Secukinumab demonstrates high efficacy and a favorable safety profile over 52 weeks in Chinese patients with moderate to severe plaque psoriasis

Lin Cai[1], Jian-Zhong Zhang[1], Xu Yao[2], Jun Gu[3], Quan-Zhong Liu[4], Min Zheng[5], Shi-Fa Zhang[6], Jin-Hua Xu[7], Cheng-Xin Li[8], Hao Cheng[9], Qing Guo[10], Wei-Li Pan[11], Shen-Qiu Li[12], Ruo-Yu Li[13], Zai-Pei Guo[14], Zhi-Qi Song[15], Shan-Shan Li[16], Xiu-Qin Dong[17], Linda Wang[18], Rong Fu[18], Pascaline Regnault[19], Pascal Charef[19], Rafal Mazur[19], Manmath Patekar[19]

[1]Department of Dermatology, Peking University People's Hospital, Beijing 100044, China;
[2]Institute of Dermatology, Chinese Academy of Medical Science & Peking Union Medical College, Beijing 100730, China;
[3]Department of Dermatology, Changhai Hospital, Shanghai 200433, China;
[4]Department of Dermatology, Tianjin Medical University General Hospital, Tianjin 300052, China;
[5]Department of Dermatology, Second Affiliated Hospital School of Medicine, Zhejiang University, Hangzhou, Zhejiang 311215, China;
[6]Department of Dermatology, General Hospital of Northern Theater Command, Shenyang, Liaoning 110016, China;
[7]Department of Dermatology, Huashan Hospital, Fudan University, Shanghai 200040, China;
[8]Department of Dermatology and Venereology, Chinese People's Liberation Army General Hospital, Beijing 100853, China;
[9]Department of Dermatology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310016, China;
[10]Department of Dermatology, Sun Yat-Sen Memorial Hospital, Guangzhou, Guangdong 510120, China;
[11]Department of Dermatology, Zhejiang Provincial People's Hospital, Zhejiang, Hangzhou, Zhejiang 310014, China;
[12]Department of Dermatology, Tongji Hospital, Tongji Medical College of Huazhong University of Science & Technology, Wuhan, Hubei 430030, China;
[13]Department of Dermatology, Peking University First Hospital, Beijing 100034, China;
[14]Department of Dermatology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China;
[15]Department of Dermatology, First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning 116011, China;
[16]Department of Dermatology, The First Hospital of Jilin University, Changchun, Jilin 130021, China;
[17]Department of Dermatology, Guangdong General Hospital, Guangzhou, Guangdong 510080, China;
[18]Beijing Novartis Pharma Co. Ltd., Shanghai 201203, China;
[19]Novartis Pharma AG, Basel 6463, Switzerland.

Abstract

Background: Psoriasis is a chronic inflammatory skin disease, affecting about 0.6% of the Chinese population. Many patients are not well controlled by conventional treatments, thus there is need for new treatment regimens. In this study, we assessed the efficacy and safety of secukinumab in Chinese patients with moderate to severe plaque psoriasis.

Methods: This study was a 52-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trial. A sub-population of study participants (≥18 years) of Chinese ethnicity were randomized to receive subcutaneous injections of 300 or 150 mg secukinumab, or placebo. The co-primary endpoints were psoriasis area severity index (PASI) 75 and Investigator's Global Assessment (IGA) 0/1 at Week 12.

Results: A total of 441 Chinese patients were enrolled in this study. Co-primary outcomes were achieved; 300 and 150 mg secukinumab were superior to placebo as shown in the proportion of patients that achieved PASI 75 (97.7% and 87.2% *vs.* 3.7%, respectively; $P < 0.001$), and IGA 0/1 (82.3% and 69.7% *vs.* 2.7%; $P < 0.001$) at Week 12. Treatment efficacy was maintained until Week 52. There was no increase in overall adverse events with secukinumab relative to placebo throughout the 52-week period.

Conclusion: Secukinumab is highly effective and well tolerated in Chinese patients with moderate to severe plaque psoriasis.

Trial Registration: ClinicalTrials.gov, NCT03066609; https://clinicaltrials.gov/ct2/show/record/NCT03066609.

Keywords: Chinese; Psoriasis; IL-17; Dermatology; Clinical trial; PASI

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001163

Correspondence to: Prof. Jian-Zhong Zhang, Department of Dermatology, Peking University People's Hospital, Beijing 100044, China
E-Mail: rmzjz@126.com

Chinese Medical Journal 2020;133(22)

Received: 29-06-2020 **Edited by:** Jing Ni and Li-Shao Guo

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory disease characterized by altered immune function and the development of scaly, erythematous skin plaques. Beyond cutaneous involvement, comorbidities of psoriasis include psoriatic arthritis,[1–3] cardiovascular disease, and metabolic syndrome.[4] Psoriasis also has a substantial negative impact on patients' quality of life (QoL).[5]

The prevalence of psoriasis varies geographically, with approximately 3% in western populations[6,7] and 0.6% in China.[8] There is evidence of substantial disease severity among Chinese patients with psoriasis, with the majority (57.3%) being moderate to severe disease according to a hospital-based study in a nationwide investigation in China.[9]

Clinical and experimental studies have identified interleukin (IL)-17A as a critical effector cytokine in the IL-23/IL-17 immunologic pathway underlying the onset and chronicity of plaque psoriasis.[10] Indeed, IL-17A is implicated in multiple psoriatic disease manifestations, including joint, scalp, nail, and palmoplantar involvement and axial symptoms.[10–15]

Secukinumab, a fully human monoclonal antibody that selectively neutralizes IL-17A, delivered rapid and sustained efficacy in patients with moderate to severe plaque psoriasis in the pivotal ERASURE and FIXTURE trials,[16,17] in which approximately one-fifth of patients were Asian.[16] Despite substantial disease severity among patients with psoriasis in China, the most common treatments are topical agents and traditional Chinese medicines (TCMs).[9] There is a significant unmet need for safe and effective treatments in the Chinese population.

