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The efficacy and safety of tofacitinib in Asian patients with moderate to severe chronic plaque psoriasis: A Phase 3, randomized, double-blind, placebo-controlled study

JianZhong Zhang[a,*], Tsen-Fang Tsai[b], Min-Geol Lee[c], Min Zheng[d], Gang Wang[e], HongZhong Jin[f], Jun Gu[g], RuoYu Li[h], QuanZhong Liu[i], Jin Chen[j], CaiXia Tu[k], ChunMei Qi[l], Hua Zhu[m], William C. Ports[n], Tim Crook[o]

[a] Peking University People's Hospital, Department of Dermatology, Beijing, China
[b] National Taiwan University Hospital, Department of Dermatology, Taipei, Taiwan
[c] Yonsei University College of Medicine, Department of Dermatology, Seoul, Republic of Korea
[d] Second Affiliated Hospital School of Medicine, Zhejiang University, Department of Dermatology, Hangzhou, Zhejiang, China
[e] Xijing Hospital, The Fourth Military Medical University, Department of Dermatology, Xi'an, Shaanxi, China
[f] Peking Union Medical College Hospital, Department of Dermatology, Beijing, China
[g] Changhai Hospital, The Second Military Medical University, Department of Dermatology, Shanghai, China
[h] Peking University First Hospital, Department of Dermatology, Beijing, China
[i] Tianjin Medical University General Hospital, Department of Dermatology, Tianjin, China
[j] Sichuan Provincial People's Hospital, Institute of Dermatology, Chengdu, Sichuan, China
[k] The Second Affiliated Hospital of Dalian Medical University, Department of Dermatology, Dalian, Liaoning, China
[l] Development China, GPD, Pfizer Investment Co. Ltd., Beijing, China
[m] Pfizer Development China, Shanghai, China
[n] Pfizer Inc., Groton, CT, USA
[o] Pfizer Ltd., Tadworth, United Kingdom

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ABSTRACT

Background: Tofacitinib is an oral Janus kinase inhibitor.
Objective: This study assessed tofacitinib efficacy and safety vs placebo in Asian patients with moderate to severe chronic plaque psoriasis.
Methods: Patients from China mainland, Taiwan, and Korea were randomized 2:2:1:1 to tofacitinib 5 mg (N = 88), tofacitinib 10 mg (N = 90), placebo → 5 mg (N = 44), or placebo → 10 mg (N = 44), twice daily (BID) for 52 weeks. Placebo-treated patients advanced to tofacitinib at Week 16. Co-primary efficacy endpoints: proportions of patients achieving Physician's Global Assessment (PGA) response ('clear' or 'almost clear') and proportion achieving ≥75% reduction from baseline Psoriasis Area and Severity Index (PASI75) at Week 16.
Results: At Week 16, more patients achieved PGA and PASI75 responses with tofacitinib 5 mg (52.3%; 54.6%) and 10 mg (75.6%; 81.1%) BID vs placebo (19.3%; 12.5%; all $p < 0.0001$). Of patients with a Week 16 response, 73.6% and 75.0% maintained PGA response, and 76.8% and 84.9% maintained PASI75 to Week 52 with tofacitinib 5 mg and 10 mg BID, respectively. Over 52 weeks, 2.2–4.5% of patients across treatment groups experienced serious adverse events, and 1.1–6.8% discontinued due to adverse events.
Conclusion: Tofacitinib demonstrated efficacy vs placebo at Week 16 in Asian patients with moderate to severe plaque psoriasis; efficacy was maintained through Week 52. No unexpected safety findings were observed. [NCT01815424]

* Corresponding author.
E-mail addresses: rmzjz@126.com (J. Zhang), tftsai@yahoo.com (T.-F. Tsai), mglee@yuhs.ac (M.-G. Lee), minz@zju.edu.cn (M. Zheng), xjpfwanggang@163.com (G. Wang), jinhongzhong@263.net (H. Jin), gujun79@163.com (J. Gu), mycolab@126.com (R. Li), liuquanzhong@medmail.com.cn (Q. Liu), chenjin99114@sina.com (J. Chen), tucx2003@163.com (C. Tu), ChunMei.Qi@Pfizer.com (C. Qi), hua.zhu@pfizer.com (H. Zhu), william.c.ports@pfizer.com (W.C. Ports), Tim.Crook@pfizer.com (T. Crook).

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1. Introduction

Plaque psoriasis is a chronic inflammatory disease, which impacts both patients' physical health and quality of life [1]. Psoriasis is a global disease, with approximately 2–4% of European and North American populations affected [2], although the prevalence of psoriasis is generally lower in East Asia (e.g. 0.2% in Taiwan [3], 0.3% in Korea [4], and 0.47% in China mainland [5]). However, differences in disease manifestation, treatment efficacy, and adverse events (AEs) have been noted in clinical trials in East Asian populations compared with other regions; therefore, it is important to assess psoriasis treatments specifically in this region [6].

Tofacitinib is an oral Janus kinase inhibitor. The efficacy and safety of tofacitinib 5 mg and 10 mg twice daily (BID) in patients with moderate to severe chronic plaque psoriasis has been demonstrated in Phase 2 [7] and global Phase 3 [8–11] trials of up to 56 weeks' duration, and in a long-term extension study with efficacy endpoints reported through 24 months and safety reported over 33 months of exposure [11]. The efficacy and safety of tofacitinib has also been studied in several immune-mediated inflammatory diseases, including rheumatoid arthritis (RA) [12–17], psoriatic arthritis (NCT01877668, NCT01882439, NCT01976364), ankylosing spondylitis [18], Crohn's disease [19] (NCT01393626, NCT01393899, NCT01470599), and ulcerative colitis [20,21].

Here, we report the efficacy and safety of tofacitinib vs placebo for the treatment of moderate to severe chronic plaque psoriasis in East Asian patients.

