [f]Also includes cases of arteriovenous thromboembolism and pulmonary embolism.

Table 4: **Safety summary: adverse events and selected TEAEs of special interest for the overall study period (SAF).**

studies in Asian patients and an inadequate response/intolerance to DMARDs (RAJ3, RAJ4), ACR20 response rates in the current study were higher for both peficitinib 100 mg and peficitinib 150 mg versus placebo.[12,13] Overall response rates were lower than those previously reported, which may be due to higher baseline disease activity (ACR components and DAS28-CRP) at baseline and lower rates of concomitant prednisolone treatment in patients enrolled in the current study versus RAJ3 and RAJ4.[12,13] An increase in missing data owing to the COVID-19 pandemic (accounting for 9% of all missing primary endpoint data) may also have contributed to the reduced response rates. However, while the RAJ3 and RAJ4 trials found numerically higher ACR20 responses for 150 mg versus 100 mg peficitinib at 12 weeks and 52 weeks,[12,13] the current study in predominantly Chinese patients showed no additional benefit associated with the higher dose at 24 or 52 weeks. Similarly, results from a Chinese subpopulation in a tofacitinib phase 3 study did not show substantial dose-dependency for ACR20 response rates after 6 months; patients treated with tofacitinib 5 mg and 10 mg BID achieved similar ACR20 rates of 67.4% and 70.6%, respectively, versus 34.1% for placebo-treated patients.[24] The reasons for this phenomenon are unclear and other ethnic differences such as

lifestyle, disease management, background RA therapies, environmental factors, could influence the response to drug treatment; furthermore, missing data may also increase the variability of study results.

Overall, peficitinib was generally well tolerated in the present study, with a numerically similar incidence of TEAEs, treatment-emergent SAEs, and rate of discontinuation owing to drug-related TEAEs in both placebo- and peficitinib-treated groups. The IR of herpes zoster-related disease increased in both of the peficitinib groups, but no dose dependency was observed. This is consistent with crude IRs of herpes zoster-related disease in previous studies of peficitinib,[12,13] and for other JAK inhibitors in Asian patients.[26] The crude IR of herpes zoster-related disease for patients receiving peficitinib in the present study (IR [95% confidence interval (CI)], 6.7 [4.3, 10.4] per 100 PYs) was slightly higher than in previous studies. Two phase 3 studies in Asian and Japanese patients with RA who were treated with peficitinib 100 mg and 150 mg over 52 weeks and had an intolerance to DMARDs[12] or MTX[13] reported IR [95% CI] of 5.8 [3.4, 9.8] per 100 PYs or 5.7 [3.8, 8.6] per 100 PYs, respectively. In contrast, studies of other JAK inhibitors have reported higher crude IRs of herpes zoster than were reported in the current study. Long-term (>6 months) treatment studies of RA in Asian populations for tofacitinib (5 mg and 10 mg) have reported IR [95% CI] of 7.7 [6.4, 9.3] per 100 PYs[27]; a similar study for has reported IRs [95% CI] of 7.8 [4.3, 12.8], 12.4 [7.9, 18.4], and 16.7 [11.1, 24.2] per 100 PYs with upadacitinib 7.5 mg, 15 mg, and 30 mg, respectively (Japan only).[28]

The 52-week duration of this study limits further assessment of the incidence of herpes zoster-related disease with increasing exposure. However, a previously published pooled analysis of phase 2/3 studies of peficitinib in Asian patients over 3 years demonstrated that the incidence of herpes zoster did not increase with extended exposure.[29] The IRs of other AEs of special interest in the present study were similar across the treatment groups, however, the rate of serious infections in patients receiving peficitinib was higher for this study (IR [95% CI], 4.3 [2.5, 7.3] per 100 PYs) than reported in other studies of peficitinib (2.0 [0.8, 4.9] per 100 PYs).[12] Notably, the incidence of serious infections in the present study was also high in the placebo group [IR [95% CI], 7.4 [2.8, 19.8] per 100 PYs]. Analyses of serious infections among patients with RA treated with other JAK inhibitors have reported IRs (95% CI) of 1.65 (1.1, 2.4) and 2.4 (2.2, 2.6) per 100 PYs with tofacitinib 5 mg and 10 mg, respectively[30,31]; 3.16 [2.1, 4.6] per 100 PYs with baricitinib 4 mg[32]; and 3.02 [0.5, 7.0] per 100 PYs with upadacitinib 15 mg.[32] Data should be interpreted with caution as peficitinib was given in combination with other non-biologic DMARDs, therefore the incidence of serious infections cannot necessarily be attributed to peficitinib alone. No patients in the current study reported COVID-19 infection so the higher rate of serious infections cannot be attributed to the pandemic. The different rates observed between studies may be due to variations in predisposing factors of the study populations, such as age, concomitant DMARD and glucocorticoids, or concurrent disease. Also, differences in clinical practice and culture may affect the criteria used by physicians for defining 'serious' infection.