Here, we studied the efficacy and safety of secukinumab, at a dose of 300 or 150 mg compared to placebo, in moderate to severe plaque psoriasis in a Chinese sub-population of the 52-week Phase 3b CAIN457A2318 clinical trial.

Methods

Ethical approval

The study protocol was reviewed by the Ethics Committee for each center. The study was conducted according to the ethical principles of the *Declaration of Helsinki*. Informed consent was obtained from each patient in writing before randomization.

Study population

Patients (≥18 years) with moderate to severe chronic plaque psoriasis for at least 6 months (psoriasis area severity index [PASI] ≥12, Investigator's Global Assessment [IGA] score ≥3, and body surface area [BSA] involvement ≥10%) and who were inadequately controlled by topical treatments, phototherapy, and/or previous systemic therapy, were eligible. Key exclusion criteria included forms of psoriasis other than chronic plaque-type psoriasis, drug-induced psoriasis, ongoing use of biologic or systemic immuno-modulating agents, ongoing phototherapy, and previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor. Previous use of biologic agents (except those targeting the IL-17 pathway) was not listed as an exclusion criteria. Treatments prohibited for the duration of the study, and respective washout periods required are shown in Table 1.

Study design

This study (Clinicaltrials.gov identifier NCT03066609, EudraCT registration number 2016-000524-25) was a 52-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trial. The first date of clinical trial registration was February 22, 2017. It consisted of four periods: Screening, Induction (Baseline–Week 12 pre-dose), Maintenance (Week 12 dosing–Week 52), and Follow-up (Weeks 53–60). Randomization was stratified by geographical region and the presence of psoriatic arthritis at Baseline. Eligible patients were randomized 2:1:1 to receive either subcutaneous secukinumab 300, 150 mg or placebo at Baseline, Weeks 1, 2, and 3, and then every 4 weeks from Weeks 4 to 48. At the end of the Induction period (Week 12), all patients were assessed for co-primary endpoints, which were PASI 75 (75% or more reduction in Baseline PASI score) and IGA 0/1 response (clear or almost clear skin). Before receiving the Week 12 dose, all PASI 75 non-responder placebo patients were reassigned to secukinumab 300 mg, while PASI 75 responder placebo patients continued on placebo. Due to treatment blinding, patients received an additional weekly secukinumab or matching placebo dose at Weeks 13, 14, and 15.

Sample size calculation and randomization

Reported PASI 75 response rate to placebo is generally in the range of 3% to 7%[18–21] whilst in a recent phase 3 trial, observed PASI 75 response rate to placebo in Chinese patients after 12 weeks of treatment was 11.1%.[22] It was estimated that in the current study, up to 10% of the patients under placebo may achieve a PASI 75 response during the Induction period. The PASI 75 and IGA 0/1 response rates of secukinumab at Week 12 week were based on previous Phase 3 trials. PASI 75 responses are reportedly approximately 79.4% (95% confidence interval [CI]: 76.2%–82.4%) for secukinumab 300 mg and 69.2% (95% CI: 65.6%–72.6%) for secukinumab 150 mg. IGA 0/1 responses at Week 12 are approximately 65.0% (95% CI: 61.3%–68.6%) for secukinumab 300 mg and 51.4% (95% CI: 47.7%–55.2%) for secukinumab 150 mg.

Since two secukinumab dose regimens were tested in parallel *vs.* placebo with respect to the co-primary endpoints, PASI 75 response and IGA 0/1 response after 12 weeks of treatment, the type-I error for each comparison split to $\alpha/2$ (family-wise $\alpha = 2.5\%$, one-sided). With 536 (using a 2:1:1 ratio) patients and assuming a response rate in the placebo group of 10% for PASI 75 response and IGA 0/1 response, the power to demonstrate a response rate of 65.6% for PASI 75 and

Table 1: Treatments prohibited for the duration of the study, and respective washout periods required.

Prohibited treatments*	Washout period (before Baseline)
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than the above (eg, adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments† (eg, methotrexate, cyclosporine A, corticosteroids, cyclophosphamide)	4 weeks
Other systemic psoriasis treatments (eg, retinoids, fumarates, apremilast)	4 weeks
Photochemotherapy	4 weeks
Phototherapy	2 weeks
Topical treatment which is likely to impact the signs and symptoms of psoriasis (eg, corticosteroids, vitamin D analogs, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)‡	2 weeks
Live vaccinations	6 weeks
Any investigational treatment (including IL23p19) or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Traditional Chinese medicine treatments of psoriasis and/or psoriatic arthritis§	4 weeks

* If the prohibited treatment was used during the study for any indication, the subject had to discontinue use of the prohibited treatment if he/she wished to continue in the study. In case of undue safety risk for the subject, the subject had to discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject had to discontinue study treatment. † Including intra-articular or peri-articular injections. Note that inhaled corticosteroids with only a topical effect (eg, to treat asthma) were not considered "systemic immunomodulating treatments" and were; therefore, acceptable as co-medication. ‡ Mild to moderate topical corticosteroids were allowed only during the Screening, if used exclusively on the face, scalp, and/or genito-anal area. Mild to moderate topical corticosteroids in the Screening were stopped at least the day before randomization. Topical corticosteroids and other topical treatments were allowed during the maintenance epoch only if (all applied): medication was started after the Week 12 visit was completed; medication was used for 14 consecutive calendar days or less; Medication was used for an indication other than psoriasis and not on the area affected with psoriasis. § Traditional Chinese medicine (TCM) was defined as a compendium of methods popular in Chinese tradition for the treatment of a wide range of conditions. TCM practitioners use herbal remedies, acupuncture, massage, mind-body and dietary therapies, and other methods. In the United States, TCM was considered part of complementary and alternative medicines.

47.7% for IGA 0/1 in the secukinumab groups was above 99%, based on Fisher exact test.