2. Materials and methods

2.1. Patients

Patients were enrolled from multiple dermatology centers in China mainland, Taiwan, and Korea. Patient inclusion and exclusion criteria were similar to those of previous global studies [10,11]. Full details are provided in the Supplementary Methods. Briefly, patients were aged ≥18 years with a diagnosis of plaque-type psoriasis for ≥12 months at screening, covering ≥10% of their body surface area (BSA), with a Psoriasis Area and Severity Index (PASI) score ≥12 and Physician's Global Assessment (PGA) score of 'moderate' or 'severe' at baseline.

2.2. Study design

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study (NCT01815424) carried out between December 2013 and July 2015 (Fig. 1). A computer-generated randomization schedule was developed by Pfizer and an automated telephone/web-based interactive response system was used to assign patients 2:2:1:1 to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo advanced to tofacitinib 5 mg BID, or placebo advanced to tofacitinib 10 mg BID. At Week 16, patients initially receiving placebo were automatically advanced to their pre-determined tofacitinib dose. Patients were treated up to Week 52. Patients, investigators, and the sponsor were blinded to study treatment. Placebo was provided as oral tablets matching those of tofacitinib.

The study was reviewed by the institutional review board and independent ethics committees of each study center, and was conducted in accordance with the International Conference on Harmonisation guidelines on Good Clinical Practice and applicable local regulatory requirements and laws. Patients provided informed consent prior to study participation.

2.3. Outcomes

The primary endpoints were the proportion of patients achieving a PGA response (PGA of 'clear' or 'almost clear' on a 5-point scale: 0 = clear; 4 = severe), and the proportion of patients achieving ≥75% improvement from baseline PASI (PASI75 response) at Week 16.

Key secondary endpoints included: % change from baseline (CFB) in BSA at Week 16; proportion of patients achieving ≥90% improvement from baseline PASI (PASI90) at Week 16; CFB in Dermatology Life Quality Index (DLQI) total score at Week 16; PGA response at Week 4; PASI75 at Week 4; CFB in DLQI at Week 4; % CFB in Nail Psoriasis Severity Index (NAPSI) at Week 16 among patients with nail psoriasis at baseline; and the proportion of patients maintaining PGA, PASI75, or PASI90 responses at Week 52, among those with a corresponding Week 16 response. Other secondary endpoints included the median time to achieve PGA or PASI75 responses up to Week 16, and PGA or PASI75 responses at each study visit through Week 52.

Safety was assessed through spontaneous reporting of AEs, physical examinations, and clinical laboratory tests. AEs of special

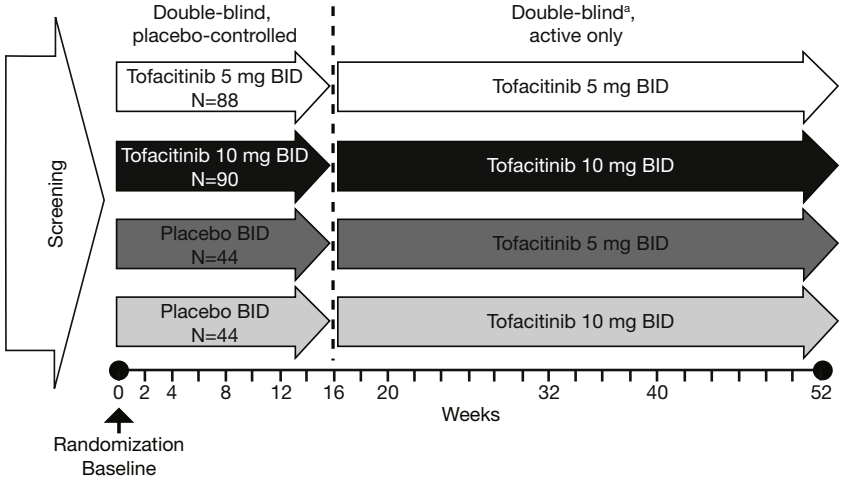

Fig. 1. Study design.
[a]Week 16–52 were double-blind with respect to dose of tofacitinib. BID, twice daily; N, number of patients randomized to treatment.

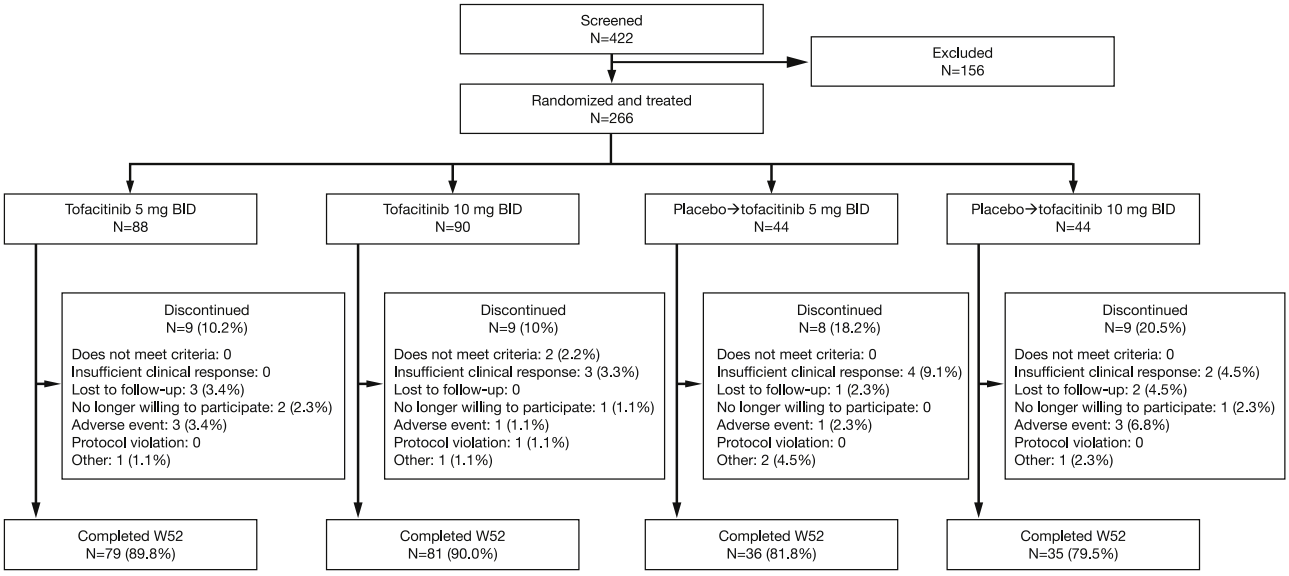

Fig. 2. Summary of patient disposition through Week 52.
BID, twice daily; W, week.

interest are described, including: serious, opportunistic, and herpes zoster infections; malignancies; major adverse cardiovascular events (MACE); and gastrointestinal perforations.

