Formulary Drug Reviews

Secukinumab

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Generic Name:	Secukinumab
Proprietary Name:	Cosentyx (Novartis)
Approval Rating:	1 BLA
Therapeutic Class:	Interleukin-17A (IL-17A) Modifiers; Monoclonal Antibodies
Similar Drugs:	Adalimumab, Alefacept, Etanercept, Infliximab, Ustekinumab
Sound- or Look-Alike Names:	Ustekinumab

INDICATIONS

Secukinumab is approved for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.¹ Secukinumab is also being evaluated for the treatment of psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and noninfectious uveitis.²⁻⁸

CLINICAL PHARMACOLOGY

Psoriasis is an immune-mediated chronic inflammatory disorder. Compared with healthy dermal tissue, psoriatic plaques show increased infiltration by activated T cells, which express proinflammatory cytokines, including interferon-gamma and tumor necrosis factor (TNF)-alpha from Th1 and Tc1 cells.⁹⁻¹⁴ Interleukin-17A (IL-17A) is a proinflammatory cytokine expressed by neutrophils, Th17, Tc17, mast cells, dendritic cells, natural killer cells, and gamma-delta T cells.^{9,10,13-15} Psoriatic plaques contain increased concentrations of IL-17A and IL-17A-producing cells.^{1,6,9,10,13-16} IL-17A acts on keratinocytes of the psoriatic plaque to increase expression of chemokines involved in recruiting neutrophils, Th17, and myeloid dendritic cells to the lesion site. Production of proinflammatory cytokines are induced by IL-17A and may help sustain a dermal immune response.^{10,14}

In patients with rheumatoid arthritis, IL-17A is thought to promote proinflammatory activities and cartilage degradation by induction of potent

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proinflammatory processes, such as stimulation of IL-1 and TNF production from macrophages, IL-6 and IL-8 secretion in synovial fibroblasts, and promotion of bone erosion via receptor activator of nuclear factor kappa B ligand upregulation.^{3,11,17,18} Secukinumab neutralizes the amplifying effect of IL-17. It has inhibited the release of the IL-6 of TNF-stimulated, fibroblast-like synoviocytes derived from patients with rheumatoid arthritis and has been shown to decrease serum C-reactive protein (CRP) in patients with moderate to severe plaque psoriasis.^{11,17-19}

Secukinumab is a fully human immunoglobulin G1 kappa monoclonal antibody that is highly selective for the IL-17A proinflammatory cytokine. Secukinumab selectively binds and neutralizes IL-17A.^{1,2,3,6,9,16,20} The molecule is produced from a recombinant Chinese hamster ovary cell line.¹

PHARMACOKINETICS

Following subcutaneous administration of secukinumab 25, 75, or 150 mg once monthly for 3 months, dose-proportional increases in concentration were observed. Trough secukinumab concentrations increased from the first dose until 4 weeks after the third dose in all treatment groups, indicating that steady state was not achieved after 3 doses.²⁰

Peak serum concentrations (C_{max}) occur within 6 days of a single subcutaneous injection of 150 or 300 mg. The mean C_{max} was 13.7 mcg/mL with secukinumab 150 mg and 27.3 mcg/mL with secukinumab 300 mg. The mean serum trough concentration was 22.8 mcg/mL with secukinumab 150 mg and 45.4 mcg/mL with secukinumab 300 mg at week 12 after multiple subcutaneous injections.¹ Secukinumab concentrations in interstitial fluid in lesional and nonlesional skin or in patients with plaque psoriasis ranged from 27% to 40% of serum levels at 1 and 2 weeks after a single subcutaneous injection.¹

Bioavailability after subcutaneous injection ranged from 55% to 77%.¹ The mean volume of distribution during the terminal phase ranged from 7.1 to 8.6 L in patients with plaque psoriasis.¹ Mean systemic clearance ranged from 0.14 to 0.22 L/day.¹ The mean elimination half-life ranged from 22 to 33 days.^{1,20} Steady-state concentrations of secukinumab were achieved by week 24 following the every-4-weeks dosing regimen.¹

The mean clearance and volume of distribution increased with increases in body weight.¹

The impact of hepatic or renal impairment on the pharmacokinetics of secukinumab has not been

determined.¹ No differences were observed in the apparent clearance of secukinumab in older and younger patients.¹

COMPARATIVE EFFICACY

Indication: Plaque Psoriasis

Guidelines

Guideline: Consensus guidelines for the management of plaque psoriasis

Reference: Hsu S, et al, 2012²¹

Comments: Adalimumab, alefacept, etanercept, and ustekinumab can be used as first-line treatment for moderate to severe plaque psoriasis. They all have similar efficacy and, compared with cyclosporine and methotrexate, they have a lower risk of adverse events. The use of secukinumab is not addressed within this guideline because it was not commercially available.

Studies

Drug: Secukinumab vs Etanercept

Reference: Langley RG, et al, 2014 (FIXTURE trial)^{6,22-24}

Study Design: Randomized, double-blind, double-dummy, placebo-controlled, active-comparator, multicenter, international trial

Study Funding: Novartis

Patients: 1,306 patients who have had chronic plaque-type psoriasis for at least 6 months and who have a severity grade of moderate to severe, defined as a Psoriasis Area and Severity Index (PASI) score greater than 12, an investigator's global assessment (IGA) score greater than 3, and involvement of greater than 10% of the body surface area (BSA). Patients were also inadequately controlled by prior treatments with topicals, phototherapy, and/or systemic therapies. Baseline patient demographics were age of about 44 years, 68.5% to 72.7% were male, and approximately 67% of patients were White and approximately 22% were Asian. Patient body weight averaged approximately 83 kg; involved BSA was approximately 34%; and approximately 15% had psoriatic arthritis. Previous therapies consisted of any systemic psoriasis therapy (64%), conventional therapy (61%), and biologic systemic agents (13%).

