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ORIGINAL RESEARCH

Safety and Effectiveness of Peficitinib (ASP015K) in Patients with Rheumatoid Arthritis: Final Results (32 Months of Mean Peficitinib Treatment) From a Long-Term, Open-Label Extension Study in Japan, Korea, and Taiwan

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ABSTRACT

Introduction: This final analysis of a long-term extension (LTE) study assessed the safety, tolerability, and effectiveness of peficitinib (ASP015K), a pan-Janus kinase inhibitor, in Asian patients with rheumatoid arthritis (RA).

Methods: Patients had previously completed the 12-week phase 2b (RAJ1), or 52-week phase 3 (RAJ3 and RAJ4) peficitinib studies in Japan, Korea, and Taiwan, and received oral peficitinib 50 or 100 mg/day. Dose increase to 150 mg/day or reduction to 50 mg/day was permitted. Efficacy endpoints included American College of Rheumatology (ACR)20/50/70 response rates, 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP), and ACR components. Safety endpoints included treatment-emergent adverse events (TEAEs), and incidence rates (IRs)

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of adverse events of special interest per 100 patient-years (PY).

Results: Overall, 843 patients received peficitinib for a mean 32.0 months (maximum 85.2 months), and most (64.4%) received peficitinib 100 mg/day as a maximum dose. Respective ACR20/50/70 response rates were maintained from baseline (week 0 of LTE; 71.6, 52.1, and 34.7%) to end of treatment (78.7, 63.3, and 44.1%); continuous improvements in ACR components and DAS28-CRP were observed from the baselines of preceding studies and throughout the LTE. Overall, 796/843 (94.4%) patients experienced TEAEs; most were severity grade 1/2. Most common TEAEs were nasopharyngitis (47.0%) and herpes zoster (17.3%). Drug-related TEAEs leading to permanent discontinuation occurred in 140 (16.6%) patients, and IRs (95% confidence interval) per 100 PY of serious infections, herpes zoster-related disease, and malignancies were 2.7 (2.1, 3.4), 7.3 (6.2, 8.6), and 1.2 (0.9, 1.8), respectively. Two deaths occurred during the study; one each from diffuse large B cell lymphoma and pneumonia, which were, respectively considered probably and possibly related to study drug.

Conclusions: Improvements in effectiveness variables were maintained during this long-term study of peficitinib in Asian patients with RA; peficitinib was generally well tolerated over a mean 32 months' duration.

Trial Registration: ClinicalTrials.gov. NCT01638013, retrospectively registered on 11 July 2012 https://clinicaltrials.gov/ct2/show/NCT01638013.

Keywords: Herpes zoster; Janus kinase inhibitors; Long-term extension study; Peficitinib; Rheumatoid arthritis; Serious infection; Targeted synthetic DMARDs

Key Summary Points

Why carry out this study?

Rheumatoid arthritis (RA) is a chronic disease requiring long-term treatment; therefore an understanding of the long-term effectiveness, safety, and tolerability of an RA therapy is key.

Interim results from an open-label long-term extension (LTE) study of peficitinib (ASP015K), a pan-Janus kinase inhibitor, in Asian patients with RA, have been published.

This final analysis of the LTE study assessed the long-term safety, tolerability, and effectiveness of peficitinib in Asian patients with RA, over a mean 32 months of treatment.

What was learned from this study?

This study showed that improvements in American College of Rheumatology response and other effectiveness variables were maintained during long-term peficitinib treatment, and peficitinib was generally well tolerated in Asian patients with RA.

These final data support peficitinib use for the long-term management of RA in Asian patients.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13582829.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic condition characterized by systemic inflammation and joint destruction, leading to severe disability and premature mortality [1]. The RA treatment landscape has been strengthened by the development of the Janus kinase (JAK) inhibitors, a class of targeted synthetic disease-modifying antirheumatic drugs (DMARDs) [2]. JAK inhibitors target enzymes belonging to the JAK family with varying specificity and selectivity, thereby inhibiting a number of proinflammatory processes involved in the pathogenesis of RA [2]. The JAK inhibitors tofacitinib (preferential JAK 1 and 3 inhibitor), baricitinib (JAK 1 and 2 inhibitor), and upadacitinib (JAK 1 inhibitor) have undergone phase 3 clinical trials, and are approved for the treatment of RA in the USA, Europe, and Asia [2–12].

Peficitinib (ASP015K) is an oral, once-daily, pan-JAK inhibitor that has demonstrated efficacy and tolerability in Asian patients with RA, as a monotherapy in a 12-week phase 2b study (RAJ1), and in two 52-week phase 3 randomized controlled trials, in combination with DMARDs (RAJ3) or methotrexate specifically (RAJ4) [13–15]. Peficitinib has been approved in Japan, Korea, and Taiwan, for the treatment of RA [16–18].

RA is a chronic disease requiring long-term treatment; therefore an understanding of the long-term effectiveness, safety, and tolerability of an RA therapy is key. Interim results (over a mean treatment duration of 22.7 months) from an open-label long-term extension (LTE) study of peficitinib in RA patients who completed the RAJ1, RAJ3, or RAJ4 clinical trials have been published [19]. Here, we report the final safety and effectiveness data after completion of this LTE study of peficitinib.

METHODS

Study Design

This open-label, LTE study was conducted at 165 sites in Japan, nine sites in Korea, and nine sites in Taiwan from June 2012 to September 2019. Eligible patients had previously completed the RAJ1, RAJ3, or RAJ4 study [13–15, 19], and consequently the duration of study treatment varied between patients (Supplementary Fig. S1). In the RAJ1 phase 2b study, patients were randomized (1:1) to receive peficitinib monotherapy or placebo for 12 weeks with a 4-week follow-up (without peficitinib treatment) [13]. RAJ3 was a phase 3 study in which patients with an inadequate response to DMARDs were randomized (1:1:1:2) to receive peficitinib 100 mg/day, peficitinib 150 mg/day, placebo or etanercept. The peficitinib and etanercept treatment duration was 52 weeks, while patients in the placebo arm were switched at week 12 to either dose of peficitinib. Patients in the etanercept control reference group of RAJ3 were not included in the extension study [14]. In the RAJ4 phase 3 study, patients with an inadequate response to methotrexate were randomized (1:1:1) to receive peficitinib 100 mg/day, peficitinib 150 mg/day or placebo in combination with methotrexate, with treatment duration of 52 weeks, and patients in the placebo arm switched to either dose of peficitinib at week 28 [15]. The LTE study design has been previously described [19]. Briefly, patients received oral peficitinib 50 mg/day (if transferring from RAJ1) or 100 mg/day (if transferring from RAJ3 or RAJ4) once daily after breakfast as the starting dose. The daily dose of peficitinib could be increased in patients with no safety issues from 50–100 mg/day at the investigator's discretion, or from 100 to 150 mg/day in those with insufficient clinical response [28-joint Disease Activity Score (DAS28) erythrocyte sedimentation rate $\geq$ 3.2] after 4 weeks of peficitinib treatment. After the increase, the dose could be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator. Subsequent to the publication of interim results, and following approval of peficitinib in Japan in March 2019, all Japanese patients receiving peficitinib 50 mg/day had their dose increased to 100 mg/day, or discontinued if the dose increase was not possible. The efficacy and safety of peficitinib were assessed by the investigator at each patient visit. Study drug

administration could be suspended, interrupted, or discontinued based on certain criteria, as previously described [19].