2.4. Statistical analysis

A sample size of 70 Chinese patients per group was determined to give ~94% power to achieve a statistical significance level of 0.05 using a two-sided test for the comparisons of tofacitinib 5 mg and 10 mg BID vs placebo for both primary endpoints. Further details are provided in the Supplementary Methods.

Data were analyzed for the full analysis set: all randomized patients who received ≥1 dose of study drug. All binary data, including the primary endpoints, were analyzed using Cochran-Mantel Haenszel statistics adjusting for the effect of site, with non-responder imputation for missing data. To preserve overall Type I error for the primary analysis, a step-down approach was used for superiority vs placebo in the following order: PGA response with

Table 1
Patient demographics and baseline characteristics.

	Tofacitinib 5 mg BID N = 88	Tofacitinib 10 mg BID N = 90	Placebo[a] N = 88	Total N = 266
Male, n (%)	65 (73.9)	67 (74.4)	62 (70.5)	194 (72.9)
Age, mean (SD) [years]	40.7 (11.3)	41.0 (12.0)	41.7 (13.7)	41.1 (12.3)
BMI, mean (SD) [kg/m^2]	25.5 (4.0)	25.1 (4.2)	25.2 (3.5)	25.3 (3.9)
Region, n (%)				
China mainland	74 (84.1)	74 (82.2)	74 (84.1)	222 (83.5)
Taiwan	8 (9.1)	10 (11.1)	9 (10.2)	27 (10.2)
Korea	6 (6.8)	6 (6.7)	5 (5.7)	17 (6.4)
Current smoker, n (%)	36 (40.9)	35 (38.9)	35 (39.8)	106 (39.8)
Duration of psoriasis, mean (SD) [years]	15.6 (9.5)	14.4 (8.5)	13.2 (9.3)	14.4 (9.1)
PASI score, mean (SD)	25.3 (10.2)	25.3 (9.1)	26.1 (9.5)	25.6 (9.6)
% affected BSA, mean (SD)	37.4 (19.6)	36.4 (18.0)	35.8 (17.1)	36.5 (18.2)
PGA, n (%)				
Moderate	77 (87.5)	77 (85.6)	67 (76.1)	221 (83.1)
Severe	11 (12.5)	13 (14.4)	21 (23.9)	45 (16.9)
DLQI score, mean (SD)	13.5 (7.3)	14.1 (7.2)	12.3 (6.8)	13.3 (7.1)
Presence of psoriatic arthritis, n (%)	6 (6.8)	4 (4.4)	8 (9.1)	18 (6.8)
Presence of nail psoriasis, n (%)	38 (43.2)	40 (44.4)	38 (43.2)	116 (43.6)
Previous exposure to systemic treatment, n (%)[b]	49 (55.7)	46 (51.1)	48 (54.5)	143 (53.8)
Previous use of biologics, n (%)[c]	17 (19.3)	14 (15.6)	8 (9.1)	39 (14.7)
Inadequate response[d] or intolerant to systemic therapies,[e] n (%)	38 (43.2)	34 (37.8)	38 (43.2)	110 (41.4)

BID, twice daily; BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PUVA, psoralen combined with ultraviolet A treatment; SD, standard deviation.

[a] Placebo group includes patients randomized to placebo → tofacitinib 5 mg BID and placebo → tofacitinib 10 mg BID.

[b] Includes conventional, biologics, phototherapy (PUVA or non-PUVA) or traditional Chinese medicine tripterygium glycoside.

[c] Includes adalimumab, etanercept, infliximab, or ustekinumab; regardless of previous use of conventional systemic agents or phototherapy.

[d] Discontinued due to lack of efficacy.

[e] Includes ciclosporin, methotrexate, methotrexate sodium, methylprednisolone, acitretin, isotretinoin, adalimumab, etanercept, infliximab, ustekinumab, phototherapy, or tripterygium glycosides.