The PASI 90 response rates of secukinumab regimens are approximately 56.6% (95% CI: 52.8%–60.3%) for the 300 mg secukinumab regimen and 41.1% (95% CI: 37.4%–44.9%) for the 150 mg secukinumab regimen. With respect to the secondary endpoint of PASI 90 response at Week 12 and with sample size of 536 (using a 2:1:1 ratio), the power to detect differences in response rates for each secukinumab dose regimen *vs.* placebo is above 99%, based on Fisher exact test with type-I error of $\alpha/2$ (family-wise $\alpha = 2.5\%$, one-sided) for each comparison and placebo response rate of 5%.

At Baseline visit, all eligible patients were randomized via interactive response technology (IRT) to one of the treatment arms. The Investigator or his/her delegate contacted the IRT after confirming that the patient fulfilled all the inclusion/exclusion criteria. A patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers for the packages of investigational treatment to be dispensed to the patient (only the medication number, but not the randomization number).

Study objectives

The objective of the study was to demonstrate the superiority of secukinumab compared to placebo, based on the co-primary endpoints, IGA 0/1 and PASI 75 at Week 12. The key secondary endpoint was PASI 90 at Week 12. Additional secondary efficacy endpoints included PASI responses and absolute PASI score over time up to Week 52, and time to PASI 75 response. Dermatology life quality index (DLQI) 0/1 response (no effect of skin disease on QoL) at Week 12 and over time up to Week 52 was included as an exploratory endpoint.

Statistical analysis

The co-primary endpoints were evaluated using a logistic regression model with treatment group, baseline body weight category, geographical region, and baseline PASI score as exploratory variables and a multiple imputations (MI) method was used for missing values. Odds ratios were computed for comparisons of secukinumab dose regimens *vs.* placebo utilizing the fitted logistic regression model. PASI 90 at Week 12 was evaluated analogously to PASI 75 and IGA 0/1 response (ie, logistic regression analysis). MI was used for missing PASI and IGA values. Sensitivity analyses of the co-primary endpoints were also performed using non-responder imputation. DLQI data were analyzed using last observation carried forward method to replace missing values.

Results

Patient characteristics

A total of 535 Chinese patients were screened and 441 were randomized to one of three treatment groups: secukinumab 300 mg ($n = 221$), 150 mg ($n = 110$), or

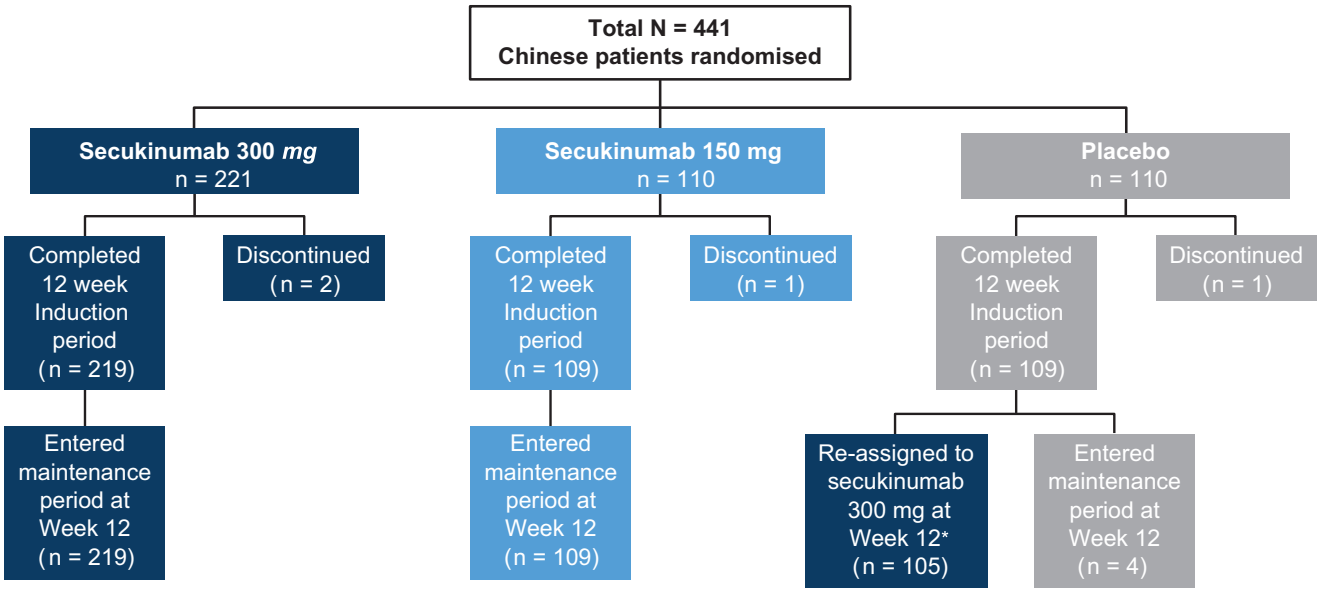

Figure 1: CONSORT flow diagram. Schematic demonstrating disposition of patients in the secukinumab 300 mg, secukinumab 150 mg, and placebo group during the induction and maintenance periods of study. *The majority of patients originally randomized to placebo (105/110) were re-assigned to the secukinumab 300 mg starting at Week 12, based on PASI 75 response status. PASI: Psoriasis area severity index.