Intervention: Patients were randomized 1:1:1:1 to receive secukinumab 150 or 300 mg, etanercept 50 mg, or matching placebos subcutaneously for

52 weeks. Treatments were given in a double-dummy fashion to maintain blinding. Secukinumab was given at baseline; at weeks 1, 2, 3, and 4; and then every 4 weeks from week 4 through 48. Etanercept was given twice weekly from baseline to week 12, and then once weekly through week 51. At week 12, placebo-treated patients who did not achieve a 75% improvement in PASI (PASI 75) were re-randomized to secukinumab 150 or 300 mg.

Results

Primary Endpoint(s)

- Secukinumab showed improved efficacy over placebo and etanercept. The percentage of patients who achieved PASI 75 at week 12 was 77.1% in the secukinumab 300 mg group, 67% in the secukinumab 150 mg group, 44% in the etanercept 50 mg group, and 4.9% in the placebo group ($P < .001$ for secukinumab vs etanercept and placebo).
- Subgroup analysis of patients with both plaque-type psoriasis and psoriatic arthritis ($n = 192$) found that the PASI 75 at week 12 was 72% for the secukinumab 300 mg group, 59% for the secukinumab 150 mg group, 39% for the etanercept 50 mg group, and 2% for the placebo group.
- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 was 62.5% in the secukinumab 300 mg group, 51.1% in the secukinumab 150 mg group, 27.2% in the etanercept group, and 2.8% in the placebo group ($P < .001$ for secukinumab vs etanercept and placebo).

Secondary Endpoint(s)

- Achievement of PASI 90 at week 12 occurred in 54.2% of the secukinumab 300 mg group, 41.9% of the secukinumab 150 mg group, 20.7% of the etanercept group, and 1.5% of the placebo group ($P < .001$ for secukinumab vs etanercept and placebo).
- Subgroup analysis of patients with both plaque-type psoriasis and psoriatic arthritis ($n = 192$) found the PASI 90 at week 16 was achieved by 39% of patients in the secukinumab 150 mg treatment group ($P < .01$ vs placebo; $P < .01$ vs etanercept 50 mg), 44% in the secukinumab 300 mg treatment group ($P < .01$ vs placebo), 18% in the etanercept 50 mg treatment group, and 2% in the placebo group. Responses were sustained through week 52.
- Achievement of PASI 100 at week 12 occurred in 24.1% of the secukinumab 300 mg group,

14.4% of the secukinumab 150 mg group, 4.3% of the etanercept group, and 0% of the placebo group ($P < .001$ for secukinumab vs etanercept and placebo).

- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 to 52 was 79.7% in the secukinumab 300 mg group ($P < .001$ vs etanercept), 67.7% in the secukinumab 150 mg group ($P = .002$ vs etanercept), and 56.8% in the etanercept group.

Comments: Phase 3 clinical trial. Secukinumab was better than etanercept for the treatment of plaque psoriasis in this study. On average, patients' symptoms were halved at weeks 3 and 8 with secukinumab 300 mg and etanercept 50 mg, respectively. The incidence of adverse events was similar between both secukinumab doses and etanercept. The most common adverse events in any treatment group, including placebo, were nasopharyngitis and headache. The preliminary results from the Comparison to Assess Long-term Efficacy, Safety and Tolerability of Secukinumab versus Ustekinumab (CLEAR) trial, another phase 3 clinical trial, showed that secukinumab was superior to ustekinumab based on the change in the PASI 75 at week 4 and PASI 90 score at week 16.^{25,26}

Drug: Secukinumab vs Placebo

Reference: Gottlieb A, 2013 (SCULPTURE trial)^{27,28}

Study Design: Randomized, double-blind, multicenter, international trial

Study Funding: Novartis

Patients: 738 patients with moderate to severe chronic plaque-type psoriasis, defined as a PASI score greater than 12, an IGA score greater than 3, and involvement of greater than 10% of BSA, for at least 6 months and inadequate control of psoriasis symptoms despite prior treatments with topicals, phototherapy, and/or systemic therapies.

Intervention: Patients were randomized 1:1:1 to receive secukinumab 150 or 300 mg or placebo subcutaneously at weeks 1, 2, and 3, and then every 4 weeks for 48 weeks. Patients who did not achieve PASI 75 at week 12 were re-randomized (1:1) to secukinumab 150 or 300 mg.

Results

Primary Endpoint(s)

- Percentage of patients maintaining a PASI 75 response relative to baseline after having

achieved PASI 75 response after 12 weeks of secukinumab treatment.

- In a subgroup of patients with both plaque-type psoriasis and psoriatic arthritis ($n = 171$), the percentage of patients who achieved PASI 75 at week 12 was 70% in the secukinumab 150 mg group, 68% in the secukinumab 300 mg group, and 4% in the placebo group. Percentage of patients maintaining PASI 75 for up to 1 year was 61% with secukinumab 150 mg and 68% with secukinumab 300 mg.

Secondary Endpoint(s)

- In a subgroup of patients with both plaque-type psoriasis and psoriatic arthritis ($n = 171$), PASI 90 response at week 12 was 44%, 53%, and 0% in the secukinumab 150 mg, secukinumab 300 mg, and placebo groups, respectively.
- Percentage of patients maintaining PASI 90 for up to 1 year was 37% with secukinumab 150 mg and 56% with secukinumab 300 mg.
- The change in Health Assessment Questionnaire Standard Disability Index (HAQ-DI) score from baseline was significantly greater at weeks 4 and 12 with secukinumab 300 mg compared with placebo ($P < .05$).
- In patients with a baseline HAQ-DI score of at least 0.5, the reduction in HAQ-DI score was significantly greater for secukinumab 150 mg at week 12 and for secukinumab 300 mg at weeks 4 and 12 compared with placebo. Responses continued up to week 52.