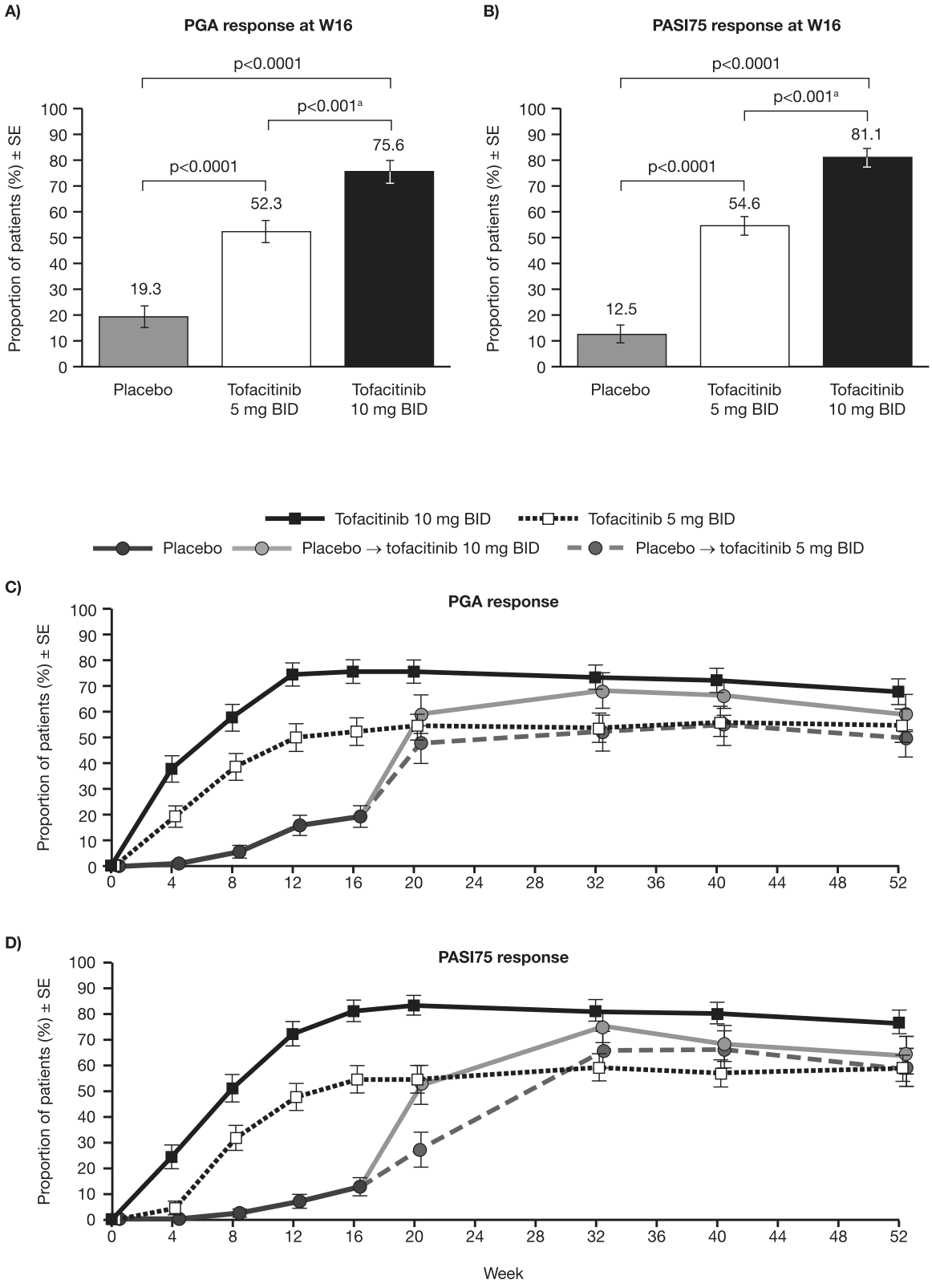

Fig. 3. PGA (A) and PASI75 (B) responses with tofacitinib vs placebo at Week 16 (primary endpoint); and PGA (C) and PASI75 (D) responses through Week 52 by treatment sequence (FAS NRI).

[a]Nominal p value from post hoc analysis that was not type 1 error controlled. Placebo group includes patients randomized to placebo → tofacitinib 5 mg BID and placebo → tofacitinib 10 mg BID. BID, twice daily; FAS, full analysis set; NRI, non-responder imputation; PASI75, ≥75% reduction in Psoriasis Area and Severity Index score relative to baseline; PGA, Physician's Global Assessment; SE, standard error; W, week.

10 mg BID; PASI75 response with 10 mg BID; PGA response with 5 mg BID; PASI75 response with 5 mg BID. Statistical significance was claimed for a given endpoint at a given dose only if the prior endpoint in the sequence met significance requirements ($p \leq 0.05$; two-sided). A Breslow-Day test was performed to test the homogeneity of the odds ratios across the investigational sites. Investigational sites with <10 patients were pooled for this analysis (16 individual study sites were combined into six pooled sites). The differences in response proportions between each tofacitinib dose and placebo with corresponding 95% confidence intervals were estimated based on the normal approximation.

Details of the statistical analysis for secondary endpoints, including the step-down procedure used for the key secondary endpoints, are provided in the Supplementary Methods. Within each tofacitinib dose, statistical significance was claimed for a given endpoint if the prior endpoint in the step-down sequence met significance requirements ($p \leq 0.025$, two-sided). Continuous variables were analyzed using the data as observed with a mixed-effect repeated measures model from which the least squares mean of difference from placebo was derived.

3. Results

3.1. Patients

Of the 266 randomized patients, 244 (91.7%) completed Week 16 (tofacitinib 5 mg BID, n = 84 [95.5%]; 10 mg BID, n = 83 [92.2%]; placebo, n = 77 [87.5%]; Fig. S1), and 231 (86.8%) completed Week 52 (Fig. 2). Patient demographics and baseline characteristics were similar across treatment groups, with the exception that the placebo group included higher proportions of patients with severe disease and biologic-naïve patients vs the tofacitinib groups (Table 1).

3.2. Efficacy

At Week 16, tofacitinib demonstrated superior efficacy vs placebo for both primary endpoints. PGA response was achieved by 52.3% and 75.6% of patients receiving tofacitinib 5 mg and 10 mg BID, respectively, vs 19.3% with placebo (both $p < 0.0001$; Fig. 3A). PASI75 was achieved by 54.6% and 81.1% of patients receiving tofacitinib 5 mg and 10 mg BID vs 12.5% with placebo (both $p < 0.0001$; Fig. 3B). There was no significant difference in odds ratio across (pooled) investigator sites for PGA response (Breslow-Day test: 5 mg BID, p = 0.50; 10 mg BID, p = 0.69) or PASI75 (Breslow-Day test: 5 mg BID, p = 0.37; 10 mg BID, p = 0.51). The median time to response was 8 weeks for both PGA and PASI75 responses with tofacitinib 10 mg BID, and 14 and 16 weeks, respectively, with tofacitinib 5 mg BID (Table S1). Both PGA and PASI75 responses were generally sustained from Week 16 through Week 52 with tofacitinib 5 mg and 10 mg BID (Fig. 3C and D).