Table 2: Demographic and disease characteristics of patient at Baseline

Characteristics	Secukinumab 300 mg ($n = 221$)	Secukinumab 150 mg ($n = 110$)	Placebo ($n = 110$)	Total ($n = 441$)
Age (years)	39.0 ± 11.6	40.5 ± 10.8	38.7 ± 10.3	39.3 ± 11.1
Male	177 (80.1)	84 (76.4)	89 (80.9)	350 (79.4)
Bodyweight (kg)	73.25 ± 14.24	72.71 ± 15.47	72.63 ± 13.27	72.96 ± 14.29
PASI				
Total	27.3 ± 10.9	26.5 ± 10.6	26.2 ± 9.3	26.8 ± 10.4
>20	154 (69.7)	76 (69.1)	78 (70.9)	308 (69.8)
BSA involvement	46.5 ± 20.7	44.8 ± 19.9	44.0 ± 19.2	45.4 ± 20.1
IGA mod 2011 score				
3-Moderate disease	117 (52.9)	64 (58.2)	63 (57.3)	244 (55.3)
4-Severe disease	104 (47.1)	46 (41.8)	47 (42.7)	197 (44.7)
Mean time since first diagnosis of plaque-type psoriasis (years)	15.0 ± 9.2	16.2 ± 9.6	14.8 ± 9.2	15.3 ± 9.3
Previous exposure to biologic psoriasis therapy	33 (14.9)	24 (21.8)	23 (20.9)	80 (18.1)
Psoriasis arthritis present*	23 (10.4)	11 (10.0)	11 (10.0)	45 (10.2)

All data are expressed as mean ± standard deviation or *n* (%). * Defined as at least three points out of the clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) criteria and at least three tender and three swollen joints at Baseline. PASI: Psoriasis Area and Severity Index; BSA: Body surface area; IGA mod 2011: Investigator's Global Assessment, 2011 modification.

placebo ($n = 110$). The rate of discontinuation during the Induction period was low and balanced between treatment arms (secukinumab 300 mg, $n = 2$ [0.9%]; secukinumab 150 mg, $n = 1$ [0.9%], and placebo, $n = 1$ [0.9%]). Nearly all patients (99.1%, $n = 437$) completed the Induction period. All patients completing the Induction period entered the Maintenance period; and overall, 97.1% ($n = 428$) of randomized patients completed it. Four patients decided to discontinue the trial (0.9%, $n = 4$), two patients were lost to follow up (0.5%, $n = 2$), and three patients withdrew due to an adverse event, lack of efficacy, and pregnancy (all 0.2%, $n = 1$) [Figure 1].

Baseline patient demographics and disease characteristics were generally well-balanced and comparable across the three treatment groups [Table 2]. A mean PASI of 26.8, BSA involvement of 45.4%, and a mean time since first psoriasis diagnosis of 15.3 years indicated a high disease

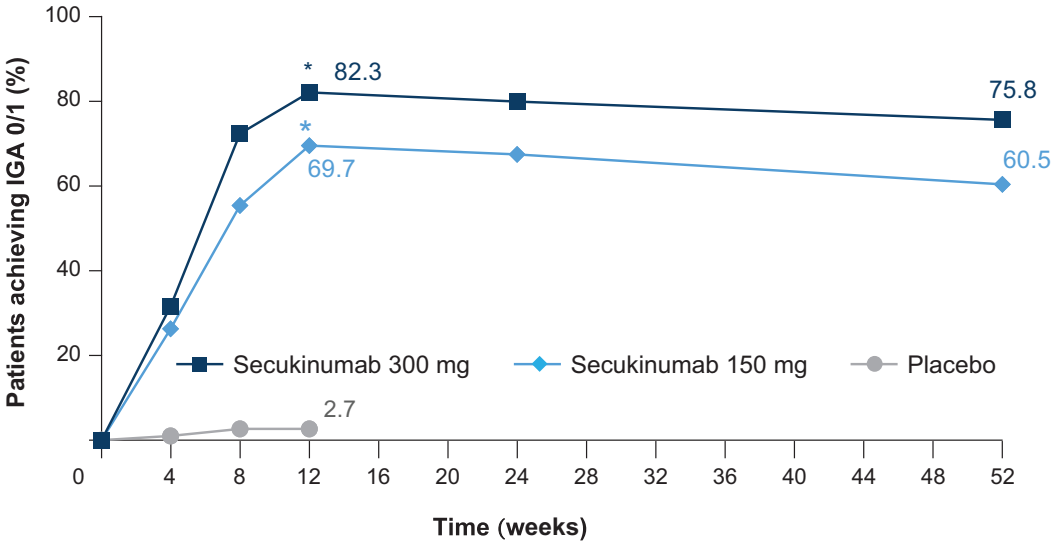

Figure 2: Patients achieving IGA mod 2011 0/1 up to Week 52. Secukinumab 300 mg ($n = 221$), secukinumab 150 mg ($n = 110$), and placebo ($n = 110$). $^{*}P < 0.001$, significantly different from placebo. IGA mod 2011 0/1: Investigator's Global Assessment, 2011 modification, clear (0) or almost clear (1) score.

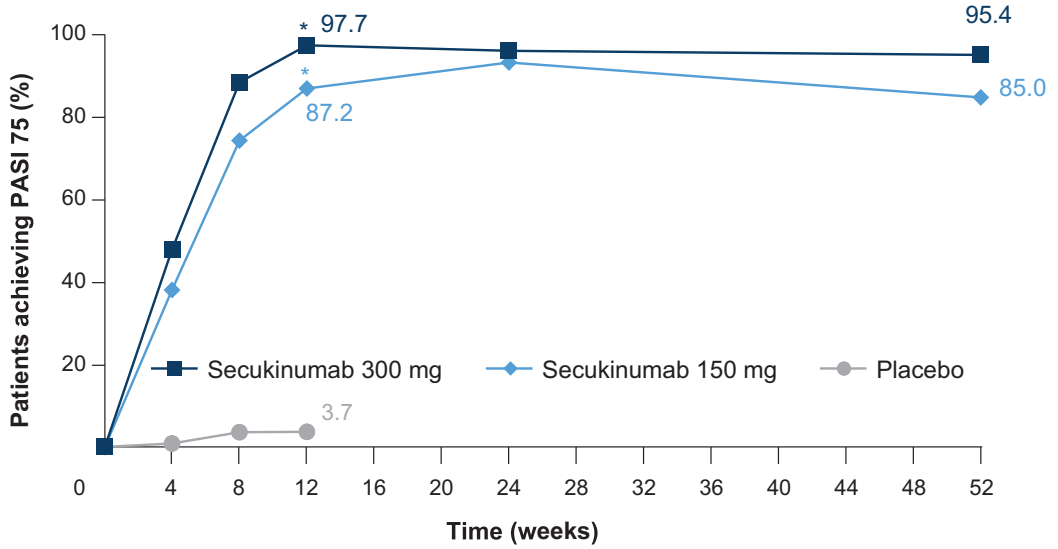

Figure 3: Patients achieving PASI 75 up to Week 52. Secukinumab 300 mg ($n = 221$), secukinumab 150 mg ($n = 110$), and placebo ($n = 110$). $^{*}P < 0.001$, significantly different from placebo. PASI 75: Psoriasis Area Severity Index 75% improvement *vs.* Baseline.