Patients

Inclusion criteria have been described previously [19]. Briefly, patients were required to have completed treatment with peficitinib and undertaken assessments at week 16 for the RAJ1 study, and week 52 for the RAJ3 and RAJ4 studies. Patients were excluded if they were judged unsuitable to participate in the study for any reason by the investigator, or if they had taken any of the contraindicated therapies detailed in Supplementary Methods.

Concomitant Medications

Concomitant medications and therapies were permitted or prohibited as described in Supplementary Methods.

Outcomes

Efficacy Endpoints

Efficacy was evaluated in the overall patient population and in patients grouped by their preceding study. Assessment of the long-term efficacy of peficitinib included American College of Rheumatology (ACR)20, ACR50, and ACR70 response rates; changes from baselines of the preceding studies in DAS28 based on C-reactive protein (CRP); proportions of patients achieving DAS28-CRP-defined remission (< 2.6) and DAS28-CRP-defined low disease activity (LDA; ≤ 3.2); changes from the baselines of the preceding studies in Clinical (CDAI) and Simplified (SDAI) Disease Activity Indices; proportions of patients achieving CDAI- and SDAI-defined remission (≤ 2.8 and ≤ 3.3, respectively); ACR/European League Against Rheumatism (EULAR) Boolean-based definition of remission; and changes from the baselines of the preceding studies in the core set of ACR components (see Supplementary Methods) [20].

Safety

Safety outcomes included treatment-emergent adverse events (TEAEs), which were defined as any adverse event (AE) that started or worsened in severity after the first dose of study drug in RAJ2 to the end of the final observation. AEs of special interest were assessed per 100 patient-years (PY), and included serious infections, malignancies, herpes zoster-related disease (including varicella), and venous thromboembolism (VTE; post hoc analysis). Mean (standard deviation [SD]) changes from baseline in hematologic, biochemical, and select laboratory parameters were recorded throughout the LTE study. Vital signs were collected at each study visit, and an electrocardiogram was obtained every 48 weeks and at end of treatment (EOT)/early termination.

Patient Populations

Patient populations and statistical analyses have been defined previously [19]. Briefly, efficacy analyses were conducted on the full analysis set (FAS; all patients who received ≥ 1 dose of study drug and had measurements for any of the efficacy endpoints), and the safety analysis set (SAF) included all patients who received ≥ 1 dose of study drug.

Statistical Analysis

The planned sample size was approximately 800 patients treated with peficitinib. This was based on the number of patients from RAJ1 who participated in the LTE study, the number of patients planned to be enrolled in RAJ3 (excluding the etanercept reference arm), and the number of patients planned to be enrolled in RAJ4.

Statistical analyses have been defined previously [19]. Briefly, TEAEs were summarized according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 11.1) System Organ Class (SOC) and Preferred Term (PT). Patients reporting ≥ 1 AE for a given MedDRA PT were counted only once for that PT. Patients reporting ≥ 1 AE within a SOC were counted

only once for the SOC total. Other safety variables were analyzed descriptively.

Missing Data

ACR components, DAS28-CRP, and safety variables at EOT were summarized by the last observation carried forward (LOCF) method for each component available, and then calculated. All outliers were included in the analyses.

Ethics

This study was conducted in accordance with Good Clinical Practice, the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, and local laws and regulations. The study protocol and amendments were reviewed and approved by an Institutional Review Board or Independent Ethics Committee (Supplementary Table S1) at each study site, and safety data were reviewed by an independent Data and Safety Monitoring Board. Each patient provided written informed consent prior to treatment initiation. This analysis, and the clinical trials from which data were included, followed the principles of the Declaration of Helsinki.

RESULTS

Interim data have been previously reported for the RAJ2 study [19], and here we report the final data.

Patient Populations

Of 873 patients screened, 843 were enrolled and included in the SAF (201, 225, and 417 patients from RAJ1, RAJ3, and RAJ4 studies, respectively) (Supplementary Fig. S2). A total of 837 (99.3%) patients were included in the FAS.

Demographics and Characteristics at the Start of the Study

Demographics and baseline characteristics have been reported previously [19]. The majority of patients were female (619/843, 73.4%), from Japan (806/843, 95.6%), with a mean age of 55.7 years, and a mean (SD) duration of RA of 6.2 (5.6) years (Supplementary Table S2). Discontinuations were reported for 330 (39.1%) patients; the most frequently reported reasons were AE (13.4%), other (7.9%), and lack of efficacy (7.6%) (Fig. 1).

Treatment Exposure

Mean peficitinib exposure was 32.0 months (max. 85.2 months) (Table 1) and was longer in patients from the RAJ1 study (47.1 months) versus RAJ3 (28.1 months) and RAJ4 (26.9 months) (Supplementary Table S3). Total peficitinib exposure was 2277.9 PY. Dose increase or decrease was reported in 382 (45.3%) and 47 (5.6%) patients, respectively (Table 1), and the proportion of patients with dose increase was higher in RAJ1 (82.1%) than RAJ3 (34.7%) and RAJ4 (33.3%) (Supplementary Table S3). The proportions of patients who received peficitinib 50 mg/day, 100 mg/day, and 150 mg/day as the maximum dose were 4.3% (36/843), 64.4% (543/843), and 31.3% (264/843), respectively (Table 1). Overall, 52.2, 68.0, and 68.3% of patients from studies RAJ1, RAJ3 and RAJ4, respectively, received peficitinib 100 mg/day (Supplementary Table S3). Mean treatment compliance was 98.3% (Table 1) ranging from 97.7 to 98.9%, depending on preceding study (Supplementary Table S3).

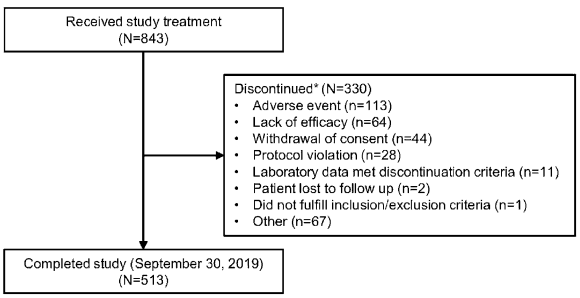


Fig. 1 Patient flow through the long-term extension study. *Discontinued during overall period: discontinued at any time from start of initial dosing of study drug through the last dose day in the overall period

Table 1 Peficitinib treatment exposure and changes in peficitinib dose during the overall period in the long-term extension study (SAF)

	Total (N = 843)
Duration of peficitinib exposure, months[a]	
Mean (SD)	32.0 (19.5)
Minimum	0.1
Median	29.9
Maximum	85.2
Duration of initial peficitinib dose, months[b]	
Mean (SD)	17.5 (16.0)
Minimum	0.1
Maximum	83.6
Treatment compliance rate (%)[c]	
Mean (SD)	98.3 (3.2)
Patients with dose increase, *n* (%)	
No	461 (54.7)
Yes	382 (45.3)
1 dose increase	309 (36.7)
2 dose increases	66 (7.8)
≥ 3 dose increases	7 (0.8)
Patients with dose decrease, *n* (%)	
No	796 (94.4)
Yes	47 (5.6)
1 dose decrease	41 (4.9)
2 dose decreases	6 (0.7)
≥ 3 dose decreases	0
Maximum peficitinib dose, *n* (%)	
50 mg	36 (4.3)
100 mg	543 (64.4)
150 mg	264 (31.3)