Based on the step-down testing procedure, patients receiving tofacitinib 10 mg BID achieved significant differences from placebo (all $p < 0.025$) for all of the tested key secondary efficacy endpoints (Table 2). Patients in the tofacitinib 5 mg BID group achieved significant differences from placebo (all $p < 0.025$) for %CFB in BSA at Week 16, PASI90 response at Week 16, CFB in DLQI at Week 16, and PGA response at Week 4 (Table 2). Patients receiving tofacitinib 5 mg BID failed to achieve statistical significance for two key secondary endpoints: PASI75 at Week 4 and %CFB in NAPSI at Week 16 (both $p > 0.025$; Table 2); therefore, step-down testing was stopped for all endpoints beyond PASI75 at Week 4; statistical significance could not be claimed for CFB in DLQI at Week 4 for tofacitinib 5 mg BID.

Among patients treated with tofacitinib 5 mg and 10 mg BID who achieved a Week 16 response, the majority maintained PGA (73.6% and 75.0%, respectively), PASI75 (76.8% and 84.9%), and PASI90 (70.5% and 74.1%) responses through Week 52 (Fig. 4).

3.3. Safety

3.3.1. Weeks 0–16

From baseline to Week 16, 64.8%, 67.8%, and 48.9% of patients receiving tofacitinib 5 mg BID, 10 mg BID, and placebo, respectively, had treatment-emergent AEs of all causality (Table 3). Two patients receiving tofacitinib 5 mg BID experienced serious AEs (SAEs); no SAEs were reported in patients receiving tofacitinib 10 mg BID or placebo. The numbers of discontinuations due to AEs were similar between treatment groups.

3.3.2. Weeks 0–52

From baseline to Week 52, patients receiving tofacitinib 5 mg and 10 mg BID had similar rates of treatment-emergent AEs and discontinuations due to AEs (all causality); the placebo to tofacitinib groups also had generally similar rates of AEs from Week 16 to Week 52 (Table 3). Four patients receiving tofacitinib 5 mg BID, two receiving tofacitinib 10 mg BID, and one patient who advanced to tofacitinib 10 mg BID from placebo had SAEs.

Table 2
Key secondary efficacy endpoints (full analysis set).

	Tofacitinib 5 mg BID N = 88	Tofacitinib 10 mg BID N = 90	Placebo[a] N = 88
%CFB in affected BSA at Week 16, LSM (SE)[b]	−54.4 (5.8)***	−73.8 (5.9)***	−2.3 (6.1)
PASI90 response at Week 16, n (%)[c]	31 (35.2)***	54 (60.0)***	3 (3.4)
CFB in DLQI score at Week 16, LSM (SE)[b]	−7.0 (0.6)***	−9.1 (0.6)***	−1.6 (0.7)
PGA response at Week 4, n (%)[c]	17 (19.3)***	34 (37.8)***	1 (1.1)
PASI75 response at Week 4, n (%)[c]	4 (4.6)	22 (24.4)***	0 (0.0)
CFB in DLQI score at Week 4, LSM (SE)[b]	−5.1 (0.5)†††	−6.0 (0.5)***	−0.9 (0.5)
%CFB in NAPSI score at Week 16, LSM (SE)[b,d]	−15.0 (10.6)	−33.3 (10.5)*	7.9 (12.0)

BID, twice daily; BSA, body surface area; CFB, change from baseline; DLQI, Dermatology Life Quality Index; LSM, least squares mean; NAPSI, Nail Psoriasis Severity Index; PASI75, ≥75% reduction in Psoriasis Area and Severity Index score relative to baseline; PASI90, ≥90% reduction in Psoriasis Area and Severity Index score relative to baseline; PGA, Physician's Global Assessment; SE, standard error.

* $p < 0.025$.

*** $p < 0.0001$ vs placebo in the step-down testing procedure.

††† $p < 0.0001$ nominal significance vs placebo.

[a] Placebo group includes patients randomized to placebo → tofacitinib 5 mg BID and placebo → tofacitinib 10 mg BID.

[b] Mixed-effect repeated measures model, no imputation for missing values.

[c] P value for the Cochran-Mantel-Haenszel statistic controlling for (pooled) investigator sites, non-responder imputation for missing values.

[d] Assessed in patients with nail psoriasis at baseline: tofacitinib 5 mg BID, n = 38; tofacitinib 10 mg BID, n = 38; placebo, n = 29.

