Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study


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Summary

Background Interleukin (IL)-17A has major proinflammatory activity in psoriatic lesional skin.

Objectives To assess the efficacy and safety of secukinumab, a fully human IgG1κ monoclonal anti-IL-17A antibody, in moderate-to-severe plaque psoriasis in a phase II regimen-finding study.

Methods A total of 404 patients were randomized to subcutaneous placebo (n = 67) or one of three secukinumab 150 mg induction regimens: single (week 0; n = 66), early (weeks 0, 1, 2, 4; n = 133) and monthly (weeks 0, 4, 8; n = 138 patients). The primary outcome was ≥ 75% improvement from baseline Psoriasis Area and Severity Index score (PASI 75) at week 12. PASI 75 responders from active treatment arms at week 12 were rerandomized to either a fixed-interval (secukinumab 150 mg at weeks 12 and 24; n = 65) or a treatment-at-start-of-relapse maintenance regimen (secukinumab 150 mg at visits at which a start of relapse was observed; n = 67).

Results At week 12, early and monthly induction regimens resulted in higher PASI 75 response rates vs. placebo (54.5% and 42.0% vs. 1.5%; P < 0.001 for both). Among PASI 75 responders at week 12 entering the maintenance period, PASI 75 and PASI 90 achievement at least once from week 20 to week 28 was superior with the fixed-interval regimen [85% (n = 55) and 58% (n = 38), respectively] vs. the start-of-relapse regimen [67% (n = 45), P = 0.020, and 21% (n = 14), respectively]. Fifteen weeks after last study drug administration, < 10% of patients in the fixed-interval and start-of-relapse groups experienced a start of relapse. No immunogenicity was observed, and no injection-site reactions were reported. Reported cases of neutropenia were mild-to-moderate (≤ grade 2); none was associated with clinically significant adverse events or resulted in study discontinuation. Due to the brief duration of the safety assessment, no firm conclusions can be drawn regarding long-term safety.

Conclusions Secukinumab shows efficacy for induction and maintenance treatment of moderate-to-severe plaque psoriasis.
Plaque psoriasis, which accounts for 90% of psoriasis cases, is a chronic, immune-mediated skin disease associated with impaired quality of life. Psoriasis affects up to 1–3% of the population worldwide.

Advances in the understanding of psoriasis pathogenesis have allowed the development of biologics targeting cytokines involved in the psoriatic inflammatory process. The proinflammatory cytokine interleukin (IL)-17A has been identified within psoriatic plaques and is recognized as playing a key role in the disease. Whereas the T helper (Th)1–Th2 paradigm has traditionally provided a framework for understanding T-cell biology and the interplay between innate and adaptive immunity, IL-17A was recently shown to be produced by Th17 cells, a distinct lineage of effector T cells.

Secukinumab (Novartis Pharma AG, Basel, Switzerland) is a fully human IgG1 monoclonal antibody that selectively binds and neutralizes IL-17A. In proof-of-concept studies, secukinumab showed efficacy and tolerability in patients with moderate-to-severe plaque psoriasis, rheumatoid arthritis and chronic noninfectious uveitis. Here, we report the results of a phase II study evaluating the safety and efficacy of three induction regimens of secukinumab in patients with moderate-to-severe plaque psoriasis. The trial also investigated maintenance treatment strategies with secukinumab administered either at fixed intervals (i.e. continuous treatment) or at the start of relapse after a secukinumab-free interval. A separate, dose-ranging study of secukinumab was also conducted in a similar patient population as part of the phase II development programme; in this study, patients were randomized to receive subcutaneous doses of secukinumab (1 × 25 mg, 3 × 25 mg, 3 × 75 mg or 3 × 150 mg) or placebo at weeks 0, 4 and 8.