burden among patients at Baseline. Nearly half of patients ($n = 197$; 44.7%) were categorized as having severe disease (IGA score of 4).

Previous exposure to biologic systemic therapy was low (18.1%), and slightly less frequent in the secukinumab 300 mg group compared to the other groups (secukinumab 300 mg, 14.9%; secukinumab 150 mg, 21.8%; placebo, 20.9%).

Efficacy

Secukinumab 300 and 150 mg was highly efficacious in Chinese psoriasis patients, in terms of IGA 0/1 and PASI 75/90 responses, compared to placebo, at each visit up to Week 12, an effect which was sustained until Week 52. For all efficacy measures, responses were greater for secukinumab 300 mg than with 150 mg. The primary objective of the study was achieved: secukinumab 300 and 150 mg were superior to placebo with respect to the proportion of patients achieving IGA 0/1 at Week 12 (82.3% and 69.7% *vs.* 2.7%; $P < 0.001$) [Figure 2] and for the proportion of patients achieving PASI 75 at Week 12 (97.7% and 87.2% *vs.* 3.7%, respectively) [Figure 3]. Similarly, the key secondary objective was also achieved; both secukinumab doses were superior to placebo with respect to PASI 90 (81.0% and 65.7% *vs.* 0.9%; $P < 0.001$) [Figure 4] and PASI 100 (32.9% and 20.0% *vs.* 0; $P < 0.001$) at Week 12. A sensitivity analysis of co-primary and key secondary endpoints using non-responder imputation showed con-

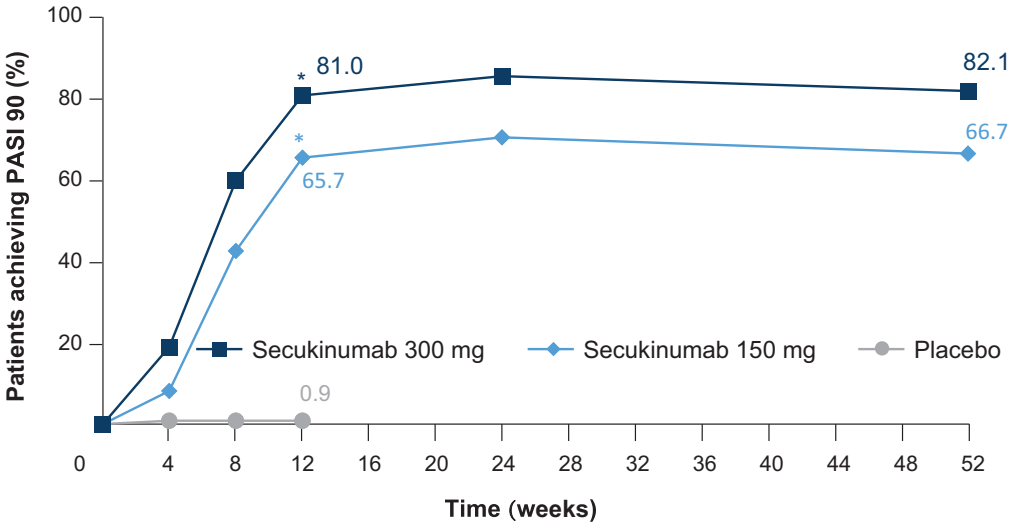

Figure 4: Patients achieving PASI 90 up to Week 52. Secukinumab 300 mg ($n = 221$), secukinumab 150 mg ($n = 110$), and placebo ($n = 110$). $^{*}P < 0.001$, significantly different from placebo. PASI 90: Psoriasis Area Severity Index 90% improvement *vs.* Baseline.

sistent results. Secukinumab maintained consistent IGA 0/1 and PASI 75/90 responses up to Week 52 [Figures 2–4]. PASI 100 responses continued to increase in the secukinumab 300 and 150 mg groups from Week 12 to Week 52 (secukinumab 300 mg, 32.9% [Week 12] and 42.1% [Week 52]; secukinumab 150 mg, 20.0% [Week 12] and 31.5% [Week 52]).

At Week 12, the mean PASI scores in both 300 and 150 mg secukinumab treatment groups were considerably lower compared to placebo (1.5 and 2.7 *vs.* 25.1, respectively). PASI was consistently reduced up to Week 52 (secukinumab 300 mg, 1.4; secukinumab 150 mg, 3.0). The mean percent change in PASI total score from Baseline to Week 12 and 52 was –94.6% and also –94.6% for secukinumab 300 mg; –89.8% and –88.6% for secukinumab 150 mg, compared to a mean change of –2.8% for placebo at Week 12.

Supporting these findings, median time to PASI 75 response was 52 days (95% CI: 29–57) in the secukinumab 300 mg group and 57 days (95% CI: 50–57) in the secukinumab 150 mg group. Placebo PASI 75 non-responders that were re-assigned to receive secukinumab 300 mg showed a rapid increase in the response rates following the switch to active treatment. At Week 28, corresponding to 16 weeks of active treatment, response rates were equivalent to those in the originally randomized secukinumab 300 mg group. Response rates thereafter paralleled the original secukinumab 300 mg group and were sustained through Week 52. Four patients continued on placebo after Week 12 and only two completed the Maintenance phase, both maintaining PASI 75 at Week 52.

