Secukinumab (COSENTYX) Injection

National Drug Monograph

September 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Secukinumab is a first in class recombinant, high-affinity, fully human monoclonal IgG1κ antibody that binds specifically to, and neutralizes the activity of, the cytokine interleukin (IL)-17A.
Indication(s) Under Review in This Document	• Treatment of moderate to severe **plaque psoriasis** in adult patients who are candidates for systemic therapy or phototherapy • Treatment of adult patients with active **psoriatic arthritis** • Treatment of adult patients with active **ankylosing spondylitis**
Dosage Form(s) Under Review	• Injection: 150 mg/mL solution in a single-use Sensoready® pen • Injection: 150 mg/mL solution in a single-use prefilled syringe • For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use only
REMS	☐ **REMS** ☐ **No REMS** ☐ **Postmarketing Requirements**
Pregnancy Rating	Category B

Executive Summary

Efficacy

Moderate to Severe Plaque Psoriasis (PPsO)

- Secukinumab 300 mg (SEC300, the approved dose for PPsO) showed consistently large effect sizes relative to placebo at Week 12 for at least 75% reduction in Psoriasis Area and Severity Index (PASI75), Investigator Global Assessment of 0 (clear) or 1 (almost clear) (IGA0/1) and PASI90 across four major efficacy trials (NNT range 1.3 to 1.9).
- Compared with EU-approved etanercept, SEC300 had a small to moderate efficacy advantage (in PASI75, IGA0/1, and PASI100) and had a faster onset of effect (3 weeks versus 7 weeks).
- SEC300 was shown to be superior to ustekinumab (NNT = 4.7 for PASI90 at Week 16).
- Efficacy has been shown to be maintained for up to 52 weeks. Trials assessing longer-term benefit are ongoing.

Active Psoriatic Arthritis (PsA)

- SEC300 and SEC150 (the approved dose for PsA) had moderate effect sizes relative to placebo in terms of ACR20 at Week 24 (NNT range: 2.5–3.0) across two major clinical trials.
- Van der Heijde-modified total Sharp Score (mTSS) showed a small but statistically significant inhibition of structural joint damage with SEC150 (0.13) in the one trial in which this measure was evaluated.
- SEC150 was superior to placebo in rates of dactylitis resolution and enthesitis resolution in one of two trials.
- Clinical benefits with SEC300, SEC150 and SEC75 were maintained through 52 weeks in both major clinical trials.

	Ankylosing Spondylitis (AS) • SEC150 showed consistent efficacy across two major efficacy trials, with a moderate effect size relative to placebo in achieving at least 20% improvement in the Assessment of Spondyloarthritis International Society response criteria (ASAS20; primary efficacy measure) at Week 16. • A statistically significant difference between SEC150 and placebo was seen as early as Week 1 in both trials. • Long-term efficacy of secukinumab up to 52 weeks was shown by the maintenance of ASAS20 responses from Week 16 to Week 52 in the patients randomized to active treatment initially.
Indirect Efficacy Comparisons for Plaque Psoriasis	• In a systematic review of longer-term treatment of plaque psoriasis, biologics and apremilast were shown to be efficacious for PPsO up to 28 weeks, with secukinumab having the second highest pooled risk ratio (RR 11.97; 95% CI 8.83–16.23) for PASI75 response at Weeks 24–28, following infliximab (13.07; 8.60–19.87) and preceding (from next highest to lowest) ustekinumab (11.39; 8.94–14.51), adalimumab (8.92; 6.33–12.57), etanercept (8.39; 6.74–10.45) and apremilast (5.83; 2.56–13.17). The quality of evidence for this measure was low. • For PASI90 response, the order of treatments based on relative risks versus placebo (from highest to lowest) was secukinumab (RR 40.15; 95% CI 20.97–76.89), ustekinumab (31.63; 19.43–51.51), infliximab (31.00; 13.45–71.46), adalimumab (23.17; 12.51–42.91), etanercept (19.14; 11.59–31.60) and apremilast (13.00; 1.74–97.25). The quality of evidence for all of these comparisons was low. • The findings of the systematic review support infliximab, secukinumab and ustekinumab as the more effective systemic agents of those evaluated in longer-term randomized clinical trials (RCTs).
Safety	• **Contraindications**: Serious hypersensitivity reaction to secukinumab or to any of the excipients. • **Warnings / Precautions**: Infections, tuberculosis (TB; pre-treatment evaluation for TB and treatment for latent TB are recommended), inflammatory bowel disease, hypersensitivity reactions, risk of hypersensitivity in latex-sensitive individuals, vaccinations (patients should not receive live vaccines during secukinumab therapy). • **Safety Considerations**: Infection or infestation; candida infections (particularly mucocutaneous candidiasis, which may be dose-related); oral herpes infections; neutropenia; major adverse cardiovascular events (MACE; was a safety concern but there was no convincing cardiovascular safety signal in clinical trials); malignancy (e.g., thyroid cancer); tuberculosis (no cases reported in clinical trials but risk of infection warranted TB warning in prescribing information); exacerbation or new-onset inflammatory bowel disease; dyslipidemia; antidrug antibodies; paradoxical autoimmune diseases; dose-related adverse events (these include infections and neutropenia). • **Common Adverse Reactions**: Generally mild to moderate nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, oral herpes, pharyngitis, urticaria and rhinorrhea.
Other Considerations	• Secukinumab was shown to be significantly better than etanercept and ustekinumab for PPsO using PASI90 response, a more difficult to achieve response than the PASI75 measure used in prior TNFI trials. • Secukinumab is the first agent to be allowed by the FDA to include PASI90 response claims in the prescribing information. • Neither secukinumab nor ixekinumab (another IL-17A inhibitor) has been associated with suicidal ideation or behavior; however, brodalumab, an investigational fully human anti-IL-17RA (receptor) monoclonal antibody has been associated with suicidal thoughts and behaviors in preliminary phase III trial results.
Projected Place in	• Most patients with moderate to severe PPsO (who are candidates for systemic therapy or phototherapy), active PsA or active AS may be treated initially with the conventional

Therapy	systemic agents and / or TNFIs, depending on the specific condition. • Secukinumab offers a moderately to highly efficacious and well tolerated alternative second- or third-line therapy for patients who have a contraindication, nonresponse, inadequate response, loss of response, or intolerance to TNFIs. • In PPsO and PsA patients for whom TNFIs are inappropriate or inadequate, ustekinumab may be preferable over secukinumab as a treatment alternative because of greater long-term safety experience. In PPsO, ustekinumab also has a lower VA drug cost but is less effective than secukinumab (NNT of 4.7 for PASI90 response rate at 16 weeks). • The long-term effectiveness and safety of secukinumab beyond 52 weeks is uncertain; during long-term therapy patients should be monitored for maintenance of beneficial effects and potential rare, serious adverse effects (e.g., infections and infestations, neutropenia, malignancy, thyroid disease / cancer; paradoxical autoimmune diseases including IBD; suicidal behavior).

Background

Purpose for Review	Recent FDA approval Issues to be determined: ✔ Does secukinumab offer efficacy advantages over available alternatives? ✔ Does secukinumab offer safety advantages over available alternatives? ✔ Are there subgroup response predictors with secukinumab? ✔ Does secukinumab require clinical guidance to ensure appropriate use?
Other Therapeutic Options	Therapeutic options at approximately the same line of therapy as secukinumab in moderate to severe plaque psoriasis (PPsO), active psoriatic arthritis (PsA) and active ankylosing spondylitis (AS) are shown in the tables below.

Formulary Alternatives	**Other Considerations**	**Clinical Guidance**
None		

Nonformulary Alternatives	**Other Considerations**	**Clinical Guidance**
Tumor Necrosis Factor Inhibitors Adalimumab Certolizumab Etanercept Golimumab Infliximab	Adalimumab, etanercept and infliximab approved for PPsO, PsA and AS. Certolizumab and golimumab are approved for PsA and AS. Effectiveness is established. Administered subcutaneously except infliximab is given intravenously. Inhibit radiographic progression in PsA and AS.	**PBM Criteria for Use** of Biologics in PPsO and PsA
Phosphodiesterase-4 Inhibitor Apremilast	Approved for PPsO and PsA. Orally administered. Disease-modifying capability is uncertain.	