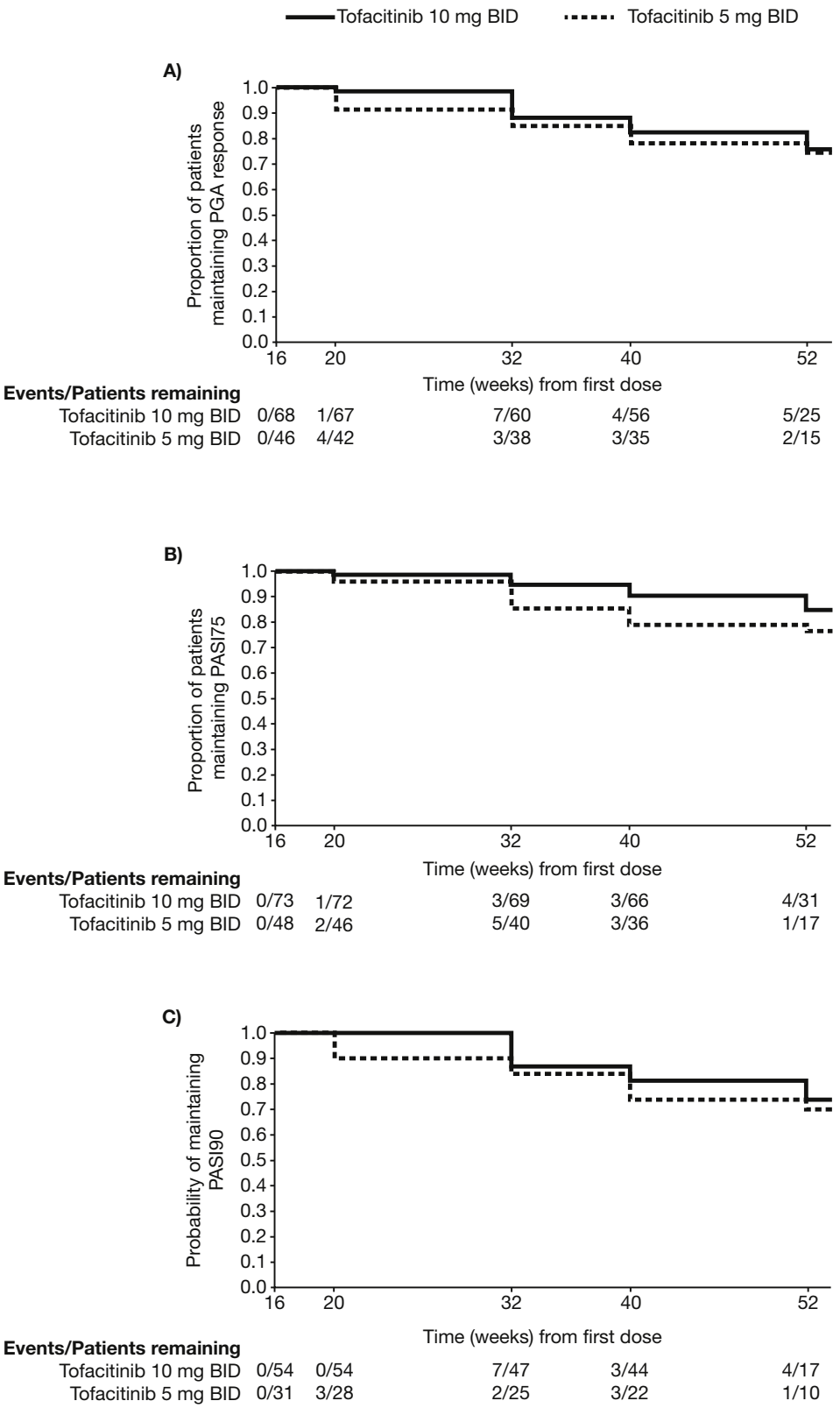

Fig. 4. Kaplan-Meier plots of the time maintaining PGA (A), PASI75 (B), and PASI90 (C) responses from Weeks 16 to 52 with tofacitinib 5 mg and 10 mg BID, among those patients with a corresponding Week 16 response (FAS observed case).
Event is loss of response. Proportion maintaining a response is: 1-proportion of loss of response. Missing values from patients who had not experienced an event were assumed to be right censored at the relevant time point using the last known data. BID, twice daily; FAS, full analysis set; PASI75, ≥75% reduction in Psoriasis Area and Severity Index score relative to baseline; PASI90, ≥90% reduction in Psoriasis Area and Severity Index score relative to baseline; PGA, Physician's Global Assessment.

The most common treatment-emergent AEs across groups were upper respiratory tract infection, nasopharyngitis, hyperlipidemia, and increased blood cholesterol (Table S2).

Two serious infections (bronchopneumonia, tofacitinib 10 mg BID; urinary tract infection, tofacitinib 5 mg BID) and two malignancies (metastatic small-cell lung cancer, tofacitinib 10 mg BID; metastatic lung adenocarcinoma, tofacitinib 5 mg BID) were reported (Table 3); both patients with malignancies were current or ex-smokers.

In total, 11 herpes zoster cases were reported (tofacitinib 5 mg BID, n = 3; tofacitinib 10 mg BID, n = 5; placebo advanced to tofacitinib 5 mg BID, n = 1; placebo advanced to tofacitinib 10 mg BID, n = 2); all were non-serious events that were categorized as mild (n = 3) or moderate (n = 8) in severity (severe events, n = 0), and all resolved without study treatment discontinuation. Four multi-dermatomal herpes zoster cases were adjudicated as opportunistic infections; no tuberculosis or other opportunistic infections were reported.

No cases of MACE were reported. One death occurred in a patient who received tofacitinib 5 mg BID, as a result of metastatic lung adenocarcinoma (the same case as described above).

Over 52 weeks, small decreases from baseline in mean lymphocyte count and neutrophil count were observed; no patients experienced confirmed (two consecutive measurements) reductions in lymphocyte count $<0.5 \times 10^9$/L or neutrophil count $<1.0 \times 10^9$/L (Fig. 5; Table S3). One patient receiving tofacitinib 10 mg BID had a confirmed hemoglobin level reduction >30% from baseline, which occurred after completing 52 weeks' treatment. No patients had confirmed hemoglobin levels <10.0 g/dL. Small initial mean increases in creatine phosphokinase were sustained over 52 weeks; no patient had confirmed creatine phosphokinase >10 x the upper limit of normal (ULN). Small mean increases from baseline in low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) were observed; there was no change in mean LDL-c/HDL-c ratio. Confirmed increases in aspartate or alanine aminotransferase ≥3 x ULN were reported in three patients who received tofacitinib 5 mg BID after completion of the 52-week study treatment period. There were no Hy's Law cases.

4. Discussion

East Asian patients with psoriasis represent a distinct population and have demonstrated differences in disease activity and treatment outcomes compared with other regions [6]. Therefore, it is important to examine the efficacy and safety of potential psoriasis therapies specifically in these patients.

In this study in patients from China mainland, Taiwan, and Korea with moderate to severe psoriasis, both tofacitinib 5 mg and 10 mg BID were superior to placebo in the primary efficacy endpoints, PGA and PASI75 responses at Week 16. PGA and PASI75 responses at Week 16 were maintained in the majority of patients (73.6–84.9%) through Week 52. In addition, tofacitinib 10 mg BID was superior to placebo for all key secondary endpoints, while tofacitinib 5 mg BID was superior to placebo for %CFB in BSA, PASI90, and CFB in DLQI at Week 16, and PGA response at Week 4. Tofacitinib 10 mg BID had a faster onset of effect and showed greater efficacy vs 5 mg BID.