Patients' QoL

For both secukinumab treatment groups, mean DLQI total scores were reduced from as early as Week 4, which continued out to Week 52. For DLQI total score, the mean percent change from Baseline to Week 12 and 52 was –76.1% and –77.4% for secukinumab 300 mg and –67.3% and –65.5% for secukinumab 150 mg, correlating to the mean percent change in PASI score from Baseline. The proportion of patients achieving a DLQI 0/1 response increased continuously in both secukinumab groups at all visits up to Week 12, where it was significantly higher compared to placebo (secukinumab 300 mg, 41.6%; secukinumab 150 mg, 28.2%; placebo, 1.8%). These responses reached a maximum at Week 24, and were maintained until Week 52 for both secukinumab groups (secukinumab 300 mg, 47.5%; secukinumab 150 mg, 34.5%) [Figure 5].

Safety

Over the entire treatment period, adverse event (AE) rates were higher in patients receiving any dose of secukinumab compared to the placebo group (90.1% *vs.* 60.0%), however, exposure adjusted incidence rates (EAIRs) were lower (any dose of secukinumab, 345.5/100 patient-year; placebo, 536.9/100 patient-year). This suggests there is no increase in overall AEs with secukinumab relative to placebo after adjusting for exposure over the 52-week period. No dose-response relationships were observed for total AEs as indicated by the respective EAIR (secukinumab 300 mg, 449.6/100 patient-year; secukinumab 150 mg, 449.6/100 patient-year). Infections and infestations were the most frequently reported AEs, however, EAIR were comparable between patients receiving any dose of secukinumab and placebo (107.4/100 patient-year *vs.* 110.9/100 patient-year, respectively). The incidence of severe AEs was low and comparable in patients treated with any dose of secukinumab (2.1%) and placebo (0.9%).

No deaths were reported in this study. The overall EAIR of non-fatal serious AEs (SAEs) was low and comparable between any dose of secukinumab (3.0/100 patient-year)

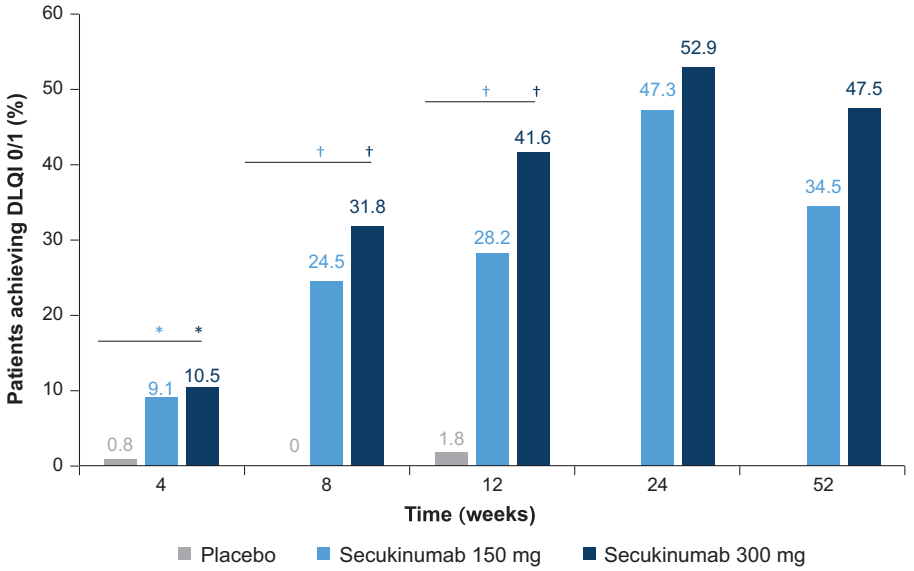

Figure 5: Patients achieving DLQI 0/1 response up to Week 52. Secukinumab 300 mg ($n = 221$), secukinumab 150 mg ($n = 110$), and placebo ($n = 110$). $^{*}P < 0.001$, $^{+}P < 0.0001$, significantly different from placebo. DLQI 0/1: Dermatology life quality index, clear (0) or almost clear (1) score.

and placebo (3.5/100 patient-year). A total of 15 patients reported 28 SAEs during the study. None of the SAEs were reported in more than one patient, with the exception of appendicitis and arteriosclerosis coronary artery, both reported in two patients each. Four patients reported a SAE that led to study discontinuation and were considered related to the study drug. These SAEs included isolated cases of Crohn disease (patient had an active medical condition of colon adenoma at study entry), pyrexia, mild pemphigus, and mouth ulceration.

Regarding immunogenicity, anti-drug antibodies (ADAs) were detected in 12 secukinumab-treated patients with four patients reporting treatment-emergent ADAs. Positive ADAs were not associated with any effect on pharmacokinetics or loss of efficacy.

Discussion

According to a hospital-based study of 12,000 psoriasis outpatients, it is reported that over 70% of Chinese psoriasis patients have severe disease as measured by PASI scores.[9] Although ultraviolet and systemic treatments are used in some patients with severe diseases, topical treatment and TCM are widely used.

Compared to FIXTURE and ERASURE, pivotal Phase 3 trials with primarily western populations,[16] patients in this study exhibited a substantial burden of disease with a higher mean PASI (26.8 *vs.* 23.7 [FIXTURE] and 22.1 [ERASURE]), BSA involvement (45.4% *vs.* 34.4% [FIXTURE] and 31.9% [ERASURE]) and rate of severe disease (44.7% *vs.* 38.3% [FIXTURE] and 36.9% [ERASURE]) at Baseline. This is in line with other analyses comparing psoriatic disease characteristics in Asian populations to western populations.[23] Secukinumab demonstrated high efficacy and a favorable safety profile up to 52 weeks of treatment in a Chinese population with a high disease burden.