SAF safety analysis set, *SD* standard deviation

[a] Duration of exposure for overall period (days) was calculated as: date of the last dose of study drug–date of initial dose of study drug + 1

[b] Duration from first peficitinib taken (50 mg/day for patients from RAJ1, 100 mg/day for patients from RAJ3 and RAJ4) up to first dose change was calculated

[c] Treatment compliance for overall period (%) was calculated as: 100 × (total number of tablets actually received in the overall period/total number of tablets planned to receive in the overall period)

Efficacy

ACR Response

The ACR20, ACR50, and ACR70 response rates were maintained throughout the LTE study from baseline (71.6, 52.1, and 34.7%, respectively) to EOT (LOCF; 78.7, 63.3, and 44.1%, respectively) in the overall population (Fig. 2), and in patients from studies RAJ3 and RAJ4 (Supplementary Fig. S3). A sudden decrease in the ACR20 response rate was observed at week 192 in RAJ3, but the number of patients was considerably lower (n = 8) than at other time points (Supplementary Fig. S3). For patients from RAJ1, response rates initially increased from baseline and were then maintained until EOT (Supplementary Fig. S3).

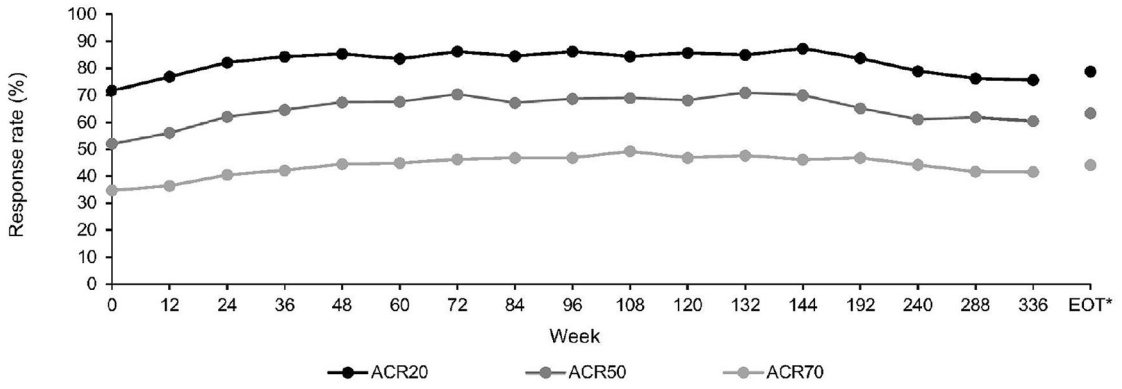
Improvements (reductions) in the core set of ACR components [tender joint count at 68 joints (TJC68), swollen joint count at 66 joints (SJC66), Subject's Global Assessment of Pain (SGAP), Subject's Global Assessment of Disease Activity (SGA), Physician's Global Assessment of Disease Activity [PGA], and Health Assessment Questionnaire–Disability Index (HAQ-DI)] were observed from the baselines of the preceding studies, and continued during the extension study (Supplementary Fig. S4).

ACR20

The ACR20 response rates were sustained during the LTE study for maximum peficitinib doses of both 100 mg/day and 150 mg/day. In patients with a maximum peficitinib dose of 50 mg/day, ACR20 response rates were maintained during the extension study after an initial increase from baseline of the LTE study (week 0) (Fig. 3).

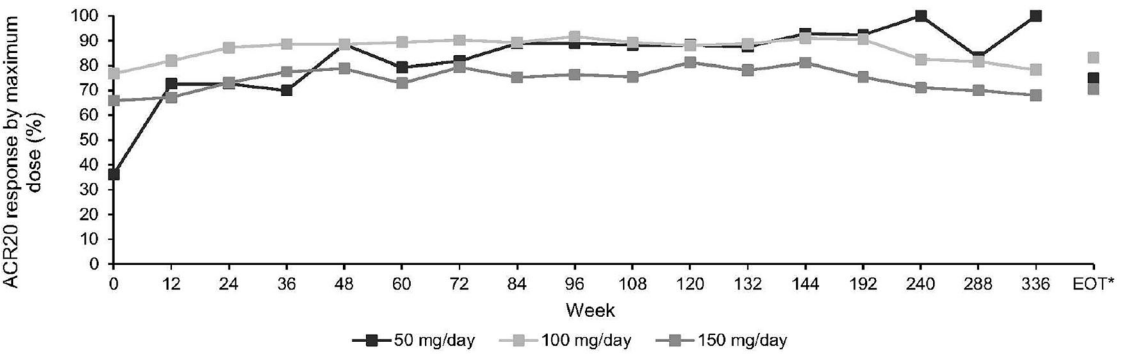
DAS28-CRP, CDAI, SDAI, and ACR/EULAR Responses

Mean changes from baseline in DAS28-CRP, CDAI, and SDAI scores remained consistent over time for the overall study population (Fig. 4), and in patients from RAJ3 and RAJ4 (Supplementary Fig. S4). Where RAJ1 was the preceding study, mean DAS28-CRP, CDAI, and SDAI scores decreased from baseline, and were then sustained until EOT (Supplementary Fig. S4). In the overall study population, the



No. with response, n/N																		
ACR20	598/835	633/824	647/788	639/758	619/726	588/704	588/682	556/658	532/617	476/564	421/491	354/417	308/353	118/141	75/95	64/84	40/53	659/837
ACR50	435/835	462/824	489/788	490/758	489/726	476/704	480/682	442/658	424/617	389/564	335/491	296/417	247/353	92/141	58/95	52/84	32/53	530/837
ACR70	290/835	300/824	319/788	320/758	323/726	316/704	316/682	308/658	289/617	278/564	230/491	199/417	163/353	66/141	42/95	35/84	22/53	369/837

Fig. 2 Response rates for ACR20, ACR50, and ACR70 over time (FAS). *Includes LOCF. *ACR* American College of Rheumatology, *EOT* end of treatment, *FAS* full analysis set, *LOCF* last observation carried forward



No. with response, n/N																		
Peficitinib 50 mg	13/36	24/33	24/33	21/30	23/26	19/24	18/22	16/18	16/18	15/17	15/17	14/16	13/14	12/13	10/10	5/6	5/5	27/36
Peficitinib 100 mg	411/535	433/529	437/501	428/483	407/460	397/444	385/427	369/413	351/383	310/347	267/303	222/250	183/201	57/63	33/40	31/38	18/23	446/537
Peficitinib 150 mg	174/264	176/262	186/254	190/245	189/240	172/236	185/233	171/227	165/216	151/200	139/171	118/151	112/138	49/65	32/45	28/40	17/25	186/264

Fig. 3 ACR20 response at each visit by maximum peficitinib dose level (FAS). *Includes LOCF. *ACR* American College of Rheumatology, *EOT* end of treatment, *FAS* full analysis set, *LOCF* last observation carried forward

proportions of patients who achieved remission (DAS28-CRP < 2.6, CDAI ≤ 2.8, SDAI ≤ 3.3 or ACR/EULAR Boolean-based remission) or DAS28-CRP LDA (≤ 3.2) increased from the baseline of the LTE study (week 0), and were then generally maintained until EOT (Fig. 5). DAS28-CRP-defined remission was reported in 60.4% (504/835) of patients, with DAS28-CRP LDA in 75.3% (629/835) at EOT. CDAI-, SDAI-, and ACR/EULAR Boolean-based remission were observed in 36.1% (302/836), 36.8% (307/835), and 26.1% (218/835) of patients, respectively. There were marked increases in the proportions of patients who achieved remission or LDA when RAJ1 was the preceding study, but the corresponding proportions of patients from both the RAJ3 and RAJ4 studies remained relatively unchanged during the LTE study (Supplementary Fig. S5).