	Anti-IL-12/23 Monoclonal Antibody Ustekinumab	Approved for PPsO and PsA. Administered subcutaneously. Every-12-week maintenance dosing. Inhibits radiographic progression. Lacks cytopenias and TNFI-related complications and contraindications.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 through March 2016) using the search term *secukinumab*. The search was limited to studies performed in humans. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. Randomized controlled trials and long-term (>1 year) observational studies were included. The FDA Medical Review of secukinumab was also reviewed for clinical trial information; however, the review mainly covered the PPsO indication.[1]

Review of Efficacy

The FDA approval of secukinumab was largely based on four PPsO randomized clinical trials (RCTs; ERASURE,[2] FIXTURE,[2] JUNCTURE[3] and FEATURE[4]), two PsA RCTs (FUTURE 1[5] and FUTURE 2[6]), and two AS RCTs published in one article[7] (MEASURE 1 and MEASURE 2). All of these RCTs were multicenter, double-blind, placebo-controlled and sponsored by Novartis Pharmaceuticals. FIXTURE also included an EU-approved etanercept product as an active comparator and double-dummy placebo injections.[8,9] The FDA did not include efficacy comparisons between secukinumab and the EU-approved etanercept because there was no verification that the EU and US etanercept products were comparable, and therefore no such claims could be made in the labeling.

Phase II dose-ranging[10] and regimen-finding[11,12] studies for PPsO, two proof-of-concept studies in AS,[13,14] and long-term observational MRI results of the AS proof-of-concept study[15] have also been published.

CLEAR was a phase IIIb trial directly comparing secukinumab with ustekinumab in patients with PPsO.[16]

SCULPTURE and STATURE were two additional supportive trials in patients with PPsO.[8] SCULPTURE compared re-treatment at the start of relapse versus fixed-interval dosing (every 4 weeks) during maintenance.[17] STATURE assessed the effect of dose escalation in partial responders after 12 weeks of active treatment in the SCULPTURE trial.[18]

Two other phase IIIb trials are ongoing.[8] TRANSFIGURE is a 132-week trial evaluating the efficacy and safety of SEC300 and SEC150 in PPsO patients with significant nail involvement. GESTURE is a 132-week trial evaluating SEC300 and SEC150 in PPsO patients with palmoplantar psoriasis. The 16-week results of these two studies have been presented at the 23rd World Congress of Dermatology.[19,20]

Table 1 describes the clinical trials.

Table 1 Overview of Secukinumab Clinical Trials

TRIAL	PURPOSE / INTERVENTIONS	POPULATION	DESIGN (STATUS)
ERASURE[2]	Assess efficacy-safety SEC300, SEC150, PBO	PPsO despite topical and systemic therapies • 19.4% Prior TNFI • 13.6% No response to prior TNFI • 13.6% Prior IL12/23 inhibitor	52-wk 88-center multinational DB Phase III RCT; extension to 4 yrs (Ongoing; up to 52 wks of data published)
FIXTURE[2]	Assess efficacy-safety Compare SEC and Etanercept SEC300, SEC150, PBO, ETA50	PPsO despite topical and systemic therapies • 4.6% Prior TNFI • 2.5% No response to prior TNFI • 6.8% Prior IL12/23 inhibitor	52-wk 231-Center Multinational DB DD Phase III RCT w/ extension to 4 yrs (Ongoing; up to 52 wks of data published)
JUNCTURE[3]	Assess efficacy, safety and usability of autoinjector / pen SEC300, SEC150, PBO	PPsO despite topical and systemic therapies • 23.6% Prior biologic	52-wk 38-center Multinational DB Phase III RCT; extension to 4 yrs (Ongoing; 12-wk data published)
FEATURE[4]	Assess efficacy, safety and usability of secukinumab via prefilled syringe SEC300, SEC150, PBO	PPsO despite topical and systemic therapies • 43.5% Prior biologic, of whom 52.4% failed treatment	52-wk 32-Center DB Phase III RCT in North America and Europe; extension to 208 wks (4 yrs) (Ongoing; 12-wk data published)
CLEAR[16]	Assess superiority of SEC versus ustekinumab SEC300, UST45/90	PPsO despite topical and systemic therapies • 13.6% Prior biologic • 10.4% Failed prior biologic	52-wk 134-Center DB Phase IIIb RCT conducted worldwide; used US-approved UST product. (Ongoing; 16-wk data published)
SCULPTURE[17]	Evaluate whether a maintenance dosing strategy using retreatment as needed is noninferior to fixed interval dosing SEC300, SEC150	PPsO despite topical and systemic therapies	260-wk 133-Center Multinational DB Phase III Noninferiority RCT with extension study (Ongoing; data up to 52 wks published)
STATURE[18]	Assess dose escalation in partial responders after 12 weeks of active treatment in SCULPTURE SEC 300 mg at Wk 0, 4 vs. SEC 10 mg/kg i.v. at Wk 0, 2, 4	PPsO despite topical and systemic therapies • 38% Prior biologic other than SEC	40-wk 23-Center DB Phase III RCT extension study with OL maintenance therapy in Austria, Canada, France, Germany, India, Japan, Slovakia and US (Completed, published)
TRANSFIGURE[19]	Assess efficacy-safety SEC300, SEC150, PBO	Nail PPsO despite topical and systemic therapies	132-wk RCT (Ongoing; poster presentation on 16-wk data)
GESTURE[20]	Assess efficacy-safety SEC300, SEC150, PBO	Palmoplantar PPsO despite topical and systemic therapies	132-wk RCT (Ongoing; verbal conference presentation on 16-wk data)
FUTURE 1[Ref 5]	Assess efficacy-safety (did not assess efficacy for axial disease) SEC150, SEC75, PBO (± stable MTX or GCs)	Active PsA (CASPAR diagnostic criteria) despite prior NSAID, DMARD or up to 3 TNFIs (inadequate response or intolerance). • 29.4% Prior TNFI	2-yr 104-Center Phase III DB RCT in North America, South America, Europe, Middle East, Australia and Asia (Ongoing; data up to 52 wks published)
FUTURE 2[Ref 6]	Assess efficacy-safety (did not assess efficacy for axial disease or radiographic progression or effects of prior TNFI therapy) SEC300, SEC150, SEC75, PBO	Active PsA (CASPAR diagnostic criteria) despite prior NSAID, DMARD or up to 3 TNFIs. • 34.7% Prior TNFI	52-wk 76-Center DB Phase III RCT in Asia, Australia, Canada, Europe, USA; randomization stratified by prior TNFI therapy (Ongoing; data up to 52 wks published)

TRIAL	PURPOSE / INTERVENTIONS	POPULATION	DESIGN (STATUS)
	(± stable MTX or GCs)		
MEASURE 1[Ref 7]	Assess efficacy-safety SEC 10 mg/kg i.v. then SEC150 SEC 10 mg/kg i.v. then SEC75 PBO i.v. then PBO s.c. → SEC150 or SEC75 ± SSZ, MTX, GC, NSAID	Active AS (modified New York criteria) despite concurrent treatment with maximum tolerated doses of NSAIDs; excluded prior cell-depleting therapies or biologics other than a maximum of 1 prior TNFI (inadequate response or intolerance) • 27% prior TNFI	2-yr MC DB PC Phase III RCT with 3-yr extension study; MEASURE 1 and MEASURE 2 conducted at a total of 106 centers across Asia, Europe, North America and South America (Ongoing; data up to 52 wks published)
MEASURE 2[Ref 7]	Assess efficacy-safety SEC150, SEC75, or PBO → SEC150 or SEC75 ± SSZ, MTX, GC, NSAID	Active AS (modified New York criteria) despite concurrent treatment with maximum tolerated doses of NSAIDs; excluded prior cell-depleting therapies or biologics other than a maximum of 1 prior TNFI (inadequate response or intolerance) • 39% prior TNFI	5-yr MC DB PC Phase III RCT (Ongoing; data up to 52 wks published)

ETA50, Etanercept 50 mg; GC, Glucocorticoid; MTX, Methotrexate; PsA, Psoriatic arthritis; PPsO, Plaque Psoriasis; all PPsO trials included patients with moderate–severe chronic PPsO despite topical and systemic therapies including phototherapy. SEC300 / 150 / 75, Secukinumab 300, 150 or 75 mg s.c. at Wk 0, 1, 2, 3 and 4 then every 4 weeks.

Plaque Psoriasis

Placebo- and Etanercept-controlled Trials in PPsO

In all placebo-controlled PPsO RCTs, study drug was administered subcutaneously at weeks 0, 1, 2, 3 and 4 then every 4 weeks for up to 12 weeks. In the ERASURE and FIXTURE[2] trials, nonresponders to placebo at Week 12 crossed over to receive secukinumab 300 mg (SEC300) or 150 mg (SEC150) at Weeks 12, 13, 14, 15 and 16 then every 4 weeks. Follow-up continued for up to 52 weeks after the first dose. In FIXTURE, etanercept 50 mg (ETA50) was given twice weekly until Week 12 then once weekly through Week 51. ERASURE and FIXTURE used lyophilized drug reconstituted with sterile water for injection. The FEATURE trial assessed the efficacy, safety and usability of secukinumab administered using a prefilled syringe.[21] The JUNCTURE trial assessed the safety, tolerability and usability of secukinumab administered by an autoinjector / pen.[22] Patients were included if they were 18 years of age and older, had chronic (≥ 6 months) plaque psoriasis affecting a minimum of 10% of body surface area, had a Psoriasis Area and Severity Index (PASI) score ≥ 12 and IGA score of ≥ 3 and were candidates for phototherapy or systemic therapy.