Although no direct comparisons can be made, generally higher PGA and PASI75 response rates were observed with tofacitinib 5 mg and 10 mg BID compared with the same doses in global psoriasis studies [8–11]. This pattern is in line with results of a regional Japanese study of tofacitinib [22], and reports of several biologic agents [6]. Higher response rates in East Asian populations may be due to differences in patient characteristics, including lower body weight, shorter disease duration, less prior use of biologic therapies, and higher baseline disease severity compared with global clinical study populations [6]. Patients in this study generally had a lower body mass index than those in the global

Table 3
Summary of adverse events (all causality).

	Weeks 0–16			Weeks 0–52		Weeks 16–52			
	Tofacitinib 5 mg BID N = 88	Tofacitinib 10 mg BID N = 90	Placebo[a] N = 88	Tofacitinib 5 mg BID N = 88	Tofacitinib 10 mg BID N = 90	Tofacitinib 5 mg BID N = 84	Tofacitinib 10 mg BID N = 83	Placebo → 5 mg BID N = 39	Placebo → 10 mg BID N = 38
Adverse events, n (%)	57 (64.8)	61 (67.8)	43 (48.9)	74 (84.1)	76 (84.4)	57 (67.9)	53 (63.9)	29 (74.4)	29 (76.3)
Serious adverse events, n (%)	2 (2.3)[b]	0	0	4 (4.5)[b,c]	2 (2.2)[d]	2 (2.4)[c]	2 (2.4)[d]	0	1 (2.6)[e]
Discontinuations due to adverse events, n (%)	3 (3.4)	1 (1.1)	3 (3.4)	3 (3.4)	1 (1.1)	0	0	1 (2.6)	0
Deaths, n (%)	0	0	0	1 (1.1)	0	1 (1.2)	0	0	0
Adverse events of special interest, n (%)									
Serious infections	1 (1.1)	0	0	1 (1.1)	1 (1.1)	0	1 (1.2)	0	0
Opportunistic infections[f]	2 (2.3)	0	0	2 (2.3)	2 (2.2)	0	2 (2.4)	0	0
Herpes zoster	2 (2.3)	3 (3.3)	0	3 (3.4)	5 (5.6)	1 (1.2)	2 (2.4)	1 (2.6)	2 (5.3)
Malignancies	1 (1.1)[g]	0	0	1 (1.1)[g]	1 (1.1)[h]	0	1 (1.2)[h]	0	0
MACE	0	0	0	0	0	0	0	0	0
Gastrointestinal perforation	0	0	0	0	0	0	0	0	0

BID, twice daily; MACE, major adverse cardiovascular event.
[a] Placebo group includes patients randomized to placebo → tofacitinib 5 mg BID and placebo → tofacitinib 10 mg BID.
[b] Urinary tract infection; lung adenocarcinoma metastatic.
[c] Arteriosclerosis coronary artery; ankle fracture.
[d] Bronchopneumonia; small-cell lung cancer metastatic.
[e] Arteriosclerosis coronary artery.
[f] All multi-dermatomal herpes zoster (non-adjacent dermatomes or >2 adjacent dermatomes); events also included in herpes zoster rates.
[g] Lung adenocarcinoma metastatic.
[h] Small-cell lung cancer metastatic.