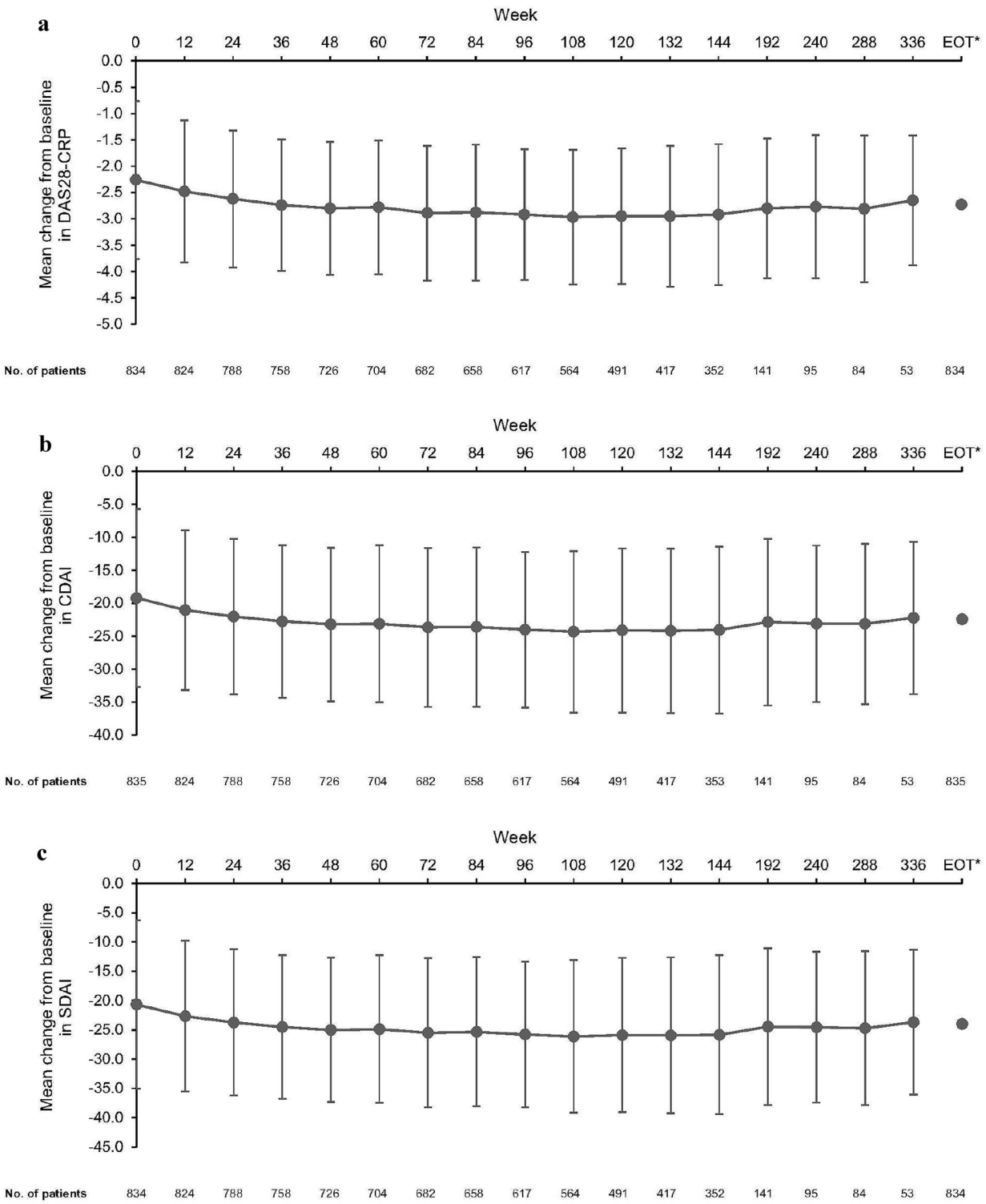


Fig. 4 Mean changes from baseline over time in **a** DAS28-CRP, **b** CDAI, and **c** SDAI scores (FAS). *Includes LOCF. *CDAI* Clinical Disease Activity Index, *DAS28-CRP* Disease Activity Score in 28 joints based on C-reactive protein, *EOT* end of treatment, *FAS* full analysis set, *LOCF* last observation carried forward, *SDAI* Simplified Disease Activity Index

Safety

Adverse Events

Overall, 796 of 843 (94.4%) patients experienced TEAEs during the LTE study, and serious adverse events (SAEs) were reported in 199 (23.6%) patients (Table 2). TEAEs were reported in 34/36 (94.4%), 505/543 (93.0%), and 257/264 (97.3%) patients who received peficitinib 50, 100, and 150 mg/day, respectively. Most TEAEs were grade 1 or 2 in severity, and the most common TEAEs by PT were nasopharyngitis (47.0%), herpes zoster (17.3%), and RA (16.1%) (Table 3). The proportions of patients reporting treatment-emergent nasopharyngitis were similar among peficitinib 50, 100, and 150 mg/day maximum dose groups (50.0, 45.9, and 48.9%, respectively), while occurrences of treatment-emergent herpes zoster were numerically higher for peficitinib 150 mg/day (22.7%) compared with 100 mg/day (15.3%) and 50 mg/day (8.3%) groups (Table 3). The proportions of patients with TEAEs and SAEs leading to permanent discontinuation of study drug were 16.6 and 8.9%, respectively (Table 2). Drug-related TEAEs and drug-related SAEs were reported in 656 (77.8%) and 113 (13.4%) patients, respectively (Table 2), and there were 92 (10.9%) patients who presented with drug-related TEAEs leading to permanent discontinuation (Table 2). The proportions of patients for each category of AE were generally higher in the RAJ1 study compared with RAJ3 and RAJ4 (Supplementary Table S4).