Of the 2077 patients in the SEC300 (N = 691), SEC150 (N = 692) and placebo groups (N = 323), 79% were naïve to biologic therapy and 45% were inadequate responders to prior nonbiologic treatment. Of those with prior biologic exposure, over one-third failed biologic therapy. About 15% to 25% of trial patients had a history of PsA.

The co-primary efficacy measures were PASI75 and IGA of clear or almost clear (IGA0/1) at Week 12 in the four placebo-controlled trials. Secukinumab and etanercept were compared using PASI75 response at Week 12 for noninferiority and PASI75 response or IGA0/1 response at Week 12 with continued response at Week 52 for superiority.

Main Results:

- SEC300 showed consistently large effect sizes relative to placebo for PASI75, IGA0/1 and PASI90 across trials (NNT range 1.3 to 1.9), whereas effect sizes for PASI100 varied, with NNTs ranging from 2.3 to 4.2 (Table 2).

Table 2 Selected Results at Week 12 of Placebo-controlled PPsO Trials

Trial	Measure	SEC300	SEC150	PBO	ETA50	NNT SEC300	NNT SEC150
ERASURE	N	245	243	246	—		
	PASI75, n (%)	200 (82)	174 (72)	11 (4)		1.3	1.5
	IGA0/1, n (%)	160 (65)	125 (51)	6 (2)		1.6	2.0
	PASI90, n (%)	145 (59)	95 (39)	3 (1)		1.7	2.6
	PASI100, n (%)	70 (29)	31 (13)	2 (1)		3.6	8.3
FIXTURE	N	323	327	324	323		
	PASI75, n (%)	249 (76)	219 (67)	16 (5)	142 (44)	1.4	1.6
	IGA0/1, n (%)	202 (62)	167 (51)	9 (3)	88 (27)	1.7	2.1
	PASI90, n (%)	175 (54)	137 (42)	5 (2)	67 (21)	1.9	2.5
	PASI100, n (%)	78 (24)	47 (14)	0 (0)	14 (4)	4.2	7.1
FEATURE	N	59	59	59	—		
	PASI75, n (%)	44 (76)	41 (70)	0 (0)		1.3	1.4
	IGA0/1, n (%)	40 (69)	31 (53)	0 (0)		1.5	1.9
	PASI90, n (%)	36 (60)	27 (46)	0 (0)		1.7	2.2
	PASI100, n (%)	25 (43)	5 (8)	0 (0)		2.3	12.5
JUNCTURE	N	60	61	61	—		
	PASI75, n (%)	52 (87)	44 (72)	2 (3)		1.2	1.5
	IGA0/1, n (%)	44 (73)	32 (53)	0 (0)		1.4	2.1
	PASI90, n (%)	33 (55)	25 (40)	0 (0)		1.8	2.5
	PASI100, n (%)	16 (27)	10 (17)	0 (0)		3.7	5.9

Sources: References 2,3,4,8
BIO, Biologic active control; ETA, EU-approved Etanercept (there was no verification that the EU and US etanercept products were comparable); IGA0/1, Investigator's Global Assessment modified 2011 of 0 (Clear) or 1 (Almost clear) = Treatment Success; NNT, Number needed to treat vs. placebo; PASI, Psoriasis Area and Severity Index (75% or 90% reduction in score from baseline to Week 12)
$P \leq 0.009$ for all comparisons versus placebo and versus ETA50.

- In FIXTURE, SEC300 was moderately more effective than ETA50 in PASI75 (NNT = 3.1) and IGA0/1 (NNT = 2.8).[2] The NNTs for SEC300 and SEC150 each versus ETA50 to achieve PASI100 were 5 and 10, respectively.
- SEC150 showed large effect sizes relative to placebo for PASI75 and IGA0/1, moderate to large effect sizes for PASI90, and consistently small effect sizes for PASI100 across trials. SEC150 had a small benefit over ETA50 in terms of PASI75 (NNT = 4.3) and IGA0/1 (NNT = 4.2).
- The median time to onset of effect based on achieving PASI50 was Week 3 with SEC300 in FIXTURE and FEATURE, Week 3.9–4 with SEC150 in FIXTURE and FEATURE, and Week 7 with ETA50 in FIXTURE ($p < 0.001$ for SEC300 and SEC150 each versus ETA50, FIXTURE trial).[2,4]
- In ERASURE, 161 (80.5%) of 200 PASI75 responders on SEC300 and 126 (72.4%) of 174 responders on SEC150 at Week 12 maintained their response at Week 52. The majority of patients who achieved *treatment success* maintained it after long-term therapy: 119 (74.4%) of 160 IGA0/1 responders on SEC300 and 74 (59.2%) of 125 IGA0/1 responders on SEC150 at Week 12 maintained their responses at Week 52.
- Similar results were seen in FIXTURE, with 210 (84.3%) of 249 SEC300, 180 (82.2%) of 219 SEC150 and 103 (72.5%) of 142 ETA50 Week-12 PASI75 responders maintaining response at Week 52. With regard to long-term *treatment success*, 161 (79.7%) of 202 SEC300, 113 (67.7%) of 167 SEC150 and 50 (56.8%) of 88 ETA50 Week-12 IGA0/1 responders maintained response at Week 52.
- In ERASURE and FIXTURE, there were no statistically significant differences between any of the active treatments and placebo in terms of Dermatology Life Quality Index (DLQI) scores, although the magnitude of the decreases in scores from baseline were numerically larger with secukinumab and etanercept relative to placebo and numerically larger with secukinumab versus etanercept.
- A prespecified subanalysis of patients with PPsO and concomitant PsA showed that SEC300 significantly improved physical functioning, as measured by the mean change from baseline to Week 12 in Health Assessment Questionnaire-Disability Index (HAQ-DI), relative to placebo (ERASURE, –0.35 vs. –0.08; $p = 0.0003$; FIXTURE, -0.41 vs. 0.02; $p = 0.0001$).[23] The corresponding values were -0.18 for SEC150 in ERASURE and –0.29 for ETA50 and –0.19 for SEC150 in FIXTURE. The Week-12 PASI75 responses were significantly better with SEC300 and SEC150 relative to placebo (ERASURE, 68% and 70% vs. 4%; FIXTURE, 72% and 59% vs. 2%; all $p < 0.0001$). SEC300 was also superior to etanercept in PASI75 response (72% vs. 39%; $p = 0.0084$) in the subpopulation with concomitant PsA.

- Separate results for the Japanese patients enrolled in ERASURE confirmed the efficacy and short-term safety of secukinumab in this subpopulation.[24]
- In a poster presentation, the results of a post hoc analysis of pooled data over 52 weeks from ERASURE and FIXTURE numerically favored SEC300 over ETA50 and SEC150, and SEC150 over ETA50 in terms of cumulative clinical benefit (CCB) as calculated by the total area under the curve of the percentage of PASI75, PASI90, PASI100 and DLQI1/0 responders over 52 weeks ($AUC_{0–52wks}$).[25] CCB ratios using PASI75 were 1.47 for SEC300 vs. ETA50, 1.25 for SEC300 vs. ETA50 and 1.17 for SEC300 vs. SEC150.
- Interim results of the ERASURE and FIXTURE extension study have been presented as a podium presentation.[26,27] The majority of SEC300 (87.1% of 363) patients and SEC150 (72.8% of 297) patients were relapse-free through Week 104 (2 years), compared with patients who discontinued active treatment and received placebo: SEC300–PBO (16.0%, N = 180) and SEC150–PBO (12.7%, N = 150).

Secukinumab Versus Ustekinumab in PPsO: The CLEAR Trial

CLEAR was a 134-center, Phase IIIb, superiority trial that involved adults aged 18 years and older who had a diagnosis of psoriasis for at least 6 months, moderate to severe plaque psoriasis at screening and disease that was inadequately controlled by topical treatments, phototherapy and/or previous systemic therapy (excluding any biologics directly targeting IL-17A/IL-17 receptor A or IL-12/IL-23).[16] Trial patients were randomized to subcutaneously administered SEC300 or ustekinumab 45 mg for patients ≤ 100 kg or 90 mg for patients > 100 kg at baseline (UST45/90). Randomization was stratified by body weight (≤ 100 kg and > 100 kg). Secukinumab doses were given at Weeks 0, 1, 2, 3 and 4 then every 4 weeks from Week 4 to Week 48. UST45/90-treated patients were administered active treatment injections at Weeks 0 and 4 then every 12 weeks from Week 16 to Week 40 and dummy placebo injections at other weeks to match injections given to patients in the SEC300 group. Treatment continued under blinded conditions until Week 52.