The superiority of both secukinumab doses over placebo was shown with respect to the co-primary efficacy endpoints of PASI 75 and IGA 0/1 at Week 12. More than 80% of patients receiving secukinumab 300 mg achieved clear/almost clear skin (IGA 0/1). As with all clinical measures of efficacy examined, a larger proportion of secukinumab 300 mg patients exhibited an IGA 0/1 response compared to secukinumab 150 mg.

With more efficacious psoriasis treatment options available to patients, ambitious treatment targets (PASI 90 or PASI 100) are becoming more attainable.[24] This is reflected in the present study where a large proportion of secukinumab-treated patients achieved a PASI 90 response at Week 12 (81.0% and 65.7% for 300 and 150 mg, respectively). A state of complete skin clearance (PASI 100) was achieved in one-third of secukinumab 300 mg treated patients, and one-fifth of 150 mg patients at Week 12. PASI 100 continued to increase through to Week 52 with both secukinumab doses.

Patients' mean PASI at Baseline in the present study was approximately 21% higher than in the ERASURE trial.[16] A criticism of the PASI 75 and PASI 90 scores is that they do not take Baseline disease severity into account, and; therefore, patients with more severe disease who achieve PASI 75/90 may still be dissatisfied with their results. Recently, it has been suggested that absolute scores, more specifically an absolute PASI ≤ 3, maybe a better benchmark of therapeutic success.[24] At Week 12, the mean PASI scores in both secukinumab treatment groups were well below a threshold of ≤ 3. Indeed in the secukinumab 300 mg group, the mean absolute PASI dropped below 3 from as early as Week 8, demonstrating

the rapid response to treatment in this cohort, which was maintained through to Week 52.

Patients' clinical responses to secukinumab tended to be greater in this study than those reported in western pivotal trials.[16] In the secukinumab 300 mg treatment group for instance, PASI 75/90/100 responses at Week 12 were 97.7%, 81.0%, and 32.9%, in comparison to 77.7%, 54.2% and 24.1% in FIXTURE and 81.6%, 59.2%, and 28.6% in ERASURE. We hypothesize that certain differences in Baseline demographics between study populations may have influenced clinical responses. For example, patients in the current study had a lower mean bodyweight in comparison to those in FIXTURE and ERASURE (73.0 kg *vs.* 83.3 and 88.5 kg, respectively). In addition, a large proportion of Chinese patients in this study had never smoked (62.6%) in comparison to patients in FIXTURE (46.4%) and ERASURE (41.9%). Further, the percentage of patients with previous biologic exposure was lower in the current study: 18.1% compared to 29.3% in ERASURE, although the rates were similar to the FIXTURE trial (12.5%).

This study demonstrates numerical superiority of secukinumab over other biologics investigated in Phase 3 trials of Chinese-specific populations. Secukinumab achieved a higher PASI 75 at Week 12 (97.7%) compared to both adalimumab (77.8%)[25] and ustekinumab (82.5%).[22] In addition to having increased efficacy in a Chinese-specific population, secukinumab demonstrated similar safety profiles to adalimumab and ustekinumab in relation to SAEs and infections. In line with previous secukinumab clinical trials, the safety profile of secukinumab remained favorable with no new safety signals identified up to Week 52 in Chinese patients.

Psoriasis is associated with a significant impairment in QoL.[26] In the current study, the proportion of patients reporting no effect of skin disease on QoL (DLQI 0/1) increased continuously in both secukinumab groups, with secukinumab 300 mg showing superiority over secukinumab 150 mg at Weeks 4, 8, 12, 24, and 52.

Key Findings/Conclusions

The results of this study confirm the high efficacy of secukinumab in Chinese patients with moderate to severe plaque psoriasis. Both doses of secukinumab were superior to placebo in all key outcomes measured, while secukinumab 300 mg showed numerically greater efficacy and QoL compared to secukinumab 150 mg up to Week 52. No dose-dependent increases in the incidence of AEs, and no new or unexpected safety signals were observed.

Data Availability

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Acknowledgements

The authors thank Trudy McGarry, PhD of Novartis Ireland Ltd. for providing medical writing support/editorial support, which was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Funding

This study was sponsored by Novartis Pharma AG, Basel, Switzerland.

Conflicts of interest

Lin Cai has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, AbbVie, Pfizer Inc. Jian-Zhong Zhang has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc. Xu Yao has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Jun Gu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Henlius, and Pfizer Inc. Quan-Zhong Liu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Min Zheng has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from AbbVie, Janssen-Cilag, Boehringer Ingelheim, LEO Pharma China, Xian-Janssen, Novartis, and Pfizer Inc. Shi-Fa Zhang has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Janssen-Cilag, Henlius. Jin-Hua Xu has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Kyowa Kirin, and Pfizer Inc. Cheng-Xin Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, AbbVie, Bayer, Janssen-Cilag, Kyowa Kirin, and Pfizer Inc. Hao Cheng has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, AbbVie, Bayer, Janssen-Cilag, Henlius, and Pfizer Inc. Qing Guo has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc. Wei-Li Pan has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay

China, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc. Shen-Qiu Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Ruo-Yu Li has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Bayer, Janssen-Cilag, MSD, and Pfizer Inc. Zai-Pei Guo has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag, and Pfizer Inc. Zhi-Qi Song has participated in advisory boards and/or as an investigator and/or speaker and received grants and/or honoraria from LEO Pharma China, Novartis, Sanofi, La Roche-Posay China, AbbVie, Bayer, Janssen-Cilag, Henlius, Kyowa Kirin, and Pfizer Inc. Shan-Shan Li has participated as an investigator and received honoraria from Novartis China. Xiu-Qin Dong has participated in advisory boards and/or as an investigator and/or speaker and received honoraria from LEO Pharma China, Novartis, Sanofi, AbbVie, Bayer, Janssen-Cilag. Linda Wang, Rong Fu, Pascaline Regnault, Pascal Charef, Rafal Mazur, and Manmath Patekar are employed by Novartis.