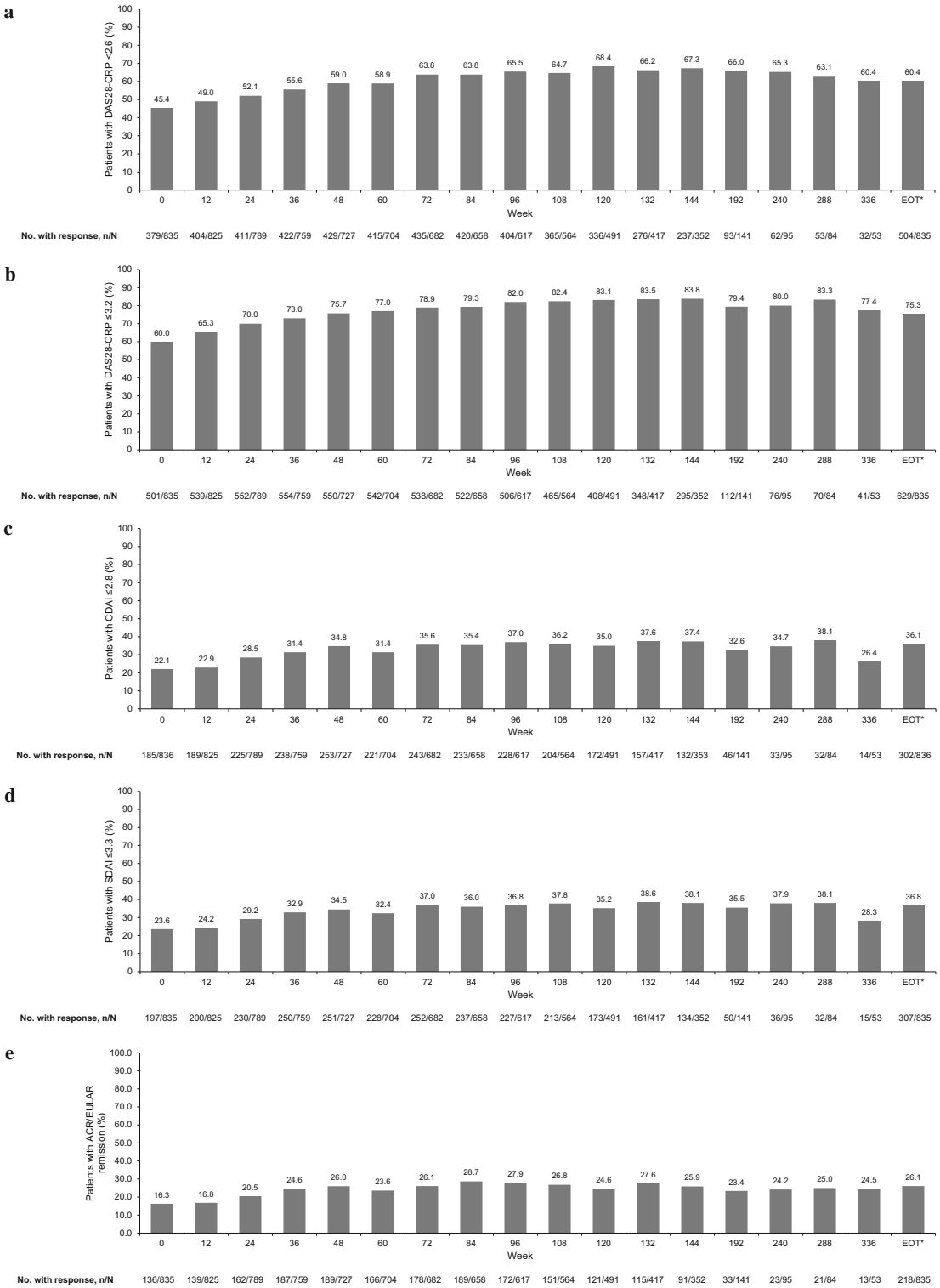
Death was reported for two (0.2%) patients during the study; one patient died from diffuse large B-cell lymphoma and one patient from pneumonia. These events were considered by the investigator to be probably and possibly related to the study drug, respectively (Supplementary Results). After study completion, there was one death due to uterine sarcoma, and this was considered by the investigator to be possibly related to the study drug (Supplementary Results).

The overall incidence rates [IRs; 95% confidence intervals (CIs)] per 100 PY of serious infections, herpes zoster-related disease, and malignancies, were 2.7 (2.1, 3.4), 7.3 (6.2, 8.6), 1.2 (0.9, 1.8), respectively (Fig. 6). In a post hoc analysis of VTE, the IR (95% CI) was 0.1 (0.0, 0.4) per 100 PY in the overall period, which related to two cases (one case of pulmonary artery thrombosis and one case of deep vein thrombosis) between 24 and 36 months; there were no cases of pulmonary embolism. The proportions of patients with TEAEs related to AEs of special interest were analyzed according to the maximum doses of 50, 100, and 150 mg/day peficitinib for serious infections [4/36 (11.1%), 31/543 (5.7%), and 24/264 (9.1%), respectively], herpes zoster-related disease [3/36 (8.3%), 85/543 (15.7%), and 60/264 (22.7%), respectively], malignancies [1/36 (2.8%), 22/543 (4.1%), and 5/264 (1.9%), respectively], and VTE [0/36 (0.0%), 1/543 (0.2%), and 1/264 (0.4%)], respectively. The IRs (95% CIs) per 100 PY for serious infection-related TEAEs were slightly higher for peficitinib 150 mg/day [3.0 (2.0, 4.5)] than 100 mg/day [2.3 (1.6, 3.3)], but both IRs were lower than reported for peficitinib 50 mg/day [4.1 (1.5, 11.0)] (Fig. 7). For herpes zoster-related disease, IRs of TEAEs increased slightly with higher doses [50 mg/day: 3.1 (1.0, 9.5); 100 mg/day: 6.9 (5.6, 8.5); and 150 mg/day: 8.6 (6.7, 11.0)] (Fig. 7). The IRs of malignancy-related TEAEs were higher for peficitinib 100 mg/day [1.6 (1.1, 2.5)] compared with 50 mg/day [1.0 (0.1, 7.0) and 150 mg/day [0.6 (0.3, 1.5)] (Fig. 7). There was a low incidence (95% CI) of VTE-related TEAEs per 100 PY for all maximum dose groups [50 mg/day: 0.0; 100 mg/day: 0.1 (0.0, 0.5); and 150 mg/day: 0.1 (0.0, 0.9)] (Fig. 7). There were 16 patients with serious herpes zoster-related disease (Supplementary Table S5).

The total exposure to peficitinib among patients who had at least one AE of special interest was 2216.7, 2031.4, 2271.4, and 2277.8 PY for serious infections, herpes zoster-related disease, malignancy, and VTE, respectively.

Laboratory Measures

Increases in blood creatine kinase and decreases in lymphocytes were observed from baseline of the extension study (week 0), and were reported as TEAEs in 97/843 (11.5%) and 43/843 (5.1%) patients, respectively (Table 4). Among these, 14 patients had elevated creatine kinase of grade


a
Patients with DAS28-CRP <2.6 (%)
45.4 49.0 52.1 55.6 59.0 58.9 63.8 63.8 65.5 64.7 68.4 66.2 67.3 66.0 65.3 63.1 60.4 60.4
0 12 24 36 48 60 72 84 96 108 120 132 144 192 240 288 336 EOT*
Week
No. with response, n/N 379/835 404/825 411/789 422/759 429/727 415/704 435/682 420/658 404/617 365/564 336/491 276/417 237/352 93/141 62/95 53/84 32/53 504/835
b
Patients with DAS28-CRP ≤3.2 (%)
60.0 65.3 70.0 73.0 75.7 77.0 78.9 79.3 82.0 82.4 83.1 83.5 83.8 79.4 80.0 83.3 77.4 75.3
0 12 24 36 48 60 72 84 96 108 120 132 144 192 240 288 336 EOT*
Week
No. with response, n/N 501/835 539/825 552/789 554/759 550/727 542/704 538/682 522/658 506/617 465/564 408/491 348/417 295/352 112/141 76/95 70/84 41/53 629/835
c
Patients with CDAI ≤2.8 (%)
22.1 22.9 28.5 31.4 34.8 31.4 35.6 35.4 37.0 36.2 35.0 37.6 37.4 32.6 34.7 38.1 26.4 36.1
0 12 24 36 48 60 72 84 96 108 120 132 144 192 240 288 336 EOT*
Week
No. with response, n/N 185/836 189/825 225/789 238/759 253/727 221/704 243/682 233/658 228/617 204/564 172/491 157/417 132/353 46/141 33/95 32/84 14/53 302/836
d
Patients with SDAI ≤3.3 (%)
23.6 24.2 29.2 32.9 34.5 32.4 37.0 36.0 36.8 37.8 35.2 38.6 38.1 35.5 37.9 38.1 28.3 36.8
0 12 24 36 48 60 72 84 96 108 120 132 144 192 240 288 336 EOT*
Week
No. with response, n/N 197/835 200/825 230/789 250/759 251/727 228/704 252/682 237/658 227/617 213/564 173/491 161/417 134/352 50/141 36/95 32/84 15/53 307/835
e
Patients with ACR/EULAR remission (%)
16.3 16.8 20.5 24.6 26.0 23.6 26.1 28.7 27.9 26.8 24.6 27.6 25.9 23.4 24.2 25.0 24.5 26.1
0 12 24 36 48 60 72 84 96 108 120 132 144 192 240 288 336 EOT*
Week
No. with response, n/N 136/835 139/825 162/789 187/759 189/727 166/704 178/682 189/658 172/617 151/564 121/491 115/417 91/352 33/141 23/95 21/84 13/53 218/835