Materials and methods

Study design

This phase II, randomized, double-blind, placebo-controlled, parallel-group study was conducted between July 2009 (first patient first visit) and December 2010 (last patient last visit) at 60 centres in France, Germany, Iceland, Israel, Japan, Norway and the U.S.A. The study consisted of screening, induction, maintenance and follow-up periods (Fig. 1). It was conducted after approval from an institutional review board or ethics committee at each participating site and in accordance with the ethical principles of the Declaration of Helsinki. Patients provided written consent. The trial is registered at ClinicalTrials.gov, number NCT00941031; the full study protocol is available from the study sponsor.

For the 12-week induction period, patients were randomly assigned in a 1 : 2 : 2 : 1 ratio to one of three subcutaneous secukinumab 150 mg regimens – single (dosing at week 0), monthly (dosing at weeks 0, 4 and 8) or early (dosing at weeks 0, 1, 2 and 4) – or to matching placebo (dosing at weeks 0, 1, 2, 4 and 8). Patients achieving at least 75% improvement from baseline in the Psoriasis Area and Severity Index score (PASI 75) in the active treatment arms were considered responders and rerandomized (1 : 1) at week 12 to one of two regimens for the 20-week maintenance period: either treatment at fixed intervals (subcutaneous secukinumab 150 mg at weeks 12 and 24, and placebo at a regularly scheduled study visit at which a start of relapse was observed); or treatment at start of relapse (placebo administration at week 12 and at week 24 in the absence of start of relapse, and subcutaneous secukinumab 150 mg at start of relapse detected during a regularly

![Fig 1. Study design and dosing regimens. *At any scheduled visit after week 12, if a patient experienced start of relapse, secukinumab or placebo was administered (blinded). †In the absence of start of relapse, placebo was administered; if start of relapse was observed, then secukinumab was administered. ‡Follow-up visits at 4, 8 and 12 weeks after the last study drug administration at week 32. s.c., subcutaneously.](https://example.com/fig1.png)
scheduled study visit). Start of relapse was defined as loss of one-third of maximum PASI improvement (compared with baseline) achieved at any visit after week 12. Randomization was stratified according to body weight (≥ 90 kg or < 90 kg).

Three categories of patients were eligible to enter an open-label phase at week 12, in which they received subcutaneous secukinumab 150 mg every 4 weeks until week 32: non-responders [patients not achieving at least 50% improvement from baseline in their PASI score (PASI 50) at week 12]; partial responders (patients achieving PASI 50, but not PASI 75, at week 12); and patients in whom two consecutive relapses (defined as at least 50% loss of best PASI gain achieved previously during the study) were observed at scheduled visits from week 12 onwards.

All randomized patients entered the treatment-free follow-up period 4 weeks after last study drug administration, for a total safety monitoring duration of 12 weeks. Patients completing 4 weeks of follow-up were eligible to enter an extension study; in this case, they proceeded directly into the extension study without completing follow-up weeks 5–12.

Randomization and masking

Randomization numbers were generated by the interactive response technology provider using a validated system that automated the random assignment of patient numbers to randomization numbers. The randomization numbers were linked to the different treatment arms, which in turn were linked to medication numbers. A separate medication randomization list was generated under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing the study drugs. Patients, investigator staff, persons performing the assessments and data analysts were blinded to the identity of the treatment from the time of randomization until primary outcome analysis. After the primary outcome analysis, the study sponsor team was unblinded; the patients, local monitors, investigator staff and persons performing the assessments remained blinded until final database lock.

Role of the funding source

The study was sponsored by Novartis Pharma AG. Academic advisors and Novartis personnel designed the study. Novartis conducted the data analyses, and all authors had access to the data and vouch for the completeness and accuracy of the data and data analyses. The first draft of the manuscript was written by a medical writer employed by Novartis, with inputs and critical revisions from all authors. All authors reviewed and provided feedback on the subsequent versions and agreed to submit the manuscript for publication. The corresponding author had final responsibility for the decision to submit for publication.