The study population had a mean age of 45 years, 71% of patients were male, and 87% were Caucasian. The mean time since psoriasis diagnosis was about 18 years and about 18% of patients reported concomitant psoriatic arthritis. The mean percentage of affected body surface area was 32% and about 38% of patients had an IGA score of 4 (severe). Of the 676 randomized patients, the majority (65%) had previously received a conventional agent (including methotrexate, cyclosporine, corticosteroids and fumaric acid esters) and had not received prior biologic therapy (i.e., 14% had received a biologic agent and 10% had failed a biologic agent).

Main Results:

- SEC300 was superior to UST45/90 in terms of PASI90 at Week 16, the primary efficacy measure, as well as PASI90 at Weeks 12 and 4 (all p-values < 0.0001; Table 3).

Table 3 Results of the CLEAR Trial (SEC vs. UST in PPsO)

Measure	SEC300 N=334	UST45/90 N=335	NNT
PASI75 at Wk 12, n (%)	304 (91.0)	265 (79.1)	8.4
PASI75 at Wk 16, n (%)	311 (93.1)	277 (82.7)	9.6
PASI90 at Wk 12, n (%)	243 (72.8)	179 (53.4)	5.2
PASI90 at Wk 16, n (%) (PEM)	264 (79.0)	193 (57.6)	4.7
PASI100 at Wk 12, n (%)	130 (38.9)	86 (25.7)	7.6
PASI100 at Wk 16, n (%)	148 (44.3)	95 (28.4)	6.3
IGA0/1+2 at Wk 12, n (%)	270 (80.8)	218 (65.1)	6.4
IGA0/1+2 at Wk 16, n (%)	277 (82.9)	226 (67.5)	6.5

Source: Ref 16
P ≤ 0.0139 for all comparisons.
IGA0/1+2, Modified investigator's global assessment modified 2011 of 0 (clear) or 1 (almost clear) and an improvement of ≥ 2 points from baseline; PEM, Primary efficacy measure

- Superiority of SEC300 was also shown in terms of PASI75, PASI100 and IGA0/1 with improvement of ≥ 2 points from baseline at Weeks 4, 12 and 16 (p-values ≤ 0.0139). The size of the incremental benefit with SEC300 over UST45/90 was small for each of the PASI and IGA outcome measures.
- At Weeks 4, 12 and 16, a significantly greater percentage of SEC300 patients than UST45/90 patients endorsed Dermatology Life Quality Index (DLQI) scores of 0 or 1 point (indicating "no effect at all" on patient's health-related quality of life). The percentage of patients with DLQI of 0 or 1 at Week 16 was 71.9% (238/331) and 57.4% (191/333) in the SEC300 and UST45/90 groups, respectively (p < 0.0001).
- SEC300 was also superior to UST45/90 in mean scores of patient-reported outcomes (pain, itching and scaling) at Week 16, although the differences between treatments in the absolute changes in scores from baseline to Week 16

were clinically small. (I.e., changes from baseline across outcomes ranged from –3.3 to –5.7 for SEC300 and –2.8 to –5.2 for UST45/90 with differences of 0.4–0.5 points on an 11-point numeric rating scale.)

- The safety profiles of SEC300 and UST45/90 were similar during the 16-week treatment period in terms of the incidences of adverse events (64.2% and 58.3%, respectively), death (0 in both groups), nonfatal serious adverse events (3.0% and without clustering in both groups), discontinuations due to adverse events (0.9% and 1.2%), and infections / infestations (29.3% and 25.3%, all mild or moderate and none led to discontinuation of treatment). The most common adverse events in both groups were headache, nasopharyngitis, diarrhea, fatigue and arthralgia. There were no reports of neutropenia, inflammatory bowel disease or tuberculosis.

Secukinumab Re-treatment As Needed Versus Fixed-interval Maintenance Regimen: SCULPTURE Trial

SCULPTURE was a multicenter, double-blind, phase III, noninferiority trial that compared re-treatment as needed for relapse with a fixed-interval (once monthly) maintenance regimen in patients with moderate to severe chronic PPsO. This study includes an ongoing long-term, safety, tolerability and efficacy extension study evaluating SEC300 and SEC150. Blinded study continues from Week 52 to Week 152, followed by open-label treatment from Week 156 through Week 260.

The primary efficacy measure was the PASI75 responder rate at Week 12. A novel end point was used to show maintenance of PASI75 response: Week 52 was the time point used for the fixed-interval regimen, Week 40 for the re-treatment-as-needed regimen in patients who did not require active treatment at Week 40, and Week 52 for the re-treatment-as-needed regimen in patients who did require active treatment at Week 40.

For induction therapy, 966 patients were randomized to self-administer SEC300 (N = 484) or SEC150 (N = 482) at Weeks 0, 1, 2, 3, 4 and 8. At Week 12, PASI75 responders were re-randomized to either re-treatment-as-needed (N = 217 for SEC300, N = 206 for SEC150) or fixed-interval (N = 217 for SEC300, N = 203 for SEC150) maintenance therapy. The re-treatment-as-needed regimen consisted of secukinumab at Week 12, then placebo until start of relapse (defined as loss of ≥ 20% of maximum PASI score improvement from baseline plus loss of PASI75 response). The fixed-interval regimen consisted of secukinumab every 4 weeks until PASI75 response was regained.

PASI partial responders at Week 12 were offered entry into the STATURE study, whereas PASI nonresponders at Week 12 were discontinued from the study.

The 843 core study patients were mostly male (66.4%), had a mean age of 45 years, and were primarily Caucasian (70%) or Asian (26%). About 55% of patients had received prior csDMARDs, 18% of patients had received prior TNFI therapy and 12.0% had received prior IL-12/23 inhibitor therapy. A total of 642 patients entered the extension study.

Main Results:

- Noninferiority of the re-treatment-as-needed relative to the fixed-interval regimen was not established.
- PASI75 response was achieved at Week 12 by 90.1% of SEC300 patients and 84.4% of SEC150 patients.
- With the SEC300 dose, 67.7% of 217 re-treatment-as-needed patients and 78.2% of 216 fixed-interval patients maintained PASI75 response from Week 12 to Week 40/52. The corresponding values for the SEC150 patients were 52.4% of 206 re-treatment-as-needed patients and 62.1% of 203 fixed-interval patients.
- PASI90 response at Week 52 was highest for SEC300 fixed-interval (59.7%), followed by SEC150 fixed-interval (45.8%), SEC300 re-treatment-as-needed (13.8%) and SEC150 re-treatment-as-needed (11.2%).
- Among the re-treatment-as-needed patients, 85.2% of SEC300 patients and 85.4% of SEC150 patients relapsed at least once during maintenance therapy, with median times to relapse of 24 weeks and 20 weeks (from Week 12), respectively. Of those who relapsed at least once, 69.2% and 55.1% of SEC300 and SEC150 patients regained PASI75 response, with a numerically greater percentage of patients achieving PASI75 response within 8 weeks with the higher dose (76.6%) than the lower dose (68.0%). Retreatment as-needed after relapse due to interruption of therapy failed to recapture response in 31% to 45% of patients; however, these failure rates reflect the stringent relapse criteria (loss of PASI75 response plus loss of 20% or more of maximum PASI score gain), which may define a degree of relapse too severe to recover response. Different failure rates may result if other criteria for relapse were used.
- Interim results of the extension study after 3 years supported the core study results. The fixed-interval SEC300 and SEC150 dosing regimens consistently maintained numerically better response rates than the corresponding re-treatment-as-needed regimens in terms of PASI75, PASI90 and PASI100.

Intravenous Versus Subcutaneous Secukinumab in PPsO: The STATURE Trial

STATURE was a multicenter, double-blind, double-dummy phase III RCT that compared the safety, tolerability and long-term efficacy of intravenous and subcutaneous secukinumab in 43 partial responders from the SCULPTURE trial. Study patients were randomized to receive secukinumab 300 mg subcutaneously at Weeks 0 and 4 or secukinumab 10 mg/kg intravenously at Weeks 0, 2 and 4. All patients then received secukinumab 300 mg subcutaneously every 4 weeks from Week 8 to Week 36. Fewer than the 132 targeted patients were randomized because fewer partial responders were eligible for the study (PASI75 response rates were higher than predicted in SCULPTURE).