Comments: Phase 3 clinical trial. Patients who initially achieved PASI 75 at week 12 were more likely to maintain their response if they received secukinumab at fixed monthly intervals. Secukinumab was well tolerated with no unexpected adverse event trends.

Limitations: Study methods and results only available from ClinicalTrials.gov Web site and meeting abstracts.

Reference: Rich, P, et al, 2012^{15,16,29-31}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter, international study

Study Funding: Novartis

Patients: 404 patients with moderate to severe plaque psoriasis, determined by a PASI score of at least 12, an IGA score of at least 3, and involvement of at least 10% of the BSA, for at least 6 months. Patients were excluded if they were using a

conventional treatment of plaque psoriasis or had received a live vaccine in the previous 6 months. Mean patient age was approximately 44 years, 75.7% were male, and approximately 87% were White. Patients had a mean PASI score of 20 and a mean of 22% of BSA was affected.

Intervention: Patients were randomized 1:2:2:1 to secukinumab 150 mg in a single subcutaneous injection at week 0 (single regimen) ($n = 66$); secukinumab 150 mg subcutaneously monthly at weeks 0, 4, and 8 (monthly regimen) ($n = 138$); secukinumab 150 mg subcutaneously at weeks 0, 1, 2, and 4 (early regimen) ($n = 133$); or matching placebo subcutaneously at weeks 0, 1, 2, 4, and 8 ($n = 67$). Patients were assessed at week 12. Additionally, patients not receiving active treatment on a certain week received placebo injections to maintain blinding. Secukinumab-treated patients achieving at least PASI 75 at 12 weeks were considered responders and were eligible for a maintenance phase evaluation. Responders were re-randomized 1:1 to secukinumab 150 mg at weeks 12 and 24 and placebo at the start of a relapse (fixed interval regimen) ($n = 65$) or secukinumab 150 mg at the start of relapse and placebo on weeks 12 and 24 (start-of-relapse regimen) ($n = 67$). Placebo-treated patients achieving at least 75% change in PASI from baseline at 12 weeks continued to receive placebo during weeks 12 and 24. Nonresponders were eligible to enter an open-label treatment with secukinumab 150 mg subcutaneously every 4 weeks from week 12 to 32. Final assessment was on week 32, and all patients were followed for an additional 12 weeks to assess safety.

Results

Primary Endpoint(s)

- The percentage of patients achieving a PASI 75 score at 12 weeks was 42% (58 of 138) with the monthly regimen, 54.4% (72 of 133) with the early regimen, and 1.5% (1 of 67) with placebo ($P < .001$ for each comparison). The number needed to treat (NNT) for the monthly group was 2.5; for the early group, NNT was 1.9.

Secondary Endpoint(s)

- The percentage of patients achieving a PASI 75 score at least once between weeks 20 to 28 was 85% (55 of 65) with the fixed interval regimen and 67% (45 of 67) for the start-of-relapse regimen ($P = .02$).

- The percentage of patients achieving an IGA score of up to 1 at week 12 was 37.1% (49 of 133) with the early regimen ($P < .001$), 22.6% (31 of 138) with the monthly regimen ($P = .003$), and 1.5% (1 of 67) with the placebo regimens ($P < .001$ and $P = .003$, respectively).
- The percentage of patients achieving PASI 90 at week 12 was 31.8% (42 of 133) with the early regimen, 17.4% (24 of 138) with the monthly regimen, and 1.5% (1 of 67) with placebo regimens ($P < .001$ for each comparison).

Comments: Phase 2 regimen-finding study. Secukinumab was able to improve plaque psoriasis among patients with moderate to severe disease when given as either a weekly or early regimen assessed after 12 weeks. A fixed-interval maintenance regimen of secukinumab was more effective in maintaining PASI 75 than treating at the start of relapse. Therapy was generally well tolerated, although nasopharyngitis occurred more frequently in patients treated with the monthly and early secukinumab regimens than with placebo. A subanalysis was conducted on secukinumab's effects on hand, foot, and nail lesions because they tend to be more difficult to treat in this patient population. In the subgroup that had hand and/or foot psoriasis, the percentage of patients who achieved an IGA response at week 12 was 54.3% with early regimen secukinumab and 19.2% with placebo ($P = .005$). In the subgroup that had fingernail psoriasis, the composite fingernail scores improved with the early (−19.1%) and monthly (−10.6%) secukinumab regimens, but worsened with placebo therapy (14.4%) (early, $P = .1$; monthly, $P = .027$).³² Of the 404 patients included in this study, 111 also had psoriatic arthritis and 119 patients also had previously used biologics; the improvement in plaque psoriasis did not differ in these subpopulations.^{15,30} Additionally, CRP was decreased from baseline in patients in the monthly cohort, which indicated a reduction in inflammatory burdens.³¹

Limitations: No comparison with other secukinumab doses and a limited duration of treatment. Power was set at 80% based on achievement of PASI 75 at least once from week 20 to 28; this was a secondary endpoint. The anticipated PASI 75 response rate of 90% with the fixed-interval regimen and 70% with the start-of-relapse regimen between weeks 20 to 28, as well as the PASI 75 response rate of 50% in the monthly group at week 12, were not achieved.

Reference: Papp K, et al, 2012^{20,33-35}

Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter, international study

Study Funding: Novartis

Patients: 125 patients with moderate to severe plaque psoriasis, determined by a PASI score of at least 12, an IGA score of at least 3, and BSA involvement of at least 10%, for at least 6 months. Patients had not responded to conventional therapy, including topical, systemic, and/or phototherapy. Patients were excluded if they had other forms of psoriasis or were currently using a conventional therapy for psoriasis. Mean patient age was approximately 46 years, 72.8% were male, and approximately 76% of patients were White. Patients had a mean PASI score of 21, and a mean of 23% of BSA was affected; 28.8% had previously used biologics.