Patients

Patients aged ≥ 18 years with moderate-to-severe plaque psoriasis [PASI score ≥ 12, Investigator’s Global Assessment (IGA) score ≥ 3, and body surface area involvement ≥ 10%] for at least 6 months were eligible for the study if their disease was inadequately controlled by topical treatments, phototherapy or previous systemic therapy. Exclusion criteria included psoriasis other than chronic plaque-type; ongoing use of prohibited psoriasis treatments such as conventional systemic therapy (e.g. methotrexate, cyclosporin), biologic systemic therapy (e.g. adalimumab, efalizumab, etanercept), topical or systemic corticosteroids, ultraviolet radiation therapy or other investigational drugs, within specified time periods prior to study entry (Table S1; see Supporting information); live vaccination within 6 weeks before first study drug administration; and known immunosuppression, active infection or history of active tuberculosis. Male patients and female patients of childbearing age were eligible if they were willing to use an effective method of contraception during the study and for 4 months after the last dose of study drug.

Outcomes and assessments

Disease activity was assessed using PASI (a composite score ranging from 0 to 72) and static IGA (6-point scale). IGA 0 or 1 response was defined as an IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline (Table S2).

The primary outcome was achievement of PASI 75 after 12 weeks of treatment vs. placebo. Key secondary outcomes were PASI 75 achievement at least once from weeks 20 to 28 and IGA response after 12 weeks of treatment. Other secondary outcomes included achievement of PASI 90 after 12 weeks of treatment vs. placebo.

Adverse events, vital signs and laboratory parameters were evaluated throughout the study. Blood samples for immunogenicity (antisecukinumab antibodies) were taken prior to dosing at the scheduled time points. Antisecukinumab antibodies were assessed in serum using the Biacore technology (surface plasmon resonance; GE Healthcare, Piscataway, NJ, U.S.A.). A disease-specific cut-off calculated from predose samples was used as a threshold to distinguish between samples screening positive or negative. In addition to samples above the cut-off, samples that showed an increase from predose to later visits of > 10 resonance units (RU; rationale is the acceptance of a 10-RU variance in the drug immobilization level stated in the method validation) in the screening assay and samples with a technical problem in the screening assay were reanalysed in a confirmation assay.

Statistical analyses

Sample size calculations were performed using NQUERY software (Statistical Solutions Ltd, Cork, Ireland). Sample size
calculation was based on the key secondary outcome of achievement of PASI 75 at least once from week 20 to week 28. A sample size of 62 patients per maintenance treatment group (pooling monthly and early) was required to reach a power of 80% applying a 1:1 randomization ratio for the two maintenance regimens, assuming that 90% of patients in the fixed-interval treatment group and 70% in the start-of-relapse treatment group were PASI 75 responders at least once from weeks 20 to 28. Hence, 124 patients with achievement of PASI 75 at week 12 were needed in the monthly and early arms. Assuming a PASI 75 response rate of 50% for these groups, at least 124 patients were needed to be randomized to the monthly and early induction groups. With a randomization scheme of 1:2:2:1 for single: monthly: early: placebo, the total sample size was at least 62 + 124 + 124 + 62 = 372. Given uncertainties with respect to response rates after 12 weeks of treatment, the aim was to randomize 396 patients in total (single: monthly: early: placebo = 66:132:132:66).

A primary outcome analysis was performed after all patients had completed the study visit at week 12. An interim analysis was performed after 103 patients had completed the visit at week 28 to assess appropriate induction and maintenance regimens for the pivotal phase III trials. The full analysis set comprised all patients who were randomized at week 0 and was identical to the randomized set. The safety analysis set included all patients who took at least one dose of study drug and had at least one post-baseline safety assessment. Following the intent-to-treat principle, data were analysed according to patients’ treatment assignment and bodyweight stratum at randomization.