◀**Fig. 5** The proportion of patients achieving remission/LDA in relation to **a** DAS28-CRP < 2.6, **b** DAS28-CRP ≤ 3.2, **c** CDAI ≤ 2.8, **d** SDAI ≤ 3.3, and **e** ACR/EULAR Boolean-based definition of remission (FAS). *Includes LOCF. *ACR* American College of Rheumatology, *CDAI* Clinical Disease Activity Index, *DAS28-CRP* Disease Activity Score in 28 joints based on C-reactive protein, *EOT* end of treatment, *EULAR* European League Against Rheumatism, *FAS* full analysis set, *LDA* low disease activity, *LOCF* last observation carried forward, *SDAI* Simplified Disease Activity Index

3 or 4 severity and 22 patients had decreased lymphocyte counts of grade 3 severity. Other laboratory variables of interest remained generally stable over time (Table 4).

DISCUSSION

This open-label extension study, with mean 32.0 months of peficitinib treatment, and peficitinib exposure of 2277.9 PY, supports the results of the interim analysis (1615.3 PY of peficitinib exposure) [19], and provides further evidence of the effectiveness and safety of peficitinib for long-term use in Asian patients with RA.

Longer-term efficacy outcomes were either maintained or improved during this extension study in patients receiving peficitinib after completing the RAJ1, RAJ3, or RAJ4 studies [13–15, 19]. Both interim and final analyses of the extension study showed that ACR20, ACR50, and ACR70 response rates were maintained from baseline (71.6, 52.1, and 34.7%, respectively) to EOT (78.9, 61.4, and 42.7%, respectively, for the interim analysis [19], and 78.7, 63.3, and 44.1%, respectively, for the final analysis). The ACR20 response rate was lower at baseline (week 0) for patients transferring from RAJ1 compared with RAJ3 and RAJ4, which was likely due to some patients in RAJ1 receiving lower doses of peficitinib and/or the shorter treatment period in this study, as discussed previously [19]. Unsurprisingly, a similar trend was observed for the ACR20 response rate in patients receiving the maximum dose of 50 mg/day peficitinib. In patients who received maximum doses of 100 mg/day or 150 mg/day peficitinib, ACR20 response rates were maintained during the LTE study.

Other measures of efficacy, DAS28-CRP, CDAI, SDAI, TJC68, SJC66, SGAP, PGA, SGA, and HAQ-DI, showed an improvement from the baselines of the preceding studies, and continued to show improvement during the current study. This was consistent with trends seen in the interim analysis of this LTE study (CDAI and SDAI not reported) [19]. An improvement from

Table 2 Overview of treatment-emergent adverse events in the overall period (SAF)

	Total (*N* = 843) *n* (%)
All TEAEs	796 (94.4)
Drug-related[a] TEAEs,	656 (77.8)
≥ Grade 3 TEAE[b]	266 (31.6)
All SAEs	199 (23.6)
Drug-related[a] SAEs	113 (13.4)
TEAEs leading to permanent discontinuation of study drug	
All	140 (16.6)
Drug-related[a]	92 (10.9)
SAEs	75 (8.9)
Drug-related[a] SAEs	50 (5.9)
Deaths[c]	2 (0.2)

TEAEs were defined as any AE that started or worsened in severity after initial dose of study drug in the extension study until the end of the final observation

AE adverse event, *SAE* serious adverse event, *SAF* safety analysis set, *TEAE* treatment-emergent adverse event

[a] Possibly or probably related to study drug, as assessed by the investigator or records where relationship was missing

[b] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE): grade 3, severe or medically significant; grade 4, life-threatening; grade 5, death related to AE

[c] One death during the study due to diffuse large B-cell lymphoma was considered probably related to the study drug. One death during the study due to pneumonia and one death after the end of the study due to uterine sarcoma were considered possibly related to the study drug

Table 3 Overview of treatment-emergent adverse events occurring in ≥ 5% of patients in the overall period by maximum dose of peficitinib (50, 100, or 150 mg/day) (SAF)

TEAEs	Maximum dose			Total (*N* = 843) *n* (%)
	50 mg (*N* = 36) *n* (%)	100 mg (*N* = 543) *n* (%)	150 mg (*N* = 264) *n* (%)	
Nasopharyngitis	18 (50.0)	249 (45.9)	129 (48.9)	396 (47.0)
Herpes zoster	3 (8.3)	83 (15.3)	60 (22.7)	146 (17.3)
Rheumatoid arthritis[a]	3 (8.3)	54 (9.9)	79 (29.9)	136 (16.1)
Influenza	5 (13.9)	59 (10.9)	37 (14.0)	101 (12.0)
Blood creatine kinase increased	5 (13.9)	62 (11.4)	30 (11.4)	97 (11.5)
Bronchitis	2 (5.6)	43 (7.9)	34 (12.9)	79 (9.4)
Contusion	2 (5.6)	44 (8.1)	29 (11.0)	75 (8.9)
Hypertension	5 (13.9)	41 (7.6)	26 (9.8)	72 (8.5)
Pharyngitis	2 (5.6)	39 (7.2)	30 (11.4)	71 (8.4)
Upper respiratory tract infection	2 (5.6)	38 (7.0)	24 (9.1)	64 (7.6)
Dental caries	2 (5.6)	40 (7.4)	20 (7.6)	62 (7.4)
Gastroenteritis	1 (2.8)	36 (6.6)	25 (9.5)	62 (7.4)
Cystitis	2 (5.6)	37 (6.8)	22 (8.3)	61 (7.2)
Constipation	3 (8.3)	30 (5.5)	27 (10.2)	60 (7.1)
Back pain	3 (8.3)	37 (6.8%)	19 (7.2)	59 (7.0)
Cough	3 (8.3)	26 (4.8)	23 (8.7)	52 (6.2)
Abnormal hepatic function	0	33 (6.1)	11 (4.2)	44 (5.2)
Headache	2 (5.6)	26 (4.8)	16 (6.1)	44 (5.2)
Lymphocyte count decreased	1 (2.8)	33 (6.1)	9 (3.4)	43 (5.1)
Eczema	3 (8.3)	22 (4.1)	17 (6.4)	42 (5.0)