Intervention: Patients randomized 1:1:1:1 to secukinumab 25 mg at week 0 and placebo at weeks 4 and 8 ($n = 29$), or secukinumab 25 mg ($n = 26$), secukinumab 75 mg ($n = 21$), secukinumab 150 mg ($n = 27$), or matching placebo ($n = 22$) subcutaneously at weeks 0, 4, and 8. Patients were evaluated after 12 weeks of treatment and followed for up to 36 weeks for safety.

Results

Primary Endpoint(s)

- The percentage of patients achieving PASI 75 at week 12 was 82% (22 of 27) for secukinumab 150 mg ($P < .001$ vs placebo), 57% (12 of 21) for secukinumab 75 mg ($P = .002$ vs placebo), and 9% (2 of 22) for placebo. NNT was 1.4 for secukinumab 150 mg and 2.1 for secukinumab 300 mg.

Secondary Endpoint(s)

- The percentage of patients achieving an IGA score of up to 1 at week 12 was 48% (13 of 27) for secukinumab 150 mg and 9% (2 of 22) for placebo ($P = .005$).
- The percentage of patients who achieved a PASI 90 score at week 12 was 52% (14 of 27) for secukinumab 150 mg and 4% (1 of 22) for placebo ($P < .001$).
- The percentage of patients achieving PASI 50 at week 12 was 85% (23 of 27) for secukinumab 150 mg ($P < .001$), 81% (17 of 21) for secukinumab 75 mg ($P < .001$), 58% (15 of 26) for secukinumab 25 mg ($P = .01$), and 18% (9 of 22) for placebo.

- The percentage of patients treated with secukinumab who maintained a PASI 75 score at week 36 was greater than placebo and decreased over time after week 12. Although not significant, 26% (7 of 27) of patients treated with secukinumab 150 mg, 19% (4 of 21) of patients treated with secukinumab 75 mg, and 4% (1 of 22) of patients treated with placebo maintained PASI 75 through week 36.

Comments: Phase 2 dose-finding study. Overall discontinuation rate was 37.6%, with a greater number in the placebo, single-dose, and secukinumab 25 mg groups. Secukinumab 75 and 150 mg given subcutaneously at weeks 0, 4, and 8 improved symptoms in patients with moderate to severe plaque psoriasis, as assessed at week 12, compared with placebo.²⁰ Efficacy was similar between treatment-naïve patients and patients with previous biologic use.³⁵ Increased response rates were observed in participants who weighed less than 90 kg, suggesting that additional dosing evaluation is needed for patients who weigh 90 kg or more.²⁰ Secukinumab treatment was not associated with effects on lipid parameters.³⁴

Limitations: Small sample size and short duration of treatment. There was a high discontinuation rate in the placebo, single-dose, and secukinumab 25 mg groups. Power was set at 80% and did not meet the required 23 patients per group and predefined 10% response rate in the placebo group.

Reference: Blauvelt A, et al (FEATURE)³⁶

Study Design: Randomized, double-blind, placebo-controlled, parallel group phase 3 study

Study Funding: Novartis

Patients: 177 patients with moderate to severe plaque psoriasis. All patients had to be 18 years and older, have had plaque psoriasis for at least 6 months, have at least 10% of their BSA affected by the disease, and have a history of inadequate response with previous topical treatment, phototherapy, or systemic therapy. Baseline demographics were patient age of about 46 years, 66% were male, 90% of patients were White, and patient body weight of about 90 kg; involved BSA was about 30%; and IGA (modified 2011) score was classified as moderate in 58% to 68% of patients. Previous therapies undergone by patients consisted of systemic psoriasis therapy (59.3% to 76.3%), conventional topical therapy (39% to 47.5%), and biologic systemic agents (39.1% to 64.3%).

Intervention: Randomized (1:1:1) to treatment with secukinumab 300 or 150 mg or placebo, with stratification by body weight (≥ 90 kg and < 90 kg). The drug was administered by subcutaneous injections given by the patient using a prefilled syringe at baseline; at weeks 1, 2, and 3; and then every 4 weeks for the remainder of the study. All patients received 2 injections during each treatment session; the secukinumab 300 mg group received two 150 mg injections, the secukinumab 150 mg group received one 150 mg injection and one placebo injection, and the placebo group received 2 placebo injections.

Results

Primary Endpoint(s)

- Achievement of PASI 75 at week 12 occurred in 75.9% of the secukinumab 300 mg group, 69.5% of the secukinumab 150 mg group, and 0% of the placebo group ($P < .001$).
- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 was 69% in the secukinumab 300 mg group, 52.5% in the secukinumab 150 mg group, and 0% in the placebo group ($P < .001$).

Secondary Endpoint(s)

- Achievement of PASI 90 at week 12 occurred in 60.3% of the secukinumab 300 mg group, 45.8% of the secukinumab 150 mg group, and 0% of the placebo group ($P < .001$).
- Achievement of PASI 100 at week 12 occurred in 43.1% of the secukinumab 300 mg group ($P < .001$ vs placebo), 8.5% of the secukinumab 150 mg group ($P = .057$ vs placebo), and 0% of the placebo group.
- A 50% reduction in mean PASI from baseline was achieved by week 3 with secukinumab 300 mg and by week 4 with 150 mg.

Comments: Patients were enrolled from North America and Europe. All patients were able to safely use the prefilled syringe, 95% were able to successfully complete all 18 steps required for self-administration, and acceptability of the self-injections was classified as “high” at baseline and was still “high” through week 12.