Main Results:

- The study failed to show statistical significance for *both* co-primary end points at Week 8. For PASI75 response, the rates were 90% (19/21) for secukinumab 10 mg/kg intravenously and 67% (14/21) for secukinumab 300 mg subcutaneously ($p = 0.06$). Only the IGA0/1 co-primary end point met the level of statistical significance (67% versus 33% for intravenous and subcutaneous dose groups, respectively; $p = 0.03$).
- PASI75 response rates at Week 40 were 62% and 48% for the intravenous and subcutaneous dose groups (no statistical analysis).
- Overall, intravenous secukinumab and subcutaneous secukinumab maintained PASI75 response from Week 8 to Week 40 in 68% and 64% of the respective treatment groups. However, an opposite pattern was seen using maintenance of IGA0/1 response from Week 8 to Week 40: 43% and 57%, respectively.
- Intravenous secukinumab was significantly better than subcutaneous secukinumab in achieving PASI90, although the confidence interval for the treatment difference was wide (62% vs. 9%; 95% CI for difference 2.9–101.1; $p < 0.01$).

Secukinumab Versus Placebo for PPsO With Significant Nail Involvement: TRANSFIGURE Trial

TRANSFIGURE is an ongoing 128-week double-blind, placebo-controlled phase IIIb RCT evaluating the efficacy and safety of subcutaneous SEC300 and SEC150 in patients who have moderate to severe PPsO with significant nail involvement. The primary efficacy measure is the percentage change from baseline to Week 16 in the total fingernail Nail Psoriasis Severity Index (NAPSI; score range, 0–80). The 16-week interim results based on data from study patients (66 SEC300, 67 SEC150 and 65 placebo) have been presented as a poster.[9,19] Of the 198 patients, 23.2% had prior biologic exposure.

Main Results:

- The mean NAPSI percentage change from baseline to Week 16 was –45.3%, –37.9% and –10.8% for SEC300, SEC150 and placebo, respectively, showing the superiority of both secukinumab doses relative to placebo (last observation carried forward analysis; $p < 0.0001$).
- Significant differences between SEC300 or SEC150 and placebo were seen as early as Week 8 ($p \leq 0.01$).
- Secondary efficacy measures showed that SEC300 and SEC150 were efficacious in terms of PASI75, IGA0/1, PASI90 and PASI100 response (p-values < 0.001).

Table 4 Unpublished Week 16 Interim Results from TRANSFIGURE (PPsO Trial)

Measure	SEC300 N=66	SEC150 N=67	PBO N=65
PASI75, n (%)	57 (87)	52 (77)	3
IGA0/1, n (%)	49 (74)	42 (63)	2 (3)
PASI90, n (%)	48 (72)	36 (54)	1 (2)
PASI100, n (%)	22 (34)	17 (25)	0 (0)

(5)

Source: Ref 9

P-values ≤ 0.01 vs. placebo for all comparisons

Secukinumab Versus Placebo for Palmoplantar PPsO: GESTURE Trial

GESTURE is an ongoing 128-week double-blind, placebo-controlled phase IIIb RCT evaluating the efficacy and safety of SEC300 and SEC150 in patients with moderate to severe chronic PPsO on the palms and soles. The primary efficacy measure was the percentage of patients with response, defined as an IGA0/1 for palmoplantar psoriasis (ppIGA0/1) and a reduction of ≥ 2 points from baseline on the ppIGA scale at Week 16. The 16-week interim results have been verbally presented.9,20 Of the 205 randomized patients, 11.7% had prior exposure to biologic therapy.

- The ppIGA0/1 response rates at Week 16 were 33.3%, 22.1% and 1.5% for SEC300 (N = 69), SEC150 (N = 68) and placebo (N = 68), respectively (nonresponder imputation analysis; $p < 0.001$ for both doses versus placebo).
- The percentage change in palmoplantar PASI from baseline to Week 16 were –54.6%, –35.3% and –4.1% for SEC300, SEC150 and placebo, respectively (multiple imputation analysis; $p < 0.05$ vs. placebo).

Psoriatic Arthritis

FUTURE 1 and FUTURE 2 were major efficacy-safety trials involving adults aged 18 years and older with a diagnosis of PsA of at least 5 years and active disease (greater than 3 swollen and greater than 3 tender joints) despite therapy with nonsteroidal antiinflammatory drugs (NSAIDs), DMARDs or TNFIs. About 70% of patients were required to be TNFI-naïve. Exclusion criteria included treatment with more than three TNFIs in FUTURE 1. Concomitant therapy with stable doses of glucocorticoids (≤ 10 mg/d prednisone or equivalent) and methotrexate (≤ 25 mg/week) were allowed. Randomization was stratified by prior TNFI therapy.[9]

In FUTURE 1, secukinumab 10 mg/kg or placebo was administered intravenously at Weeks 0, 2 and 4, then SEC75, SEC150 or placebo was given subcutaneously every 4 weeks.[5] Based on responder status, placebo patients were re-randomized at Week 16 or Week 24 to receive SEC75 or SEC150 every 4 weeks.

The dosage regimen in FUTURE 2 differed from that in FUTURE 1. In FUTURE 2, SEC75, SEC150 or SEC300 was administered subcutaneously at Weeks 0, 1, 2, 3 and 4, then every 4 weeks to Week 52.[6] At Week 16 or Week 24, based on nonresponse or response, respectively, placebo patients were re-randomized to receive SEC300 or SEC150 every 4 weeks.

The population of both FUTURE 1 and FUTURE 2 trials consisted of a mixture of patients with various PsA subtypes, of which the main types were polyarticular arthritis with no evidence of rheumatoid nodules (80%), asymmetric peripheral arthritis (62%), and distal interphalangeal involvement (59%).[8] More than 47% of patients had dactylitis and more than 62% had enthesitis at baseline. Overall, 55% continued baseline methotrexate during secukinumab therapy, and 32% had an inadequate response or intolerance to prior TNFIs.

Main Results:

- In terms of the primary efficacy measure, ACR20 response at Week 24, the SEC300, SEC150 and SEC75 treatment groups were significantly better than placebo. SEC300 and SEC150 had moderate effect sizes, whereas SEC75 had small to moderate effect sizes across the two trials (Table 5).

Table 5 Primary Efficacy Results at Week 24 in PsA Trials

Measure	SEC300	SEC150†	SEC75†	PBO	NNT SEC300	NNT SEC150	NNT SEC75
FUTURE 1	—	N=202	N=202	N=202			
ACR20 Response, Wk 24, n (%)		101 (50)*	102 (50)*	35 (17)	—	3.0	3.0
FUTURE 2	N=100	N=100	N=99	N=98			
ACR20 Response, Wk 24, n (%)	54 (54)*	51 (51)*	28 (29)*	14 (15)	2.5	2.8	7.1

Sources: References 5,6,9.

P-values < 0.001 versus placebo for all comparisons in FUTURE 1 and ≤ 0.0399 in FUTURE 2.

† In FUTURE 1, secukinumab 10 mg/kg was administered intravenously at Weeks 0,2 and 4 then doses of 150 or 75 mg were injected subcutaneously every 4 weeks. In FUTURE 2, the loading and maintenance doses were given subcutaneously. See text for details.

- The secondary efficacy measures supported the primary efficacy results, with SEC300 showing consistent efficacy across outcome measures and SEC150 and SEC75 having inconsistent efficacy across measures and across the two trials (Table 6). FUTURE 2 was a smaller trial and treatment differences may not have reached the level of statistical significance (type II error).

Table 6 Secondary Efficacy Results at Week 24 in PsA Trials

Measure	SEC300	SEC150	SEC75	PBO
FUTURE 1				
ACR50, n/N (%)	—	70/202 (35)*	62/202 (31)*	15/202 (7)
PASI75, n/N (%)	—	66/108 (61)*	70/108 (65)*	9/109 (8)
PASI90, n/N (%)	—	49/108 (45)*	53/108 (49)*	4/109 (4)
Δ DAS28-CRP, mean (SE)	—	–1.62 (0.08)*	–1.67 (0.09)*	–0.77 (0.12)
Δ HAQ-DI, mean (SE)	—	–0.40 (0.04)*	–0.41 (0.04)*	–0.17 (0.05)
Δ SF-36-PCS, mean (SE)	—	5.91 (0.53)*	5.41 (0.52)*	1.82 (0.72)
Dactylitis Resolved, n/N (%)		109/208 (52)* – pooled data		18/116 (16)
Enthesitis Resolved, n/N (%)		121/255 (48)* – pooled data		15/117 (13)
Δ mTSS, mean (SE)	—	0.02 (0.12)*	0.13 (0.09)*	0.57 (0.19)
FUTURE 2				
ACR50, n/N (%)	35/100 (35)*	35/100 (35)	18/99 (18)	7/98 (7)
PASI75, n/N (%)	26/41 (63)*	28/58 (48)*	14/50 (28)	7/43 (16)
PASI90, n/N (%)	20/41 (49)*	19/58 (33)*	6/50 (12)	4/43 (9)
Δ DAS28-CRP, LSM (SE)	–1.61 (0.11)*	–1.58 (0.11)*	–1.12 (0.11)	–0.96 (0.15)
Δ HAQ-DI, LSM (SE)	–0.56 (0.05)*	–0.48 (0.05)	–0.32 (0.05)	–0.31 (0.06)
Δ SF-36-PCS, LSM (SE)	7.25 (0.74)*	6.39 (0.73)*	4.38 (0.75)	1.95 (0.97)
Dactylitis Resolved, n/N (%)		52/111 (47) – pooled data		4/27 (15)
Enthesitis Resolved, n/N (%)		76/188 (40) – pooled data		14/65 (22)

Sources: References 5,6,9. * P < 0.05 versus placebo. Δ, Change from baseline to Week 24.