SAF safety analysis set; *TEAE* treatment-emergent adverse event

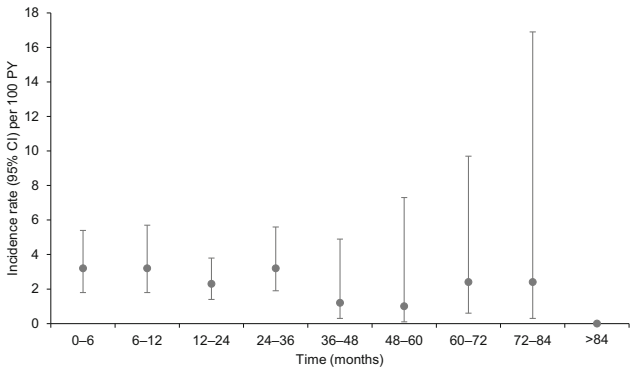
[a] The reported terms 'progression of rheumatoid arthritis' and 'rheumatoid arthritis aggravated' were collated as the preferred term 'rheumatoid arthritis'

baseline was also observed for measures of remission in the final analysis of this LTE study, and by EOT more than half of patients (60.4%) had achieved DAS28-CRP-defined remission, and 75.3% had achieved DAS28-CRP-defined LDA.

The safety profile of peficitinib in the final analysis of the LTE study was consistent with observations from the preceding studies and the

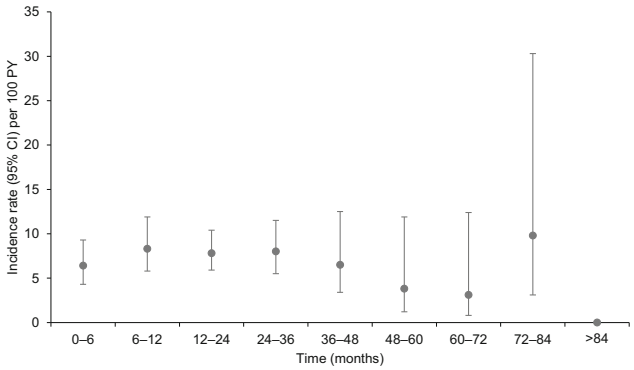
Fig. 6 Incidence of adverse events of special interest per 100 PY during the overall period for **a** serious infections, **b** herpes zoster-related disease, and **c** malignancies (SAF). PY were calculated from initial dose up to first incidence of the event for patients who had ≥ 1 event, and from initial dose through follow-up for patients who had no events; incidence rate was calculated as (100 × number of patients who had ≥ 1 incidence)/total PY. *CI* confidence interval, *IR* incidence rate, *PY* patient-years, *SAF* safety analysis set

a



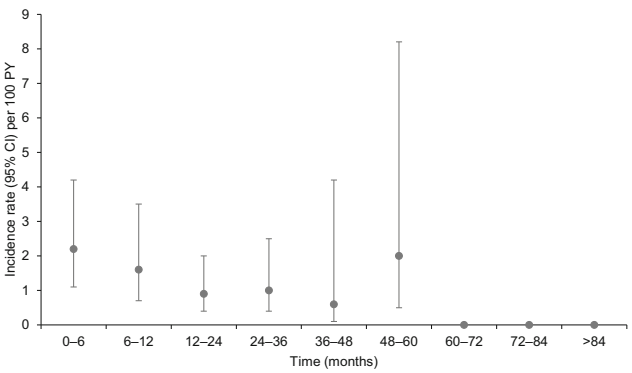
	0–6	6–12	12–24	24–36	36–48	48–60	60–72	72–84	>84
PY	411.2	373.2	646.6	401.0	162.8	97.4	82.3	42.0	0.1
Patients with serious infection, n	13	12	15	13	2	1	2	1	0
IR (95% CI) per 100 PY	3.2 (1.8, 5.4)	3.2 (1.8, 5.7)	2.3 (1.4, 3.8)	3.2 (1.9, 5.6)	1.2 (0.3, 4.9)	1.0 (0.1, 7.3)	2.4 (0.6, 9.7)	2.4 (0.3, 16.9)	0.0

b

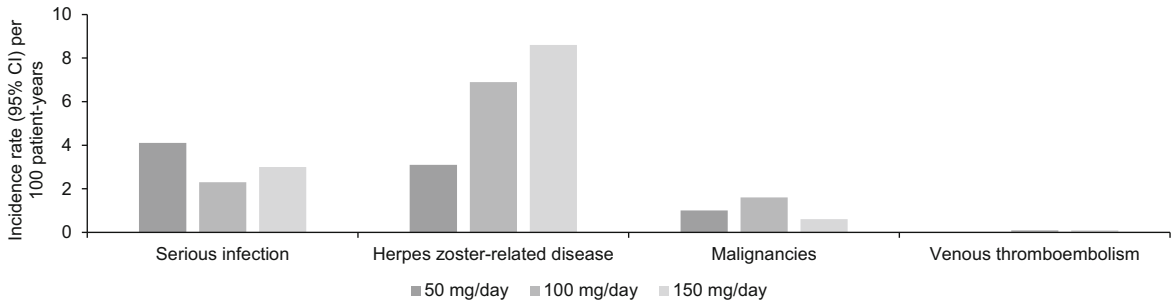


	0–6	6–12	12–24	24–36	36–48	48–60	60–72	72–84	>84
PY	408.5	360.3	599.0	352.0	138.3	78.1	64.6	30.7	0.0
Patients with herpes zoster-related disease, n	26	30	47	28	9	3	2	3	0
IR (95% CI) per 100 PY	6.4 (4.3, 9.3)	8.3 (5.8, 11.9)	7.8 (5.9, 10.4)	8.0 (5.5, 11.5)	6.5 (3.4, 12.5)	3.8 (1.2, 11.9)	3.1 (0.8, 12.4)	9.8 (3.1, 30.3)	0.0

c



	0–6	6–12	12–24	24–36	36–48	48–60	60–72	72–84	>84
PY	412.4	377.7	664.9	420.8	170.6	98.1	84.3	42.5	0.1
Patients with malignancies, n	9	6	6	4	1	2	0	0	0
IR (95% CI) per 100 PY	2.2 (1.1, 4.2)	1.6 (0.7, 3.5)	0.9 (0.4, 2.0)	1.0 (0.4, 2.5)	0.6 (0.1, 4.2)	2.0 (0.5, 8.2)	0.0	0.0	0.0



	Serious infection			Herpes zoster-related disease			Malignancies			Venous thromboembolism		
	50 mg/day	100 mg/day	150 mg/day	50 mg/day	100 mg/day	150 mg/day	50 mg/day	100 mg/day	150 mg/day	50 mg/day	100 mg/day	150 mg/day
PY	97.0	1331.4	788.4	97.5	1233.4	700.5	101.8	1356.1	813.6	101.9	1360.8	815.1
n	4	31	24	3	85	60	1	22	5	0	1	1
IR (95% CI) per 100 PY	4.1 (1.5, 11.0)	2.3 (1.6, 3.3)	3.0 (2.0, 4.5)	3.1 (1.0, 9.5)	6.9 (5.6, 8.5)	8.6 (6.7, 11.0)	1.0 (0.1, 7.0)	1.6 (1.1, 2.5)	0.6 (0.3, 1.5)	0.0	0.1 (0.0, 0.5)	0.1 (0.0, 0.9)