Reference: Paul C, et al (JUNCTURE)³⁷

Study Design: Randomized, double-blind, placebo-controlled, parallel group phase 3 study

Study Funding: Novartis

Patients: 182 patients with moderate to severe plaque psoriasis. All patients had to be 18 years

and older, have had plaque psoriasis for at least 6 months, have at least 10% of their BSA affected by the disease, and have a history of inadequate response with previous topical treatment, phototherapy, or systemic therapy. Baseline demographics were patient age of about 44 years, 62% to 77% were male, 95% of patients were White, and patient body weight was about 90 kg; involved BSA was about 27%; and IGA (modified 2011) score was classified as moderate in 58% to 65%. Previous therapies consisted of any systemic psoriasis therapy (55%), conventional therapy (47.5% to 51%), and biologic systemic agents (21.3% to 25%).

Intervention: Randomized (1:1:1) to treatment with secukinumab 300 or 150 mg or placebo, with stratification by body weight (≥ 90 kg and < 90 kg). The drug was administered by subcutaneous injections given by the patient using an autoinjector pen at baseline; at weeks 1, 2, and 3; and then every 4 weeks for the remainder of the study. All patients received 2 injections during each treatment session; the secukinumab 300 mg group received two 150 mg injections, the secukinumab 150 mg group received one 150 mg injection and one placebo injection, and the placebo group received 2 placebo injections.

Results

Primary Endpoint(s)

- Achievement of PASI 75 at week 12 occurred in 86.7% of the secukinumab 300 mg group, 71.7% of the secukinumab 150 mg group, and 3.3% of the placebo group ($P < .001$).
- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 was 73.3% in the secukinumab 300 mg group, 53.3% in the secukinumab 150 mg group, and 0% in the placebo group ($P < .001$).

Secondary Endpoint(s)

- Achievement of PASI 90 at week 12 occurred in 55% of the secukinumab 300 mg group, 40% of the secukinumab 150 mg group, and 0% in of the placebo group ($P < .001$).
- Achievement of PASI 100 at week 12 occurred in 26.7% of the secukinumab 300 mg group ($P < .001$ vs placebo), 16.7% of the secukinumab 150 mg group ($P = .057$ vs placebo), and 0% of the placebo group.
- A 50% reduction in mean PASI from baseline was achieved by week 3 with secukinumab 300 mg and by week 4 with 150 mg.

Comments: Patients were enrolled from North America and Europe. All patients were able to safely use the autoinjector, 93.3% were able to successfully complete all 14 steps required for self-administration, and acceptability of the self-injections was classified as “high” at baseline and was still “high” through week 12.

Reference: Langley RG, et al, 2014 (ERASURE trial)^{22,38}

Study Design: Randomized, double-blind, placebo-controlled, parallel group phase 3 study

Study Funding: Novartis

Patients: 738 patients with moderate to severe plaque psoriasis. All patients had to be 18 years and older, have had plaque psoriasis for at least 6 months, have at least 10% of their BSA affected by the disease, and have a history of inadequate response with previous topical treatment, phototherapy, or systemic therapy. Baseline demographics were patient age of about 45 years, approximately 69% were male, approximately 70% of patients were White and approximately 21% were Asian, and patient body weight was approximately 89 kg; involved BSA was approximately 33%; IGA (modified 2011) score was classified as moderate in approximately 62%; and psoriatic arthritis ranged from 18.8% to 27.4%. Previous therapies consisted of any systemic psoriasis therapy (58.9% to 66.5%), conventional therapy (43.5% to 52.2%), and biologic systemic agents (28.6% to 29.8%).

Intervention: Randomized (1:1:1) to treatment with secukinumab 300 or 150 mg or placebo, with stratification by body weight (≥ 90 kg and < 90 kg). The drug was administered by subcutaneous injections given by the patient using an autoinjector pen at baseline; at weeks 1, 2, and 3; and then every 4 weeks for the remainder of the study. All patients received 2 injections during each treatment session; the secukinumab 300 mg group received two 150 mg injections, the secukinumab 150 mg group received one 150 mg injection and one placebo injection, and the placebo group received 2 placebo injections.

Results

Primary Endpoint(s)

- Achievement of PASI 75 at week 12 occurred in 81.6% of the secukinumab 300 mg group, 71.6% of the secukinumab 150 mg group, and 4.5% of the placebo group ($P < .001$).

- Subgroup analysis of 87 patients from Japan who were enrolled in this study found the achievement of PASI 75 at week 12 occurred in 82.8% of the secukinumab 300 mg group, 86.2% of the secukinumab 150 mg group, and 6.9% of the placebo group ($P < .001$).
- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 was 65.3% in the secukinumab 300 mg group, 51.2% in the secukinumab 150 mg group, and 2.4% in the placebo group ($P < .001$).
- Subgroup analysis of 87 patients from Japan who were enrolled in this study found the proportion of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 was 55.2% in the secukinumab 300 mg group, 55.2% in the secukinumab 150 mg group, and 3.4% in the placebo group ($P < .001$).

Secondary Endpoint(s)

- Achievement of PASI 90 at week 12 occurred in 59.2% of the secukinumab 300 mg group, 39.1% of the secukinumab 150 mg group, and 1.2% of the placebo group ($P < .001$).
- Subgroup analysis of 87 patients from Japan enrolled in this study found the achievement of PASI 90 at week 12 occurred in 62.1% of the secukinumab 300 mg group, 55.2% of the secukinumab 150 mg group, and 0% of the placebo group ($P < .001$).
- Achievement of PASI 100 at week 12 occurred in 28.6% of the secukinumab 300 mg group, 12.8% of the secukinumab 150 mg group, and 0.8% of the placebo group ($P < .001$).
- The percentage of patients who achieved an IGA (modified 2011) score of 0 or 1 at week 12 to 52 was 74.4% with the secukinumab 300 mg group and 59.2% with the secukinumab 150 mg group.