- In FUTURE 1, the mean changes from baseline in the van der Heijde-modified total Sharp Score (mTSS) showed a small but statistically significant inhibition of structural joint damage with SEC150 (0.13) and SEC75 (0.02) versus placebo (0.57; $p < 0.05$ for comparisons with both doses).
- In the prespecified exploratory subgroup analysis in FUTURE 1, secukinumab was efficacious in terms of ACR20 response at Week 24 regardless of prior TNFI exposure (inadequate response or unacceptable adverse effects), although response rates were numerically higher in patients naive to TNFI therapy than those with prior TNFI exposure: 54.5% and 39.0% for SEC150, 55.6% and 38.3% for SEC75 versus 17.5% and 16.9% for placebo, respectively. In FUTURE 2, the effect of prior exposure to TNFIs was assessed using ACR70. This analysis also showed no significant interaction between treatment and TNFI status, with the magnitude of response tending to be higher in the TNFI-naïve subgroup.[6]
- Clinical benefits in the secukinumab groups were maintained through 52 weeks of therapy in both trials. The conservative estimates of Week-52 ACR20 response were 59.9% for SEC150 and 56.9% for SEC75 in FUTURE 1. In FUTURE 2, those estimates were 64% for both SEC300 and SEC150 and 51% for SEC75.
- Although not a predefined end point, there was no apparent dose-response relationship with secukinumab in FUTURE 1, possibly because of the intravenous loading doses given to both treatment groups prior to switching to subcutaneous administration. A dose-response relationship was noted for psoriasis symptoms (PASI75 and PASI90) with the 300-mg and 150-mg doses in FUTURE 2.

Ankylosing Spondylitis

MEASURE 1 and MEASURE 2 are ongoing, long-term major efficacy-safety trials comparing SEC75 and SEC150 with placebo in 371 and 219 randomized patients with AS, respectively.[7] MEASURE 1 randomly assigned patients to receive an intravenous loading dose of secukinumab 10 mg/kg at Week 0, 2 and 4 then secukinumab 150 mg subcutaneously every 4 weeks (N = 125) or an intravenous loading dose regimen then 75 mg subcutaneously every 4 weeks (N = 124) or placebo intravenously then subcutaneously to match the drug administration intervals in the active groups (N = 122). In MEASURE 2, patients were randomized to receive a subcutaneous loading dose of secukinumab 150 mg (N = 72) or 75 mg (N = 73) at Week 0, 1, 2, 3, and 4 then every 4 weeks or placebo at matching intervals (N = 74). At Week 16 of both trials, placebo patients were randomized to receive secukinumab 150 mg or 75 mg every 4 weeks starting at either Week 16 (for nonresponders to placebo) or Week 24 (for responders to placebo) until the end of the study. In MEASURE 1, 33%, 15% and 13% of patients received concomitant treatment with sulfasalazine, methotrexate and glucocorticoids, respectively. In MEASURE 2, the corresponding percentages were 14%, 12% and 5%, respectively.

The primary efficacy measure was at least 20% improvement in the Assessment of Spondyloarthritis International Society response criteria (ASAS20) at Week 16. Further definition of ASAS20 and the secondary efficacy measures are described in Table 7.

Table 7 Descriptions of Efficacy Measures in AS Trials

ASAS20	At least 20% improvement in the Assessment of Spondyloarthritis International Society response criteria including absolute improvement of ≥ 1 unit on a 10-unit scale in at least three of the four main ASAS domains (patient global assessment, pain, function and inflammation), with no worsening by ≥ 20% in the remaining domain)
ASAS40	Improvement of ≥ 40% on ASUS and absolute improvement of ≥ 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain.
hsCRP	High-sensitivity C-reactive protein level
ASAS5/6 response	≥ 20% improvement in 5 of the 6 ASAS response domains (patient global, pain, function, inflammation, CRP and spinal mobility)
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index (score range, 0–10 with higher scores indicating more severe disease activity)
SF-36 Physical Component	Version 2 of the Medical Outcomes Study 36-item Short-Form Health Survey (scores range from 0 = Maximum Disability to 100 = No Disability) for individual domains, with a normative composite summary score of 50
ASQoL	Ankylosing Spondylitis Quality of Life score (range 0 = Best Quality to 18 = Poorest Quality)
ASAS partial remission	Score of ≤ 2 units in each of the four core ASAS domains

The mean age of patients was about 42 years and 70% of patients were male across MEASURE 1 and MEASURE 2. About 61% of patients were white and 17% Asian in MEASURE 1, while 96% were white and 4% Asian in MEASURE 2. The percentage of patients who had an inadequate response to prior TNFI therapy was 27% in MEASURE 1 and 39% in MEASURE 2. Inflammatory bowel disease was present at baseline in 3% of MEASURE 1 patients and 2% of MEASURE 2 patients. The percentages of discontinuations from the studies were 5% in MEASURE 1 and 9% in MEASURE 2 at Week 16, and 14% and 17% for each study, respectively, at Week 52.

Main Results:

- SEC150 showed consistent efficacy across both trials with a moderate effect size relative to placebo in achieving ASAS20 response, and the ASAS20 response rates were similar with the higher dose regardless of whether patients had received an intravenous or a subcutaneous loading dose (Table 8).

Table 8 Efficacy Results at Week 16 in AS Trials

Outcome Measure	SEC150†	SEC75†	PBO	NNT SEC150	NNT SEC75
MEASURE 1	N=125	N=124	N=122		
ASAS20 Response, Wk 16, n (%) (PEM)	76 (61)*	74 (60)*	35 (29)	3.1	3.2
ASAS40 Response, n (%)	52 (42)*	41 (33)*	16 (13)	3.4	5.0
hsCRP, ratio of post-baseline vs. baseline level	0.40*	0.45*	0.97		
ASAS5/6 response, n (%)	61 (49)*	56 (45)*	16 (13)	2.8	3.1
BASDAI score, mean Δ	–2.32*	–2.34*	–0.59		
SF-36 Physical Component Summary Score, mean Δ	5.57*	5.64*	0.96		
ASQoL score, mean Δ	–3.58*	–3.61*	–1.04		
ASAS partial remission, n (%)	19 (15)*	20 (16)*	4 (3)	8.3	7.7
MEASURE 2	N=72	N=73	N=74		
ASAS20 Response, Wk 16, n (%) (PEM)	44 (61)*	30 (41)	21 (28)	3.0	NSD
ASAS40 Response, n (%)	26 (36)*	19 (26)	8 (11)	4.0	NSD
hsCRP, ratio of post-BL vs. BL level	0.55*	0.61	1.13		
ASAS5/6 response, n (%)	31 (43)*	25 (34)	6 (8)	2.9	NSD
BASDAI score, mean Δ	–2.19*	–1.92	–0.85		
SF-36 Physical Component Summary Score, mean Δ	6.06*	4.77	1.92		
ASQoL score, mean Δ	–4.00*	–3.33	–1.37		
ASAS partial remission, n (%)	10 (14)	11 (15)	3 (4)	NSD	NSD

Source: Reference 7. * P < 0.01 versus placebo. † SEC150 / 75, Secukinumab 150 or 75 mg subcutaneously every 4 weeks; these maintenance doses were preceded by an intravenous loading dose in MEASURE 1 and by subcutaneous loading dose in MEASURE 2. See text for details. Δ, Change from baseline; PEM, Primary efficacy measure. See Table 7 for other abbreviations.