Demographic and other baseline characteristics were summarized descriptively. The primary outcome was analysed by Dunnett’s test procedure for proportions; additional sensitivity analyses included the stratified Cochran–Mantel–Haenszel (CMH) test, with region and bodyweight as strata, and logistic regression to assess the effect of bodyweight and baseline PASI. The active treatment groups were also compared using the CMH test and logistic regression. Missing values were replaced using the last-observation-carried-forward approach. However, data observed during follow-up were also considered for early discontinuations. Adverse events were summarized by absolute and relative frequencies, by treatment group.

For safety analyses, patients who were allocated to placebo at randomization and received ≤2, 3 or ≥4 active treatments during the induction period were analysed in the single, monthly and early regimens, respectively.

In cases where a patient was allocated to placebo during randomization and received active treatment at least once during the maintenance period, patients switching to open-label were analysed in the open-label group, whereas those not switching from placebo to open-label who received active treatment during the maintenance period were analysed in the fixed-interval group (if they received active treatment doses at weeks 12 and 24 only) and in the start-of-relapse group.

Results

Patients

Of 404 randomized patients, 380 (94.1%) completed the induction period and 24 (5.9%) discontinued, primarily due to unsatisfactory therapeutic effect, withdrawal of consent and adverse events (Fig. 2). One patient discontinued the study after completing the induction period. In total, 379 patients entered the maintenance period, of whom 321 (84.7%) completed the study. Patient demographic features and baseline characteristics are summarized in Table 1.

Efficacy

Primary outcome

After 12 weeks of treatment, the secukinumab early and monthly induction regimens resulted in significantly higher rates of PASI 75 response than placebo [54.5% (n = 72) and 42.0% (n = 58), respectively, vs. 1.5% (n = 1); P < 0.001 for both], while the single regimen did not [10.6% (n = 7); P = 0.225] (Fig. 3a).

Secondary outcomes

PASI 90 response rates were significantly greater with the early and monthly regimens than with placebo [31.8% (n = 42) and 17.4% (n = 24), respectively, vs. 1.5% (n = 1); P < 0.001 for both] but not with the single regimen [3.0% (n = 2); P = 0.556] (Fig. 3b).

At week 12, the early and monthly induction groups achieved a significantly higher IGA 0 or 1 response rate than the placebo group [37.1% (n = 49) and 22.6% (n = 31) vs. 1.5% (n = 1); P < 0.001 and P = 0.003 for early and monthly regimens, respectively], but the single regimen group did not [4.5% (n = 3); P = 0.338 vs. placebo] (Fig. 3c).

Among the PASI 75 responders at week 12 entering the maintenance period, achievement of PASI 75 at least once from week 20 to week 28 was superior with the fixed-interval regimen (85%, n = 55) vs. the start-of-relapse regimen (67%, n = 45; P = 0.020). Fifteen weeks after the last study drug administration, in both the fixed-interval and start-of-relapse groups, < 10% of patients experienced a start of relapse (Fig. 4; additional details in Table S3). The rate of PASI 90 achievement at least once from week 20 to week 28 was higher with the fixed-interval regimen (58%, n = 38) than with the start-of-relapse regimen (21%, n = 14). The IGA 0 or 1 response rate was significantly higher with the fixed-interval regimen (49%, n = 32) than with the start-of-relapse regimen (22%, n = 15; P = 0.002) at week 32.

Four weeks into the follow-up, 55% (n = 36) of patients on the fixed-interval regimen and 31% (n = 21) of patients on the start-of-relapse regimen showed a PASI 75 response. A PASI 90 response at week 4 of follow-up was achieved by 29% (n = 19) and 10% (n = 7) of patients in the fixed-interval and
start-of-relapse treatment arms, respectively. Of the partial responders and nonresponders at week 12 assigned to the open-label arm, 46.2% (n = 114) of patients achieved PASI 75 responder status 4 weeks into the follow-up. Four weeks after last study drug administration, 42% (n = 27) of patients in the fixed-interval regimen (P = 0.004 vs. start-of-relapse) and 18% (n = 12) of patients in the start-of-relapse arm showed IGA 0 or 1 response. In the open-label arm, 30.0% (n = 74) of patients achieved IGA response 4 weeks into the follow-up period.