Comments: Phase 3 clinical trial. Secukinumab was better than placebo in the treatment of plaque psoriasis in this study; the secukinumab 300 mg dose was numerically better than the secukinumab 150 mg dose. Response with secukinumab was sustained through week 52.

Indication: Psoriatic Arthritis

Studies

Drug: Secukinumab vs Placebo

Reference: McInnes IB, et al, 2014²

Study Design: Randomized, double-blind, placebo-controlled, multicenter study

Study Funding: Novartis

Patients: 42 patients with active moderate to severe psoriatic arthritis (based on the Classification Criteria for Psoriatic Arthritis of at least 3 swollen/tender joints), a Physician's Global Assessment score of at least 40 (based on visual analog scale [VAS] 0 to 100), an inflammatory pain scale score of at least 40 (based on VAS 0 to 100), uncontrolled on at least 1 disease-modifying antirheumatic drug, and rheumatoid factor up to 100 units. Patients excluded from the study included those with ankylosing spondylitis, malignancy, hepatitis B, hepatitis C, HIV, active infection, renal impairment, or cardiac disease. The mean age of patients was 47 years, 64% were female, and 93% of patients were White. The mean disease activity score in 28 joints was 4.8.

Intervention: Patients were randomized 2:1 to receive 2 doses (day 1 and 22) of secukinumab 10 mg/kg or matching placebo administered intravenously (IV) 21 days apart. Patients were followed up to 21 weeks.

Results

Primary Endpoint(s)

- The percentage of patients achieving an American College of Rheumatology 20% response (ACR20) at week 6 was 39% for secukinumab and 23% for placebo. The difference was not significant (95% confidence interval [CI], 0.38 to 15.15; $P = .27$).

Secondary Endpoint(s)

- The percentage of patients achieving ACR50 at week 6 was 17% for secukinumab and 8% for placebo ($P = .39$).
- The percentage of patients achieving ACR70 at week 6 was 9% for secukinumab and 0% for placebo ($P = .4$).
- Mean change in HAQ-DI at weeks 6, 12, and 24 was significantly different from placebo ($P = .002$, $P = .004$, and $P = .019$, respectively). Additionally, there was a greater portion of secukinumab-treated patients with a more than 3% reduction from baseline at week 6 ($P = .038$).
- Mean change in Medical Outcomes Study Short Form Survey (SF-36) score from baseline was 15.2 and 20.4 for secukinumab and -0.51 and -3.25 for placebo at weeks 6 and 12 ($P = .03$ and $P = .037$), respectively.

Comments: Phase 2a study conducted in Germany, the Netherlands, and the United Kingdom. Study

did not meet the primary ACR20 endpoint. A post hoc subgroup analysis comparing TNF-naïve patients and patients previously treated with a TNF-alpha-targeting therapy demonstrated greater ACR20 response rates for the TNF-naïve patients.

Limitations: Small sample size and limited dosing regimens. Study may have been underpowered because of the small number of participants.

Indication: Rheumatoid Arthritis

Studies

Drug: Secukinumab vs Placebo

Reference: Genovese M, et al, 2013³

Study Design: Randomized, double-blind, placebo-controlled, multicenter, international study

Study Funding: Novartis

Patients: 237 patients with rheumatoid arthritis for at least 3 months who were on a stable methotrexate dosage of 7.5 to 25 mg per week, corticosteroids of up to 10 mg/day prednisone equivalents, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks. Patients with rheumatoid arthritis functional class IV and other forms of rheumatic disease were excluded. Mean age was approximately 54 years and 76% of patients were women. Mean duration of rheumatoid arthritis was 7 years and 20% of patients had previously used a biologic agent.

Intervention: Patients were randomized 1:1:1:1 to monthly subcutaneous injections of secukinumab 25 mg ($n = 54$), 75 mg ($n = 49$), 150 mg ($n = 43$), 300 mg ($n = 41$), or placebo ($n = 50$) for 16 weeks. Patients not achieving an ACR20 at week 16 were administered an increased secukinumab dose from week 20 through 52. Nonresponders receiving secukinumab 25 or 75 mg or placebo were increased to secukinumab 150 mg and nonresponders on secukinumab 150 mg were increased to secukinumab 300 mg. Patients were followed up to 60 weeks for safety.

Results

Primary Endpoint(s)

- The percentage of patients who achieved ACR20 at week 16 was 34% in the secukinumab 25 mg group, 46.9% in the secukinumab 75 mg group, 46.5% in the secukinumab 150 mg group, 53.7% in the secukinumab 300 mg group, and 36% in the placebo group. No statistical values were provided.

Secondary Endpoint(s)

- The mean change in disease activity score in 28 joints CRP at week 16 compared with placebo was -0.51 in the secukinumab 75 mg group (95% CI, -0.99 to -0.03 ; $P = .037$).
- The mean change in high-sensitivity CRP at week 16 compared with placebo was -9.4 in the secukinumab 75 mg group (95% CI, -15.1 to -3.7 ; $P < .05$), -8.01 in the secukinumab 150 mg group (95% CI, -13.9 to -2.09 ; $P < .05$), and -7.2 in the secukinumab 300 mg group (95% CI, -13.18 to -1.22 ; $P < .05$).

Comments: Phase 2 dose-finding study. This article states that the primary endpoint was not achieved, but statistical values were not provided. Some of the secondary endpoint data suggest secukinumab may have a dose-dependent effect in the treatment of rheumatoid arthritis based on its effects on changes in the ACR, disease activity score in 28 joints, and high-sensitivity CRP parameters. The impact of secukinumab therapy on the primary endpoint may have been influenced by the higher than expected placebo response. Calculation of power assumed a placebo response rate of 28%, and the response rate in the study was 36%. Using the HAQ-DI, SF-36, and Functional Assessment of Chronic Illness Therapy-Fatigue, the data from this study found incremental improvements with secukinumab therapy compared with placebo.³⁹

Limitations: Interim analysis results of efficacy up to week 16 of a 52-week study.