- SEC75 showed efficacy in MEASURE 1 (with intravenous loading dose) but not in MEASURE 2 (with subcutaneous loading dose).
- A statistically significant difference between SEC150 and placebo was seen as early as Week 1 in both trials.[9]
- The efficacy of SEC150 was supported by all secondary efficacy measures in both trials, with the exception of ASAS partial remission, which showed no significant difference versus placebo in MEASURE 2 (Table 8).
- SEC150 had moderate effect sizes in terms of the ASAS40 response and ASAS5/6 response, whereas the effect size was small in terms of the ASAS partial remission rate.
- SEC75 showed efficacy only in MEASURE 1, in which the subcutaneous maintenance doses were preceded by an intravenous loading dose.
- Long-term efficacy of secukinumab up to 52 weeks was shown by the maintenance of ASAS20 responses from Week 16 to Week 52 in the patients randomized to active treatment initially.[7] Placebo patients improved in terms of ASAS20 response rates after they were randomly reassigned to active therapy at Week 16 or Week 24 (depending on response status).

Indirect Efficacy Comparisons for Plaque Psoriasis

A systematic review evaluated the available evidence from RCTs on the efficacy and safety of longer-term systemic treatments for treatment of adults with moderate to severe PPsO.[28] None of the conventional treatments were found to have placebo-controlled data. The biologics and apremilast have been shown to be efficacious for PPsO up to 28 weeks, with secukinumab having the second highest pooled risk ratio (11.97; 95% CI 8.83–16.23) for PASI75 response, following infliximab (13.07; 8.60–19.87) and preceding (from next highest to lowest) ustekinumab (11.39; 8.94–14.51), adalimumab (8.92; 6.33–12.57), etanercept (8.39; 6.74–10.45) and apremilast (5.83; 2.56–13.17) (Table 9). The quality of evidence for this measure was low.

Table 9 Biologics or Apremilast Versus Placebo: PASI75 at Weeks 24–28

Intervention	K	PASI75 Response (n/N), Active Tx	PASI75 Response (n/N), Placebo	Risk Ratio	95% CI
Adalimumab 40 mg e.o.w. – wk 24	1	25/38	6/46	5.04	2.31–11.01
Adalimumab 80 mg at 0 wks then 40 mg e.o.w. – wk 24	3	627/899	37/496	8.71	5.93–12.77
Adalimumab 80 mg e.o.w. – wk 24	1	34/42	6/46	6.21	2.90–13.28
Adalimumab (All Dosages)	*3*	*686/979*	*37/496*	*8.92*	*6.33–12.57*
Apremilast 30 mg b.i.d. – wk 24	1	35/88	6/88	5.83	2.56–13.17
Etanercept 50 mg q.w. – wk 24	4	253/513	31/471	7.04	4.94–10.03
Etanercept 50 mg b.i.w. (24 wk) or 50 mg b.i.w. (12 wk) / 50 mg q.w. (12 w) – wk 24	5	605/1056	72/1056	8.43	6.70–10.60
Etanercept (All Dosages)	*7*	*858/1569*	*78/1166*	*8.39*	*6.74–10.45*
Infliximab 5 mg/kg – wk 24/26	4	439/534	21/349	13.07	8.60–19.87
Secukinumab 300 mg – wk 24	2	491/572	39/572	12.59	9.28–17.08
Secukinumab (All Dosages)	*2*	*932/1142*	*39/572*	*11.97*	*8.83–16.23*
Ustekinumab 45 mg – wk 28	5	680/922	62/919	10.92	8.56–13.94
Ustekinumab 90 mg – wk 28	3	547/702	47/697	11.60	8.77–15.33
Ustekinumab (All Dosages)	*5*	*1227/1624*	*62/919*	*11.39*	*8.94–14.51*

B.i.d., Twice a day; b.i.w., Twice weekly; e.o.w., Every other week; K, Number of trials

For PASI90 response, the order of treatments based on relative risks versus placebo (from highest to lowest) was secukinumab (RR 40.15; 95% CI 20.97–76.89), ustekinumab (31.63; 19.43–51.51), infliximab (31.00; 13.45–71.46), adalimumab (23.17; 12.51–42.91), etanercept (19.14; 11.59–31.60) and apremilast (13.00; 1.74–97.25). The quality of evidence for all of these comparisons was low.

A different order of treatments based on relative risks was seen for Physician Global Assessment of 'Clear' or 'Almost Clear': infliximab (13.13; 95% CI: 8.45, 20.38), ustekinumab (9.91; 7.76, 12.66), secukinumab (9.84; 7.25, 13.36), adalimumab (8.06; 5.89, 11.04), etanercept (7.16; 5.35, 9.57), and apremilast (5.00; 2.19, 11.41). The quality of evidence was low.

For the patient-reported outcome Dermatology Life Quality Index (DLQI), high-quality data showed that infliximab was statistically significantly superior to placebo in terms of the absolute reduction in mean DLQI (mean difference: 9.80; 95% CI 8.19–11.41). Low- to moderate-quality data showed that adalimumab (80 mg every other week, 80 mg loading dose followed by 40 mg every other week, and 40 mg every other week) was also better than placebo but the effects were small for the two regimens using maintenance doses of 40 mg every other week. High-quality evidence showed that etanercept 50 mg twice weekly was efficacious relative to placebo in the percentage reduction in mean DLQI (mean difference: 57.00; 38.52–75.48).

Head-to-head trials showed EU-approved etanercept to be inferior to secukinumab 150 mg (RR 0.80; 0.72–0.89), secukinumab 300 mg (0.72; 0.65–0.79) and infliximab (0.48; 0.26–0.89) in terms of PASI75 response (moderate quality evidence for these results). For the same measure, methotrexate (15–20 mg every week) was inferior to infliximab (5 mg/kg). The FIXTURE trial comparing secukinumab and EU-approved etanercept was the only included head-to-head trial with efficacy data extending beyond 28 weeks.[2]

None of the biologic agents and apremilast differed from placebo in the evaluated safety measures (incidences of adverse events, serious adverse events and withdrawals due to adverse events).

In summary, the findings of the systematic review support infliximab, secukinumab and ustekinumab as the more effective systemic agents of those evaluated in longer-term RCTs.

Potential Off-Label Use

Evidence of Inefficacy

- Crohn's Disease – In a proof-of-concept study (N = 59), secukinumab was ineffective or worsened Crohn's disease and had a higher rate of adverse events including infections.[29]
- Noninfectious Uveitis – Four trials have been conducted. A small (N = 37) phase II trial involving patients with noninfectious uveitis requiring steroid-sparing immunosuppressive therapy showed that intravenous dosages (30 mg/kg every 4 weeks for 2 doses and 10 mg/kg every 2 weeks for 4 doses) produced better responder rates than subcutaneous

dosages (300 mg every 2 weeks for 4 doses).[30] Only the 30 mg/kg intravenous dosage being statistically and clinically superior to the subcutaneous dosage. Subsequently, three phase III multicenter, double-blind, placebo-controlled RCTs evaluated secukinumab in patients with Behçet's uveitis (SHIELD trial, N = 118); patients with active, noninfectious, non-Behçet's uveitis (INSURE trial; N = 31); and patients with quiescent, noninfectious, non-Behçet's uveitis (ENDURE trial; N = 125).[31] The SHIELD trial failed to show significant benefit with secukinumab therapy in terms of reducing recurrences (primary efficacy measure), and consequently the INSURE trial was terminated early. The ENDURE trial was also terminated early because interim analyses suggested no treatment benefit in any primary or secondary measures. However, secondary efficacy measures in the SHIELD trial suggested that secukinumab may reduce immunosuppressive medication use.

- Dry Eye – A double-blind, placebo-controlled RCT in 72 outpatients with dry eye showed no evidence of improvement in the signs and symptoms of dry eye.[32]

Ongoing Trials

- Rheumatoid Arthritis – Secukinumab showed some efficacy in secondary efficacy measures but not the primary efficacy measure (ACR20 response at Week 16) and had an acceptable safety profile in patients with rheumatoid arthritis inadequately responding to DMARDs or biologics in a 52-week phase II trial (N = 237).[33,34,35]
- Palmoplantar Psoriasis – Phase III trial[1]
- Nail Psoriasis – Phase III trial[1]
- Multiple Sclerosis, Relapsing-Remitting – Limited raw data suggest potential benefit.[36] Three phase II trials.[1]
- Asthma – Phase II trial[1]
- Polymyalgia Rheumatica – Phase II trial[1]

Safety

The safety profile of secukinumab was comparable to that of ustekinumab in PPsO (CLEAR trial).[16]

For more detailed information, refer to the prescribing information.

Boxed Warning	• None
Contraindications	• Serious hypersensitivity reaction to secukinumab or to any of the excipients
Warnings / Precautions	• Infections – Use caution in patients with chronic infection or history of recurrent infection. If a serious infection develops, discontinue secukinumab until the infection resolves. • Tuberculosis (TB) – Prior to initiating secukinumab therapy, evaluate for TB and initiate treatment for latent TB. • Inflammatory Bowel Disease (IBD) – New onset or exacerbation of IBD may occur. Use caution in patients with IBD. • Hypersensitivity Reactions – If an anaphylactic reaction or other serious allergic reaction occurs, discontinue secukinumab immediately and initiate appropriate therapy. • Risk of Hypersensitivity in Latex-sensitive Individuals – The removable cap of the secukinumab Sensoready pen and the prefilled syringe contains natural rubber latex. • Vaccinations – Prior to initiating therapy with secukinumab, consider completion of all age appropriate immunizations according to current immunization guidelines. Patients treated with secukinumab should not receive live vaccines.