Safety

The safety population consisted of all patients who took at least one dose of study drug and had at least one post-baseline safety assessment. The majority of adverse events reported were mild or moderate in severity in both the induction and the maintenance periods. No deaths occurred during the study.

During induction, the most frequently reported adverse events were nasopharyngitis (20.0%, n = 81), headache (6.9%, n = 28), and worsening of psoriasis (6.2%, n = 25). Overall, infections occurred in 34.9% (n = 141) of patients; most were mild or moderate in severity. Two patients had infections rated as serious: acute tonsillitis (single regimen) and bacterial pneumonia (early regimen). The proportion of patients experiencing an infection in the monthly (40.6%, n = 56), early (33.8%, n = 45) or single (21.1%, n = 14) group was similar to, or lower than that in the placebo group (39.0%, n = 26) (Table 2). Five patients discontinued treatment because of adverse events (worsening of psoriasis (single), pharyngitis (placebo) and bacterial pneumonia (early)) in one patient each and erythrodermic psoriasis in two patients (early); Table S4.

During the maintenance period, the most frequently reported adverse events were nasopharyngitis (12.1%, n = 46), worsening of psoriasis (7.1%, n = 27) and upper respiratory tract infections (5.0%, n = 19). Overall, 31.9%
(n = 121) of patients experienced infections, mostly mild or moderate in severity. Four patients had infections rated as serious: anal abscess (fixed-interval), appendicitis (start-of-relapse), enterocolitis and staphylococcal infection (cellulitis; open-label group). The proportion of patients experiencing an infection was slightly higher in the fixed-interval (29%, n = 19) and open-label (35%, n = 87) groups than in the start-of-relapse group (22%, n = 15). Overall, 10 patients discontinued treatment because of adverse events, eight in the open-label group [worsening of psoriasis, erythrodermic psoriasis, diarrhoea, appendicitis, ear infection, colon cancer, testicular cancer and rhabdomyosarcoma (considered by the investigators to be of viral origin) in one patient apiece] and two in the start-of-relapse group (prurigo and lower gastrointestinal haemorrhage; Table S5).

Serious adverse events were reported in 13 patients (3.2%) during the induction period; the percentage was slightly higher in the single (4.5%, n = 3) and early (4.5%, n = 6) regimen groups than in the monthly (2.2%, n = 3) and placebo (1.5%, n = 1) groups. During the maintenance period, serious adverse events were reported in 18 (4.7%) patients (fixed-interval 6.2%, n = 4, open-label 4.9%, n = 12, start-of-relapse 3.0%, n = 2). No evidence of immunogenicity against secukinumab was detected with either the fixed-interval (continuous therapy) or start-of-relapse regimen, and no injection-site reactions were reported during the course of the study. No significant shifts in clinical chemistry and haematology parameters, including lipid values, from baseline to the final post-baseline value relative to the normal range were reported during the induction or maintenance period. Grade 1 or 2 neutropenia was reported in 20 patients [19 secukinumab (4.7%), one placebo (0.2%)] in the induction phase and in 30 secukinumab patients (7.9%) in the maintenance phase; it resolved during the course of the study in all cases. No cases of grade 3 or 4 neutropenia were reported; no clinically significant adverse events were associated with the development of neutropenia; and no patients discontinued the study due to neutropenia.

During the follow-up period, seven serious adverse events were reported in six patients [monthly/open-label: malignant lung neoplasm, malignant melanoma in situ, worsening of psoriasis; placebo/open-label: bladder cancer (reporting already for the maintenance period), ventricular fibrillation, septic shock; placebo: breast cancer]. For the subgroup of patients in follow-up treated only in the induction period, the overall percentage of patients experiencing an adverse event was 20% (n = 5). For the subgroup of patients in follow-up treated in the maintenance period, the overall percentage of patients experiencing an adverse event was 24% (n = 25).