Indication: Ankylosing Spondylitis

Studies

Drug: Secukinumab vs Placebo

Reference: Baeten D, et al, 2013⁴

Study Design: Randomized, double-blind, placebo-controlled, multicenter, international study

Study Funding: Novartis

Patients: 30 patients with active ankylosing spondylitis (defined by the New York criteria), a score of at least 4 on the Bath Ankylosing Spondylitis Disease Activity Index, total back pain, and a nocturnal pain score of 40 or more on the VAS 0 to 100 scale, irrespective of the maximum tolerated doses of NSAIDs. Concurrent use of sulfasalazine, methotrexate, prednisone or prednisone equivalent, or NSAIDs was allowed if the patient's dosage was stable for at least 4 weeks before the baseline

visit. Mean patient age was 41.9 years and 63% were male; 87% of patients were White and 3% were Black. The mean duration of disease was 11.95 years.

Intervention: Patients were randomized 4:1 to receive 2 doses of secukinumab 10 mg/kg IV ($n = 24$) or placebo ($n = 6$), each administered 3 weeks apart (days 1 and 22).

Results

Primary Endpoint(s)

- The percentage of patients achieving an improvement of 20% in Assessments in Ankylosing Spondylitis (ASAS20) at week 6 was 59.2% in the secukinumab group and 24.5% in the placebo group; the absolute difference was 34.7% (95% CI, 11.5% to 56.4%) and the NNT was 2.9.

Secondary Endpoint(s)

- The percentage of patients achieving ASAS40 at week 6 was 30% in the secukinumab group and 17% in the placebo group. No statistics were reported.
- The percentage of patients achieving ASAS improvement in 5 of 6 domains without deterioration in the sixth domain at week 6 was 35% for secukinumab and 0% for placebo. No statistics were reported.

Comments: Phase 2 study. Eight study centers (4 in Germany, 2 in the Netherlands, and 2 in the United Kingdom).

Limitations: Small sample size. Unable to make statistical comparisons of secondary endpoints because of the limited placebo sample size.

[11.4% vs 8.6%], upper respiratory tract infection [2.5% vs 0.7%], and mucocutaneous infections with *Candida* [1.2% vs 0.3%]). Caution should be taken in treating patients with a chronic infection or a history of recurrent infection and patients should be monitored for signs and symptoms of infections. If the patient develops a serious infection, the secukinumab therapy should be discontinued until the infection resolves.^{1,16,20}

If the patient has active tuberculosis or a history of latent tuberculosis for which adequate treatment cannot be confirmed, the tuberculosis must be treated prior to starting the secukinumab therapy.¹

Exacerbations of Crohn disease were observed during the clinical trials. Patients with active Crohn disease should be treated with caution and monitored for exacerbations.¹

If an anaphylactic reaction or other serious allergic reaction occurs during treatment, the drug should be discontinued immediately and appropriate treatment initiated.¹ Patients with latex allergies should avoid the use or handling of the *Cosentyx* Sensoready pen and the prefilled syringe because the removable cap contains natural rubber latex.¹

Secukinumab is classified as Pregnancy Category B; no adequate and well-controlled studies have been conducted, and animal studies found no evidence of harm to the fetus.¹

Use caution in breast-feeding mothers; it is unknown if secukinumab is excreted in human milk.¹

Safety and effectiveness of secukinumab in pediatric patients have not been evaluated. No differences in safety or efficacy were noted between older and younger patients in the clinical trials.¹

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Secukinumab is contraindicated in patients with a history of a serious hypersensitivity reaction to secukinumab or any of its ingredients (L-histidine/L-histidine hydrochloride monohydrate, polysorbate 80, sucrose, and sterile water for injection).¹

Warnings and Precautions

Serious infections have occurred in patients with psoriasis treated with secukinumab therapy. All patients should be evaluated for tuberculosis prior to starting secukinumab therapy.¹ Upper respiratory tract infections and nasopharyngitis occurred at a greater rate in secukinumab-treated patients compared with placebo in clinical trials (nasopharyngitis

ADVERSE REACTIONS

The most common adverse events reported (1% or greater) included nasopharyngitis, diarrhea, and upper respiratory tract infections.¹

Adverse reactions generally occurred more frequently during the induction period and less during maintenance treatment with secukinumab.¹⁶ Most of the adverse events were mild or moderate in severity.^{16,20} The common adverse reactions are summarized in Table 1.¹

Pooled analysis from 10 phase 2 and 3 clinical studies of secukinumab with over 3,000 patients with moderate to severe plaque psoriasis treated for up to 52 weeks found the infection rate during the induction period (up to week 12) was higher than placebo (25.8% with secukinumab 300 mg, 26.9% with secukinumab 150 mg, and 20.6% with placebo) but

Table 1. Adverse reactions reported during 12 weeks of therapy for plaque psoriasis with secukinumab or placebo in trials 1, 2, 3, and 4¹