A retrospective database analysis of Taiwanese patients with RA suggests that the safety profiles of JAK inhibitors and TNF inhibitors are comparable in real-world settings.[33] However, the post-marketing ORAL surveillance study (ORALSURV) comparing the safety of tofacitinib, the first approved JAK inhibitor, with anti-TNF therapy in older patients with RA and cardiovascular risk factors, raised concerns regarding the risk of venous thromboembolism with JAK inhibitor use in high-risk patients.[34] In the current study, no venous thromboembolism was reported during the study period, however, one patient experienced an arterial thromboembolism after switching from placebo to 150 mg peficitinib. This event was considered as possibly related to the study treatment, with underlying RA and smoking as additional confounders.

This study addresses the evidence gap for the efficacy and safety of peficitinib in Chinese patients with RA. Strengths of this study include the 52-week treatment period that allowed the assessment of long-term efficacy and safety. Also, the study population of patients with a prior inadequate response or intolerance to either conventional synthetic or biologic DMARDs represented a broad range of patients, potentially with refractory disease.

In general, the extent of missing efficacy data was balanced across the treatment groups and multiple sensitivity analysis were conducted to confirm the robustness of the study results. However, the study was conducted in the same period during which the COVID-19 pandemic occurred, which had some impact on study interventions and assessments over the 52-week study period. This included reduced onsite visits, which meant that efficacy parameters could not be collected and as mentioned previously, an increase in missing data may have reduced the response rates in this study. However, given the double-blind, randomized nature of the current study, the potential biases introduced by COVID-19 (e.g., major protocol deviations or missing data in efficacy assessments), were also generally balanced across the treatment groups. Thus, the COVID-19 pandemic had no major impact on the integrity and interpretation of results of the study. No patients tested positive for COVID-19 during the study period; as such, we cannot speculate how treatment affects the course of COVID-19 infection. However, a real-world retrospective analysis of patients with spondyloarthritis (SpA) treated with tofacitinib in India revealed that patients who tested positive for COVID-19 (19/100) were only mildly symptomatic.[35]

Some limitations of the study include the small sample size in Korea and Taiwan, which did not allow for comparisons across study regions. No radiographic assessments were conducted for this study, and it is, therefore, uncertain whether peficitinib inhibits radiographical progression in this population.

In summary, once-daily oral administration of peficitinib at doses of 100 mg and 150 mg demonstrated statistically significant superiority over placebo for reduction of RA symptoms, and this improvement was maintained throughout the 52-week study period. No additional benefit was observed with use of the higher peficitinib dose in this study population of predominantly Chinese patients. Treatment with peficitinib was generally safe and well tolerated up to Week 52.

Contributors

Data acquisition: Yue Yang, Jingyang Li, Ju Liu, Lin Liu [Xuzhou Central Hospital], Yongfu Wang, Jiankang Hu, Zhijun Li, Jieruo Gu, Xiao Zhang, Zhengyu Xiao, Junjie Zheng, Zhanguo Li, James Cheng-Chung Wei.

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Critical revision of the manuscript and significant intellectual contribution: All authors.

Data sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions, Astellas will provide access to anonymized patient-level data from completed Astellas-sponsored phase 1–4 interventional clinical studies conducted for products and indications which have been approved in any country and also for studies conducted for terminated compounds. Approval must have been granted by the agencies of the main regions US, EU, and Japan. If approval is sought in only one or two regions, approval must have been granted by those agencies. Where available, the following anonymized patient-level data and information is provided for each clinical study: raw dataset, analysis ready dataset, protocols with any amendments or addenda, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Additionally, data may be available upon request. Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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Declaration of interests

James Cheng-Chung Wei received research grants, speaker fees and/or participated in advisory boards for Abbott, Abbvie, Bristol-Myers Squibb, Celgene, Chugai, Eli Lilly, GSK, JNJ, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, and UCB.

Yue Yang, Ju Liu, Yongfu Wang, Jingyang Li, Jiankang Hu, Zhijun Li, Jieruo Gu, Lin Liu (Xuzhou Central Hospital), Xiao Zhang, Zhengyu Xiao, and Zhanguo Li report no conflicts of interest.

Junjie Zheng and Lin Liu (Astellas) are employees of Astellas Pharma China Inc.

Acknowledgements

This study was sponsored by Astellas Pharma China Inc. Medical writing/editorial support was provided by Dylan Mori, PhD and Glen Dorrington, PhD of Lumanity, and funded by Astellas Pharma. We would sincerely like to thank the investigators who participated in this trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100925.

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