**Bodyweight analysis**

The analysis of the effect of bodyweight on treatment response in the induction period showed slightly higher PASI 75 response rates for all the treatment regimens among patients weighing <90 kg [single: 18% (n = 6); monthly: 53.6% (n = 37); early: 60.9% (n = 42); placebo: 3% (n = 1)] than among those weighing ≥90 kg [single: 3% (n = 1); monthly: 30.4% (n = 21); early: 47.6% (n = 30); placebo: 0% (n = 0)].
Fig 3. Clinical response to treatment over time, as assessed by Psoriasis Area and Severity Index (PASI) and Investigator’s Global Assessment (IGA). By week 12, a significantly higher rate of PASI 75 response (a) and PASI 90 response (b) was achieved in patients on the early and monthly induction regimens; IGA 0 or 1 response rate for overall psoriatic disease was significantly higher with the early and monthly induction regimens (c). Patients on the fixed-interval regimen received the last dose of study drug at week 24; patients on the start-of-relapse regimen received the last dose of study drug based on their individual start of relapse; and in the open-label phase, nonresponders and partial responders were treated with secukinumab every 4 weeks, with the last dose at week 32. *P < 0.001 vs. placebo; **P = 0.003 vs. placebo.

Fig 4. Cumulative incidence rate for time to start of relapse.
Weeks 8, 12, and 32. It is important to note that significantly different from placebo). This suggests that a loading response rate was seen with the single regimen (not significantly higher PASI 75 response rates achieved with the early and monthly regimens than with placebo after 12 weeks of treatment. Based on the PASI 75 and IGA 0 or 1 responses at week 32. With the fixed-interval regimen, more than two-thirds (71%, n = 46) of patients maintained their PASI 75 response before retreatment at week 24; moreover, the majority (95%, n = 62) were PASI 75 responders 4 weeks after week 12 administration of secukinumab. In addition, a notable proportion of patients achieved PASI 75 responder status after 12 weeks of treatment with secukinumab every 4 weeks in the open-label phase. These results

Table 2. Adverse events during induction and maintenance period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Induction period (N = 404)</th>
<th>Maintenance period (N = 379)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secukinumab</td>
<td>Secukinumab</td>
</tr>
<tr>
<td></td>
<td>Single (n = 66)</td>
<td>Monthly (n = 138)</td>
</tr>
<tr>
<td></td>
<td>Early (n = 133)</td>
<td>Placebo (n = 67)</td>
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<tr>
<td></td>
<td>Fixed-interval (n = 65)</td>
<td>Start-of-relapse (n = 67)</td>
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<tr>
<td></td>
<td>Open-label (n = 247)</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>41 (62-1)</td>
<td>91 (65-9)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse event*</td>
<td>3 (4-5)</td>
<td>3 (2-2)</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>1 (1-5)</td>
<td>0</td>
</tr>
<tr>
<td>Common adverse events*</td>
<td>Nasopharyngitis</td>
<td>8 (12-1)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>6 (9-1)</td>
</tr>
<tr>
<td></td>
<td>Psoriasis*</td>
<td>6 (9-1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (4-5)</td>
<td>6 (43)</td>
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<td>Back pain</td>
<td>0</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (4-5)</td>
<td>1 (0-7)</td>
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<td>Cough</td>
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<td>2 (1-4)</td>
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<tr>
<td>Arthralgia</td>
<td>2 (3-0)</td>
<td>8 (5-8)</td>
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<tr>
<td>Infection</td>
<td>14 (21-2)</td>
<td>56 (40-6)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
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<td>0</td>
</tr>
<tr>
<td>Neoplasms, benign, malignant and unspecified (including cysts and polyps)</td>
<td>2 (3-0)</td>
<td>2 (1-4)</td>
</tr>
</tbody>
</table>