Adverse reaction	Secukinumab 300 mg (n = 691)	Secukinumab 150 mg (n = 692)	Placebo (n = 694)
Nasopharyngitis	11.4%	12.3%	8.6%
Diarrhea	4.1%	2.6%	1.4%
Upper respiratory tract infection	2.5%	3.2%	0.7%
Rhinitis	1.4%	1.4%	0.7%
Oral herpes	1.3%	0.1%	0.3%
Pharyngitis	1.2%	1%	0%
Urticaria	0.6%	1.2%	0.1%
Rhinorrhea	1.2%	0.3%	0.1%

similar to etanercept (25.7%). However, the rate of serious infections was low (0.1% with secukinumab 300 mg, 0.2% with secukinumab 150 mg, 0% with etanercept, and 0.3% with placebo). The exposure-adjusted incidence rate of infection per 100 subject-years was 91.1 with secukinumab 300 mg, 85.3 with secukinumab 150 mg, 93.7 with etanercept, and 101.9 with placebo. The key difference was the incidence of *Candida* infections, which had an exposure-adjusted incidence rate per 100 subject-year of 3.55 with secukinumab 300 mg, 1.85 with secukinumab 150 mg, 1.37 with etanercept, and 1 with placebo.⁴⁰ The same studies were evaluated for malignancy risk. The incidence rate of malignant or unspecified tumors was 0.77 with secukinumab 300 mg, 0.97 with secukinumab 150 mg, 0.68 with etanercept, and 1.49 with placebo.⁴¹

DRUG INTERACTIONS

Drug interaction studies have not been conducted.¹

The Centers for Disease Control and Prevention recommends avoiding live vaccines in patients being treated with immunosuppressive agents.⁴² However, there were no differences in the proportion of healthy subjects achieving an immune response at 4 weeks (evaluated by virus antibody titer) to influenza and meningococcal vaccines when it was given 2 weeks after the administration a single dose of secukinumab 150 mg (*n* = 25) or no treatment with secukinumab (*n* = 25).⁴³ However, secukinumab's product labeling states that live vaccines should not be given with

secukinumab and non-live vaccines may not elicit an immune response sufficient to prevent disease.¹

Secukinumab's impact on cytochrome P450 (CYP-450) enzymes has not been assessed. However, the formation of CYP-450 enzymes is influenced by cytokines, including IL-17A, during chronic inflammation. Thus, as the chronic inflammation is improved with the secukinumab therapy, there may be changes in CYP-450 enzyme activity. The product labeling cautions that change in the metabolism of CYP-450 substrates, particularly those with a narrow therapeutic index, may be altered during initiation or discontinuation of secukinumab therapy.¹

RECOMMENDED MONITORING

Patients should be monitored for signs and symptoms of infection throughout therapy. Assessment for neutropenia may be necessary.

DOSING

The recommended dose of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy is 300 mg by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks. However, secukinumab 150 mg may be acceptable for some patients.¹ The 300 mg dose requires the use of 2 *Cosentyx* Sensoready pens, prefilled syringes, or vials.¹

Each injection should be administered at a different anatomic location (eg, upper arms, thighs, any quadrant of the abdomen) than the previous injection. The drug should not be injected into areas that are tender, bruised, erythematous, indurated, or affected by psoriasis.¹

Secukinumab is available in 3 different types of packaging, *Cosentyx* Sensoready pen, prefilled syringe, and lyophilized powder in vial for reconstitution. Patients can be trained to use the *Cosentyx* Sensoready pen and the prefilled syringe formulations; however, the lyophilized powder for reconstitution is limited to use by health care providers.¹

The *Cosentyx* Sensoready pen and prefilled syringe must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and, prior to administration, allowed to reach room temperature (15 to 30 minutes) without removing the needle cap. The contents of the *Cosentyx* Sensoready pen or prefilled syringe must be administered within 1 hour after removal from the refrigerator. Then, any remaining product in the pen should be discarded.¹

If the lyophilized powder is used (1 vial for the 150 mg dose and 2 vials for the 300 mg dose), it should be prepared and reconstituted with sterile water for injection by a trained health care provider. The preparation time should take 20 minutes and should not exceed 90 minutes. The vial must be stored in a refrigerator prior to preparation. It should be removed from the refrigerator and allowed to stand at room temperature for 15 to 30 minutes prior to reconstitution. The sterile water for injection should be at room temperature prior to being injected into the vial. During the reconstitution process, the vial should not be shaken or inverted but rotated between the fingertips for approximately 1 minute. It should stand for about 10 minutes after the injection of the sterile water for injection to allow for dissolution. The vial should then be rotated between the fingertips for approximately 1 minute, without shaking or inverting the vial. Allow the vial to once again stand at room temperature for about 5 minutes. If no particles or problems are noted in the vial, the solution can be drawn up into a syringe and administered. If the solution is not used immediately, it can be stored in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours.¹

The solution should not be frozen. If the solution is refrigerated, it should be warmed to room temperature (15 to 30 minutes) prior to administration and used within 1 hour.¹

PRODUCT AVAILABILITY

The New Drug Application was approved on January 21, 2015.⁴⁴ Secukinumab is supplied in 3 different dosage forms that each contain 150 mg/mL. The *Cosentyx* Sensoready pen is available in 2 different carton sizes; the 300 mg dose carton contains 2 *Cosentyx* Sensoready pens, whereas the 150 mg dose carton contains 1 *Cosentyx* Sensoready pen. The packaging for the prefilled syringes is the same. The vial carton contains only 1 single-use vial with secukinumab 150 mg lyophilized powder.¹

All of the secukinumab formulations should be stored in a refrigerator, between 2°C and 8°C (36°F and 46°F), in their original carton to protect from light until the time of use. If the reconstituted solution from the vial is not used immediately, it can be refrigerated in the vial at 2°C to 8°C (36°F to 46°F) for up to 24 hours.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for secukinumab.⁴⁴

CONCLUSION

Secukinumab is a novel fully human immunoglobulin G1 monoclonal antibody that selectively binds to and neutralizes the proinflammatory cytokine IL-17A. This mechanism of action is different from all of the drugs that were previously used for the treatment of psoriasis and may be useful in the treatment of patients who could not tolerate or did not respond to the previous drugs. Secukinumab is generally well tolerated; nasopharyngitis, pharyngitis, and upper respiratory tract infections are the most common adverse events associated with treatment.

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