Fig. 7 Incidence of treatment-emergent adverse events of special interest per 100 PY during the overall period (SAF). PY were calculated from initial dose up to first incidence of the event for patients who had ≥ 1 event, and from initial dose through follow-up for patients who had no events; incidence rate was calculated as (100 × number of patients who had ≥ 1 incidence)/total PY. *CI* confidence interval, *IR* incidence rate, *PY* patient-years, *SAF* safety analysis set

interim LTE study analysis, indicating that peficitinib was generally well tolerated over a treatment duration of up to 7 years [13–15, 19]. Of note, the proportion of patients reporting each category of AE was generally higher in the RAJ1 study compared with RAJ3 and RAJ4, perhaps due to the longer mean treatment exposure in patients from the RAJ1 study (47.1 months) versus RAJ3 and RAJ4 (28.1 and 26.9 months, respectively). TEAEs were similar in frequency for each peficitinib dose, and most events were grade 1 or 2 in severity. The most commonly reported TEAE was nasopharyngitis, and its incidence did not increase with higher doses of peficitinib.

We compared the incidences of AEs of special interest observed in our study of Japanese, Korean, and Taiwanese patients with studies of other JAK inhibitors in Asian populations. There were no notable differences in the incidences of AEs of special interest between the phase 3 studies (RAJ3 and RAJ4) [14, 15], our LTE study, or published rates from studies of JAK inhibitors in Asian populations. The IRs (95% CI) per 100 PY of serious infections were 2.3 (1.6, 3.1) and 2.7 (2.1, 3.4) in the interim and final analyses of our extension study, respectively, and 3.7 (3.2, 4.3) and 4.2 (3.1, 5.4) in Asian patients receiving tofacitinib and baricitinib, respectively [19, 21, 22]. Studies have reported that JAK inhibitors can increase the risk of herpes zoster infection, particularly in Asian patients [21–24], so it was not surprising that the most frequently occurring serious infection in our study was herpes zoster-related disease, which had an IR (95% CI) of 7.3 (6.2, 8.6) per 100 PY. This was consistent with IRs (95% CI) per 100 PY from the interim analysis of the extension study [6.8 (5.6, 8.3)], and was similar to results reported for other JAK inhibitors in Asian populations [5.9 (5.2, 6.6) for tofacitinib and 6.2 (4.9, 7.7) for baricitinib] [19, 22, 25]. In our study, there were no major differences among the incidences of TEAEs for the different doses of peficitinib; however, IRs (95% CI) per 100 PY were slightly higher in patients receiving peficitinib 150 mg/day compared with 100 mg/day for serious infections [3.0 (2.0, 4.5) and 2.3 (1.6, 3.3), respectively] and herpes zoster-related disease [8.6 (6.7, 11.0) and 6.9 (5.6, 8.5), respectively]. These results indicate that the peficitinib dose should be carefully selected if

Table 4 Mean changes from baseline (week 0) in laboratory measurements at end of treatment (SAF)

	Mean (SD) at baseline (week 0)	Mean (SD) at EOT[a]	Mean (SD) change from baseline at EOT[a]
Absolute neutrophil count, 10^6/l	4826.2 (1920.5)	4609.6 (1989.2)	− 217.3 (1756.1)
Hemoglobin, g/l	126.0 (14.3)	126.4 (15.2)	0.3 (11.1)
Lymphocytes, 10^6/l	1429.8 (555.9)	1193.9 (472.5)	− 233.9 (465.8)
Platelets, 10^9/l	273.9 (71.0)	273.6 (75.4)	0.0 (52.8)
LDL cholesterol, mmol/l	3.115 (0.858)	3.145 (0.818)	0.026 (0.782)
HDL cholesterol, mmol/l	1.889 (0.547)	1.917 (0.541)	0.032 (0.367)
Creatinine, μmol/l	58.17 (14.55)	63.05 (16.50)	4.83 (9.47)
Creatine kinase, U/l	131.2 (124.8)	169.8 (251.2)	38.6 (246.0)
ALT, U/l	22.9 (16.5)	23.2 (15.7)	0.3 (16.7)
AST, U/l	27.1 (11.9)	27.4 (12.0)	0.4 (12.8)

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *EOT* end of treatment, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SAF* safety analysis set, *SD* standard deviation

[a] EOT assessments and tests were to be performed promptly once administration of peficitinib had ended; in cases of early termination of peficitinib administration, these assessments and tests were to be performed within 2 days of the last dose of peficitinib, if possible

general risks, such as advanced age, are identified. There were no major differences in malignancy IRs (95% CI) per 100 PY in our extension study [1.2 (0.9, 1.8)] and those reported previously for tofacitinib [0.8 (0.6, 1.1)] and baricitinib [1.0 (0.5, 1.7)] in Asian populations [21, 22]. It was difficult to interpret the IRs of malignancy-related TEAEs in our study, due to the low numbers of patients with malignancies; however, there appeared to be no evidence of dose-dependency.

There have been concerns around the potential for thromboembolic events in RA patients receiving tofacitinib or baricitinib, leading to dose restrictions in this group of patients [26]. The two cases of VTE reported for our extension study were considered not related to peficitinib.

The strengths and limitations of this study have been discussed in full previously [19]. Specifically, our study provides data from a large number of patients for a mean treatment duration of 32.0 months. Furthermore, the patients received a variety of peficitinib dosing regimens, which is likely to be more representative of routine clinical practice than the preceding trials. Key limitations include the lack of either a placebo or active comparator arm. It was also difficult to compare different dose groups due to the lack of randomization and the ability to adjust the dose, which may have resulted in individual patients experiencing different disease states during the course of treatment. Additionally, it should be taken into consideration that almost all patients were from Japan, a population known to be particularly susceptible to herpes zoster reactivation when treated with tofacitinib [24], and also to respond uniquely to biologic DMARDs [27].

CONCLUSIONS

Improvements in ACR response and other clinical effectiveness variables were maintained over a mean treatment duration of 32 months

in Asian patients with RA, and peficitinib was generally well tolerated for a period of up to 7 years. These final data are consistent with the interim analysis of the LTE study, and support peficitinib use for long-term management of RA in Asian patients.

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Prior Presentation. Interim data from this study were published as Takeuchi and Tanaka et al. Safety and effectiveness of peficitinib (ASP015K) in patients with rheumatoid arthritis: interim data (22.7 months mean peficitinib treatment) from a long-term, open-label extension study in Japan, Korea, and Taiwan. Arthritis Research & Therapy (2020) 22:47. The final data from this study (32 months mean peficitinib exposure, as included in this manuscript) were presented in part as a virtual poster at the 22nd Asia-Pacific League of Associations for Rheumatology, 24–29 October 2020, Virtual Congress; and were accepted as an abstract to the 2020 JCRA Annual Meeting.

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Compliance with Ethics Guidelines. This study was conducted in accordance with Good Clinical Practice, the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines, and local laws and regulations. The study protocol and amendments were reviewed and approved by an Institutional Review Board or Independent Ethics Committee (Supplementary Table S1) at each study site, and safety data were reviewed by an independent Data and Safety Monitoring Board. Each patient provided written informed consent prior to treatment initiation. This analysis and the clinical trials from which data were included followed the principles of the Declaration of Helsinki.

Data Availability. 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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