Values are n (%). *The serious adverse events during the induction period included: acute tonsillitis, colon adenoma and hypertensive crisis (single regimen), worsening of psoriasis, road traffic accident and abdominal pain (monthly regimen), erythrodermic psoriasis, angina pectoris, coronary artery disease, bacterial pneumonia, injury and acute respiratory failure (early regimen); and worsening of psoriasis (placebo). The serious adverse events during the maintenance period included: anal abscess, upper limb fracture, back pain, intervertebral disc disorder and hepatic cirrhosis (fixed-interval regimen); infectious enterocolitis and lower gastrointestinal haemorrhage (start-of-relapse regimen), and appendicitis, staphylococcal infection (cellulitis), bladder cancer (also reported in follow-up), colon cancer, testicular cancer, colonic stenosis, muscle injury, erythrodermic psoriasis, worsening of psoriasis, arrhythmia, cataract, rhabdomyolysis (considered by the investigators to be of viral origin) and nephrolithiasis in the open-label group. Includes events occurring in at least 5% of patients in any treatment group. Indicates worsening of psoriasis; the protocol suggested that psoriasis, being the studied indication, was not to be reported as an adverse event by the investigators.

Discussion

The results of this regimen-finding study of subcutaneously administered secukinumab induction and maintenance (continuous vs. start-of-relapse) therapy suggest that this agent is efficacious for the treatment of patients with moderate-to-severe plaque psoriasis. During the induction period, significantly higher PASI 75 response rates were achieved with the early and monthly regimens than with placebo after 12 weeks of treatment. Based on the PASI 75 and IGA 0 or 1 data, a clear regimen-response relationship was established: the highest response rate was achieved with the early regimen, followed by the monthly regimen, and a limited response rate was seen with the single regimen (not significantly different from placebo). This suggests that a loading dose of secukinumab is beneficial, based on the PASI and IGA 0 or 1 response at week 12. It is important to note that patients in the early arm did not receive secukinumab at week 8.

The results from the induction phase of our study corroborate the findings of an earlier proof-of-concept study of secukinumab in patients with moderate-to-severe plaque psoriasis. Combined with data presented in recently published studies of other investigational agents that act on the Th17 pathway, they reinforce the concept that IL-17A is a key proinflammatory cytokine and a valid therapeutic target in plaque psoriasis.

This study also provided insight into the maintenance of response with secukinumab. The fixed-interval (continuous treatment) regimen was effective for maintenance of PASI 75 and IGA 0 or 1 responses at week 32. With the fixed-interval regimen, more than two-thirds (71%, n = 46) of patients maintained their PASI 75 response before retreatment at week 24; moreover, the majority (95%, n = 62) were PASI 75 responders 4 weeks after week 12 administration of secukinumab. In addition, a notable proportion of patients achieved PASI 75 responder status after 12 weeks of treatment with secukinumab every 4 weeks in the open-label phase. These results...
Indicate that secukinumab every 4 weeks is an appropriate regimen for fixed-dose maintenance therapy; consequently, this regimen has been selected for use in upcoming phase III trials, which should enable more definitive conclusions regarding the efficacy of secukinumab as maintenance therapy.

Our results are the first to demonstrate the feasibility of treatment at start of relapse in plaque psoriasis. In the fixed-interval group, 71% (n = 46) of patients maintained PASI 75 response for 3 months after week 12 administration of secukinumab, indicating that these patients might not need retreatment earlier than this time point. These findings suggest that with an improved retreatment-at-start-of-relapse regimen, secukinumab may allow flexibility of dosing, including the ability to stop and restart treatment.