References

1. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Ann Rheum Dis* 2013;72:736–740. doi: 10.1136/annrheumdis-2012-201706.
2. Papadavid E, Katsimbri P, Kapniari I, Koumaki D, Karamparpa A, Dalamaga M, *et al*. Prevalence of psoriatic arthritis and its correlates among patients with psoriasis in Greece: results from a large retrospective study. *J Eur Acad Dermatol Venereol* 2016;30:1749–1752. doi: 10.1111/jdv.13700.
3. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based multinational assessment of psoriasis and psoriatic arthritis (MAPP) survey. *Rheumatol Ther* 2016;3:91–102. doi: 10.1007/s40744-016-0029-z.
4. Puig L. Cardiometabolic comorbidities in psoriasis and psoriatic arthritis. Int J Mol Sci 2017;19:58. doi: 10.3390/ijms19010058.
5. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005;64:pii18–23. doi: 10.1136/ard.2004.033217.
6. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol* 2014;70:512–516. doi: 10.1016/j.jaad.2013.11.013.
7. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *J Am Acad Dermatol* 2009;60:218–224. doi: 10.1016/j.jaad.2008.09.022.
8. Ding X, Wang T, Shen Y, Wang X, Zhou C, Tian S, *et al*. Prevalence of psoriasis in China: a population-based study in six cities. *Eur J Dermatol* 2012;22:663–667. doi: 10.1684/ejd.2012.1802.
9. Chen K, Wang G, Jin H, Xu J, Zhu X, Zheng M, *et al*. Clinic characteristics of psoriasis in China: a nationwide survey in over 12000 patients. *Oncotarget* 2017;8:46381–46389. doi: 10.18632/oncotarget.18453.
10. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. *Clin Rev Allergy Immunol* 2018;55:379–390. doi: 10.1007/s12016-018-8702-3.
11. Zeichner JA, Armstrong A. The role of IL-17 in the pathogenesis and treatment of psoriasis. *J Clin Aesthet Dermatol* 2016;9:S3–S6.
12. Bagel J, Duffin KC, Moore A, Ferris LK, Siu K, Steadman J, *et al*. The effect of secukinumab on moderate-to-severe scalp psoriasis: results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. *J Am Acad Dermatol* 2017;77:667–674. doi: 10.1016/j.jaad.2017.05.033.
13. Armstrong AW, Vender R, Kircik L. Secukinumab in the treatment of palmoplantar, nail, scalp, and pustular psoriasis. *J Clin Aesthet Dermatol* 2016;9:S12–S16.
14. Deodhar AA, Dougados M, Baeten DL, Cheng-Chung Wei J, Geusens P, Readie A, *et al*. Effect of secukinumab on patient-reported outcomes in patients with active ankylosing spondylitis: a phase III randomized trial (MEASURE 1). *Arthritis Rheumatol* 2016;68:2901–2910. doi: 10.1002/art.39805.
15. Strand V, Mease P, Gossec L, Elkayam O, van den Bosch F, Zuazo J, *et al*. Secukinumab improves patient-reported outcomes in subjects with active psoriatic arthritis: results from a randomised phase III trial (FUTURE 1). *Ann Rheum Dis* 2017;76:203–207. doi: 10.1136/annrheumdis-2015-209055.
16. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, *et al*. Secukinumab in plaque psoriasis–results of two phase 3 trials. *N Engl J Med* 2014;371:326–338. doi: 10.1056/NEJMoa1314258.
17. Bissonnette R, Luger T, Thaci D, Toth D, Lacombe A, Xia S, *et al*. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). *J Eur Acad Dermatol Venereol* 2018;32:1507–1514. doi: 10.1111/jdv.14878.
18. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, *et al*. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008;58:106–115. doi: 10.1016/j.jaad.2007.09.010.
19. Papp KA, Miller B, Gordon KB, Caro I, Kwon P, Compton PG, *et al*. Efalizumab retreatment in patients with moderate to severe chronic plaque psoriasis. *J Am Acad Dermatol* 2006;54 (4 Suppl 1):S164–S170. doi: 10.1016/j.jaad.2005.10.032.
20. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371:1675–1684. doi: 10.1016/S0140-6736(08)60726-6.
21. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665–1674. doi: 10.1016/S0140-6736(08)60725-4.
22. Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary PO, *et al*. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). *J Drugs Dermatol* 2013;12:166–174.
23. Tsai YC, Tsai TF. A review of clinical trials of biologic agents and small molecules for psoriasis in Asian subjects. *G Ital Dermatol Venereol* 2016;151:412–431.
24. Gladman DD, Poulin Y, Adams K, Bourcier M, Barac S, Barber K, *et al*. Treating psoriasis and psoriatic arthritis: position paper on applying the treat-to-target concept to Canadian daily practice. *J Rheumatol* 2017;44:519–534. doi: 10.3899/jrheum.161473.
25. Cai L, Gu J, Zheng J, Zheng M, Wang G, Xi LY, *et al*. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study. *J Eur Acad Dermatol Venereol* 2017;31:89–95. doi: 10.1111/jdv.13746.
26. Armstrong AW, Schupp C, Wu J, Bebo B. Quality of life and work productivity impairment among psoriasis patients: findings from the National Psoriasis Foundation survey data 2003-2011. *PLoS One* 2012;7:e52935. doi: 10.1371/journal.pone.0052935.

How to cite this article: Cai L, Zhang JZ, Yao X, Gu J, Liu QZ, Zheng M, Zhang SF, Xu JH, Li CX, Cheng H, Guo Q, Pan WL, Li SQ, Li RY, Guo ZP, Song ZQ, Li SS, Dong XQ, Wang L, Fu R, Regnault P, Charef P, Mazur R, Patekar M. Secukinumab demonstrates high efficacy and a favorable safety profile over 52 weeks in Chinese patients with moderate to severe plaque psoriasis. Chin Med J 2020;133:2665–2673. doi: 10.1097/CM9.0000000000001163