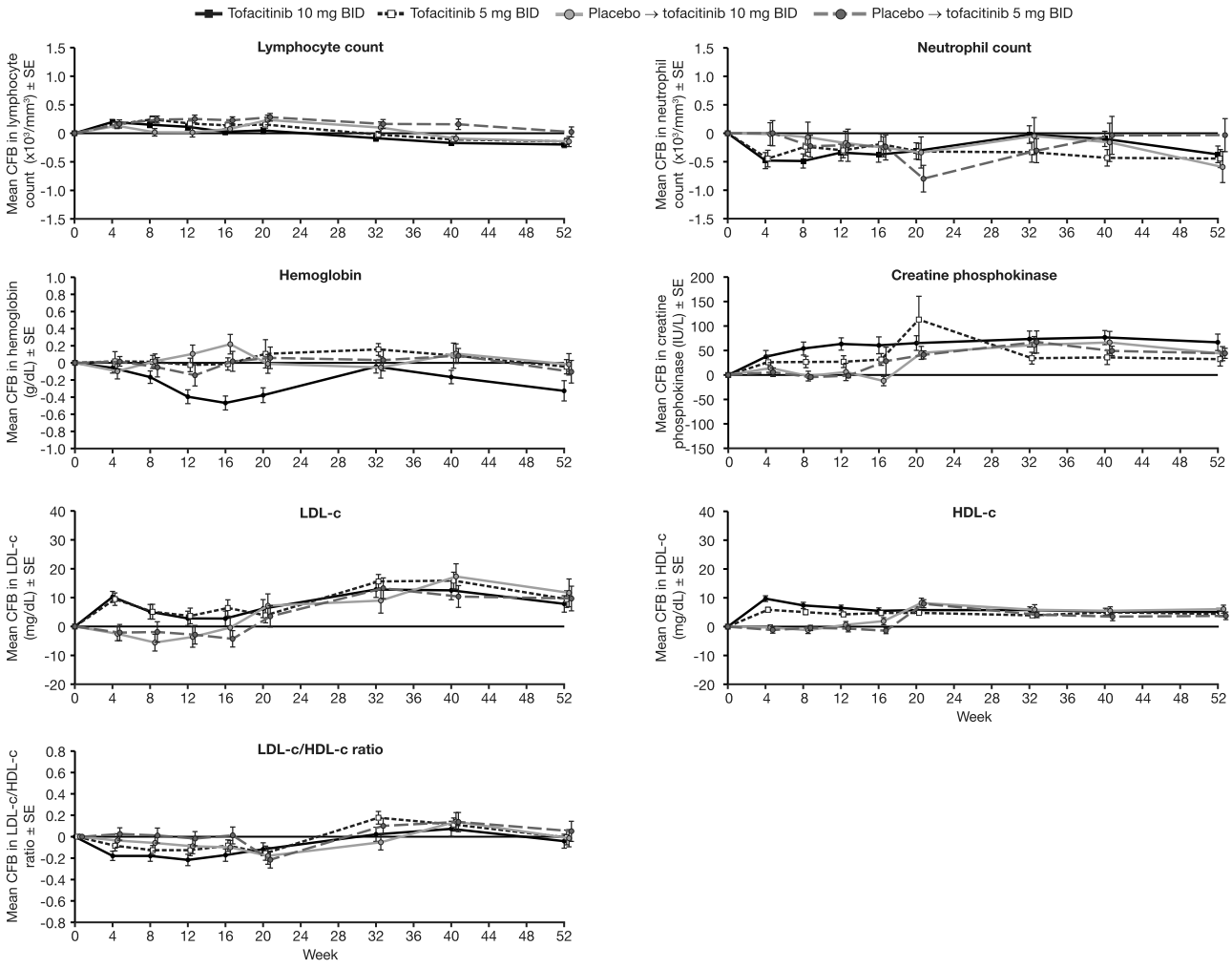

Fig. 5. Mean changes in laboratory parameters over time through Week 52.
BID, twice daily; CFB, change from baseline; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SE, standard error.

tofacitinib psoriasis trials, and included more biologic-naïve patients [8–10].

The overall safety profile of tofacitinib in this study was generally consistent with that observed in the global studies [8–11]. The rates of most AEs of special interest were comparable with those reported in the global studies [8–11]. However, the rate of herpes zoster in this East Asian study population (11 cases in total [9 China mainland, 2 Taiwan]; 4.3% of all patients, 3.1% of those receiving tofacitinib 5 mg BID from Weeks 0 to 52 and 5.5% of those receiving 10 mg BID from Weeks 0 to 52) appeared to be higher than observed in the global psoriasis studies (0.8–1.5%) [11], but was lower than that reported with tofacitinib in a study in Japanese patients with psoriasis (17.0%) [22]. Background incidence of herpes zoster is higher in Korea (10.4/1000 patient-years) [23] compared with the global population (4.0–4.5/1000 patient-years) [24], however annual incidence is similar in certain China mainland regions (3.4–5.8/1000 patient-years) [25,26], and Taiwan (5.0/1000 patient-years) [27]. An increased incidence rate of herpes zoster in tofacitinib-treated patients from Japan and Korea, compared with other regions, has been reported in previous global studies of tofacitinib in psoriasis and RA [28–30]. No association between Asian race and increased risk of herpes zoster has been reported with other psoriasis therapies [31]. However, the reasons for increased risk of herpes zoster remain undetermined.

Two malignancies were reported, one of which resulted in death, both in patients who were smokers. An analysis of malignancies reported in clinical trials of tofacitinib in patients with RA, which included 5671 patients with up to 72 months of exposure, indicated that the overall incidence rates (IRs), standardized IRs (SIRs; comparison with Surveillance, Epidemiology and End Results program), and types of malignancies, most commonly lung cancer, remained stable over time with increasing tofacitinib exposure; SIRs in tofacitinib-treated patients were within the range expected for patients with moderate to severe RA [32].

Limitations to this study include the lack of placebo arm beyond Week 16 and the lack of any active comparator control arm throughout the study. In addition, although the 52-week study duration and study population size were large enough to show common AEs, accurate assessment of the frequency of rare or uncommon AEs or those with long latency (e.g. malignancy or cardiovascular AEs) may require a larger sample size and longer timeframe; longer-term safety data for global studies of tofacitinib have been published up to 33 months in psoriasis [11] and up to 8 years in RA [33]. As this was not a head-to-head study comparing efficacy between global and East Asian patients, no formal statistical comparisons were made and therefore only general indirect observations are possible. Finally, it is unclear how

applicable the results from this study are to East Asian patients living outside the region.

In summary, tofacitinib demonstrated efficacy vs placebo in patients in East Asia with moderate to severe psoriasis at Week 16, which was maintained through Week 52. SAEs were infrequent and no unexpected safety findings were observed compared with previous tofacitinib studies in global populations.

Clinical trial registration

Clinicaltrials.gov: NCT01815424; Registered, March 18, 2013; First patient first visit, December 12, 2013

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Conflicts of interest

J.Z. Zhang conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Bayer, Janssen-Cilag and Pfizer Inc.

T.F. Tsai conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Leo, Novartis Pharmaceuticals, Pfizer Inc, and Serono International SA (now Merck Serono International).

M.G. Lee conducted clinical trials for Eli Lilly, Janssen-Cilag, Novartis Pharmaceuticals, and Pfizer Inc, and received honoraria for acting as a speaker for Janssen-Cilag.

M. Zheng conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Janssen-Cilag and Pfizer Inc.

G. Wang has conducted clinical trials for AbbVie, Janssen-Cilag, and Pfizer Inc, and has acted as a consultant or speaker for La Roche-Posay China, LEO Pharma China, and Xian-Janssen.

H.Z. Jin conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, Galderma, Janssen-Cilag, and Pfizer Inc.

J. Gu conducted clinical trials or received honoraria for serving as a speaker for AbbVie, Galderma, Janssen-Cilag, Novartis, and Pfizer Inc.

R.Y. Li conducted clinical trials or received honoraria for serving as a consultant for AbbVie, Galderma, Leo Pharma China, Novartis Pharmaceuticals, Pfizer Inc, and Xian-Janssen Pharmaceuticals.

Q.Z. Liu conducted clinical trials for Bayer, Ipsen, and Pfizer Inc.

J. Chen conducted clinical trials for AbbVie, AstraZeneca, and Pfizer Inc.

C.X. Tu conducted clinical trials for Janssen-Cilag and Pfizer Inc, and has acted as a consultant for Astellas Pharma Inc and Janssen-Cilag.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2017.05.004.

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