Overall, secukinumab was well tolerated. Most of the adverse events were mild or moderate in severity in both the induction and maintenance periods. No deaths occurred during this study. Serious adverse events were reported for 3.2% (n = 13) and 4.7% (n = 18) of patients in the induction and maintenance periods, respectively. Infections were the most commonly reported adverse events for the active-treatment as well as the placebo groups, but the majority of events were mild or moderate in severity. None of the patients developed antiseukinumab antibodies during the study; these findings are consistent with the efficacy reported for the start-of-relapse regimen. There were no reports of injection-site reactions, and reported cases of neutropenia were mild or moderate in severity. Moreover, no clinically significant adverse events were associated with the development of neutropenia, and no patients discontinued the study due to neutropenia. Due to the brief duration of the safety assessment, it should be noted, no firm conclusions can be drawn regarding the long-term safety of secukinumab.

In view of the limitation that our study did not contain a dose-ranging component, it is unclear whether better response rates could have been achieved with a higher dose. Dose-ranging data were gathered in a separate phase II study in a similar patient population;22 this study found that secukinumab 3 × 150 mg and 3 × 75 mg resulted in significantly higher PASI 75 response rates vs. placebo after 12 weeks of treatment (82% and 57% vs. 9%; P < 0.001 and P = 0.002, respectively); significant differences from placebo were not observed for the 3 × 25 mg and 1 × 25 mg dosage groups at this time point.22 In addition, during the maintenance period, patients received the last dose of secukinumab at different time points, adding complexity to the interpretation of results.

In conclusion, our results indicate that secukinumab is an efficacious therapy for patients with moderate-to-severe plaque psoriasis. A regimen–response relationship was established, with the early arm achieving the highest response rate. Based on the response–relapse results, secukinumab may offer patients and physicians the choice of either a fixed-interval treatment regimen or flexible dosing. Secukinumab was generally well tolerated. The clinical efficacy of secukinumab observed in this study supports the initiation of confirmatory phase III studies in moderate-to-severe plaque psoriasis.

**What’s already know about this topic?**
- Conventional systemic therapies for plaque psoriasis have not fully met patient needs.
- Biologics, although effective and generally well tolerated, have a still-developing long-term safety profile.
- Monoclonal antibodies against interleukin (IL)-17A have shown early promise.

**What does this study add?**
- In this regimen-finding study, the investigational anti-IL-17A monoclonal secukinumab (150 mg subcutaneously) showed significant efficacy for induction and maintenance treatment and was well tolerated in moderate-to-severe plaque psoriasis.
- Secukinumab may offer new therapeutic options in plaque psoriasis.

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**References**
9 Leonard CL, Kimball AB, Papp KA et al. PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-
Secukinumab induction/maintenance for moderate-to-severe plaque psoriasis, P. Rich et al.


Supporting information

Additional Supporting information may be found in the online version of this article.

Table S1. Prohibited treatments and duration of washout.
Table S2. Investigator’s Global Assessment (IGA) rating scale for overall psoriatic disease.
Table S3. Patients receiving secukinumab injections and relapse rate during maintenance period.
Table S4. Adverse events leading to permanent discontinuation of study drug by primary system organ class and preferred term, by induction treatment.
Table S5. Adverse events leading to permanent discontinuation of study drug by primary system organ class and preferred term, by maintenance treatment.

Figure S1. Psoriasis Area and Severity Index (PASI) 75 response rates in open-label phase for nonresponders and partial responders from induction regimens (single, monthly, and early) and placebo at week 12.

Appendix

P.R. has received honoraria for lecturing in industry-sponsored meetings and has received research grants from pharmaceutical companies as an investigator. B.S. has consulted for Novartis and several other pharmaceutical companies; he has served on an advisory board for Novartis and several other pharmaceutical companies. D.T. has served as a speaker and served on advisory boards for Abbott, Biogen-Idec, Janssen-Cilag, Leo, MSD, Novartis and Pfizer. C. Paul has received honoraria from and has been a paid consultant to Abbott, Amgen, Celgene, Janssen-Cilag, Novartis and Pierre Fabre. K.R., E.H., A.G., M.M. and C. Papavassilis are full-time employees of, and own stock in Novartis. J.-P.O., A.M. and R.E.S. declare no conflicts of interest.