Short-term (≤ 24 Weeks) Safety Considerations

Infection or Infestation	Based on observations of individuals with genetic defects involving the Th17 pathway or IL-17 signaling, inhibition of IL-17 would be expected to increase the risk of fungal infections, particularly mucocutaneous candidiasis, and staphylococcal skin infections. • The most common types of infections in clinical trials were upper respiratory tract infection and nasopharyngitis. • In PPsO trials, secukinumab therapy was associated with more frequent reports of infections, including pneumonia and bacterial abscess.[1] SEC300 and ETA50 had similar incidences of infection and infestation SAEs (both 1.4 events per 100 patient-years) and higher incidences

	than SEC150 and PBO (1.1 and 1.0, respectively).[1] The rate of infections seemed to be dose-related particularly for candidiasis.[1] • PPsO Trials (SEC300, SEC150, PBO, ETA, respectively): 28.3%, 29.3%, 19.3%, 25.7% at 12 wks); 91.1, 85.3, 101.9, 93.7 events per 100 patient-years at 52 wks. • SEC and UST had similar incidences of infections and infestation – CLEAR (PPsO): 29.3% vs. 25.3%.[16] • FUTURE 1 and FUTURE 2 (PsA, SEC vs. PBO): 29.7% vs. 23.3% and 27.3% vs. 31.0%
Candida Infections	IL-17 inhibition may affect immunity against bacteria, parasites and fungi, particularly in mucosa (e.g., oral and vulvovaginal candidiasis). • PPsO Trials (SEC300, SEC150, PBO, ETA, respectively): 1.2%, 0.4%, 0.3%, 0.3% at 12 wks; 3.6, 1.8, 1.0, 1.4 events per 100 patient-years at 52 wks. SEC-treated patients had a higher risk of candida infections than PBO patients at both 12 and 52 weeks. Most candida infections were mild–moderate, manageable with oral therapy or resolved spontaneously, and did not result in discontinuation of therapy. • FUTURE 1 and FUTURE 2 (PsA, SEC pooled vs. PBO): 0.7% vs. 0% and 3.7% vs. 0% • MEASURE 1 and MEASURE 2 (AS): 0.9 vs. NR events per 100 patient-years of exposure
Herpes Infections, Oral	• CLEAR (PPsO, SEC vs. UST): "10 cases" (treatment group(s) not identified)
Neutropenia, Grade 3 or 4 (<1.0–0.5 x 10^9/L or <0.5 x 10^9/L, respectively)	Neutropenia was a safety issue of interest because IL-17A potentially plays a role in mediating granulopoiesis. • PPsO Trials (SEC300, SEC150, PBO, ETA): 0.7%, 0.6%, 0.1%, 0.3% • FUTURE 1 and FUTURE 2 (PsA): Not reported and 1 patient, respectively • MEASURE 1 and MEASURE 2 (AS, pooled): 0.7 events per 100 patient-years of exposure
Major Adverse Cardiovascular Events (MACE)	Patients with certain inflammatory diseases (e.g., rheumatoid arthritis, PsA) have an increased risk of MACE. • PPsO Trials (SEC300, SEC150, PBO, ETA, respectively): 0.51, 0.44, 0.50 and 0.34 events per 100 patient-years.[1] The FDA did not believe there was a convincing cardiovascular safety signal to warrant labeling for cardiovascular risk. • FUTURE 1 (PsA; events per 100 patient years): 0.6 (95% CI 0.2–1.5) for stroke and 0.3 (0.0–1.0) for MI in SEC group vs. 0 in PBO group • FUTURE 2 (PsA): 0.3% (1 MI) • MEASURE 1 and MEASURE 2 (AS, pooled; events per 100 patient-years): 0.4 (2 MIs [one fatal], 1 stroke)
Malignancy	• PPsO Trials (PPsO; SEC300, SEC150, PBO, ETA, respectively): Week 52 incidence rates of malignancy including 2 cases of thyroid cancer were higher on placebo (0.77, 0.97, 1.49, 0.68 events per 100 patient-years). The FDA medical reviewer suggested that monitoring for thyroid disease should be done in long-term extension trials and postmarketing surveillance. • FUTURE 1 (PsA, SEC150, SEC75 vs. PBO): 0.3%, 1.0% vs. 0.5% • FUTURE 2 (PsA, SEC vs. PBO): 1.0% vs. NR; 3 patients on SEC (squamous cell carcinoma) • MEASURE 1 and MEASURE 2 (AS): 4 patients on SEC (B-cell lymphoma, breast cancer, transitional cell carcinoma of the bladder, and malignant melanoma) versus 1 patient on PBO (lymphoma)
Tuberculosis (New or Reactivation)	• PPsO Trials: No cases • FUTURE 1 and FUTURE 2 (PsA): No cases • MEASURE 1 and MEASURE 2 (AS): No cases
Inflammatory Bowel Disease, Exacerbation or New Onset	• PPsO Trials (SEC300, SEC150, PBO, ETA; events per 100 patient-years): 0.26, 0.35, 0.0, 0.34 at 52 weeks; Crohn's disease – 0.0, 0.18, 0.0, 0.0 at 52 weeks • FUTURE 1 (PsA): Not reported • FUTURE 2 (PsA): 2 pts (UC) • MEASURE 1 and MEASURE 2 (AS): 0.7 events per 100 patient-years of exposure
Dyslipidemia (Cholesterol and Triglyceride Increases to >ULN)	• PPsO Trials (SEC pooled, PBO, ETA): 19.4%, 17.8%, 14.1% at Wk 12. Small increased rate with SEC; considered to be not clinically important. • MEASURE 1 (PsA): 10% of SEC pts (pooled; grade 1 or 2). An increased risk was not seen in MEASURE 2.
Treatment-emergent Antidrug Antibodies During Secukinumab Therapy	• PPsO Trials: 0.4% (10/2842) SEC (3 positive for neutralizing antibodies (nAbs); 5 negative for nAbs; 2 not characterized for nAb status. • FUTURE 1 and FUTURE 2 (PsA): 0.2% and 0.3%, respectively (not associated with loss of efficacy

	or immunity-related AEs) • MEASURE 1 and MEASURE 2 (AS): 2 pts (neither had loss of efficacy or immunity-related AEs)
Paradoxical Autoimmune Diseases	The FDA medical reviewer had concerns that secukinumab may be associated with paradoxical development of autoimmune disease and that additional data from long-term studies and postmarketing surveillance were warranted. • PPsO Trials (SEC, PBO, ETA): 0.6%, 0.1%, 0.9% – FDA-adjusted rates of autoimmune adverse events including ulcerative colitis, Crohn's disease and relapse of multiple sclerosis.1
Dose-related Adverse Events	The incidences of infections and grade 1 or 2 neutropenia seemed to show dose-related effects.[1] The dose-related effects were observed with administration of 300-mg vs. 150-mg doses and administration of the same dose in lighter patients (< 90 kg) vs. heavier patients. Overall, both doses were considered to be reasonably safe, although it was not clear whether the small differences in neutrophil count and infections would predict more serious adverse reactions when secukinumab is used in clinical practice for longer periods.

Adverse Reactions

Common Adverse Reactions	Generally mild to moderate nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, oral herpes, pharyngitis, urticaria, rhinorrhea.
Deaths / Serious Adverse Reactions	Safety data did not suggest an increased risk of deaths with secukinumab and none of the deaths (6 in PPsO trials, 10 in other indications) were considered to be related to study drug. There was no clustering of SAEs in any of the SEC clinical trials.
Discontinuations Due to Adverse Reactions	Overall, rates of discontinuation of SEC due to adverse events were low. • PPsO trials (SEC pooled, PBO, ETA): 1.2%, 1.3%, 1.9% at 12 wks; 3.4%, 1.4%, 3.7% at 52 wks • FUTURE 1 (PsA, SEC vs. PBO): 1.7% vs. 2.5% at Wk 16; 3.9% SEC at Wk 52 • FUTURE 2 (PsA, SEC vs. PBO): 2.0% vs. 3.0% at Wk 16; 2.1% vs. 4% at Wk 52 • MEASURE 1 and MEASURE 2 (AS, SEC75, SEC150, PBO: 1.6%, 0.8%, 4.1% at Wk 16; 3.2%, 4.8%, NA at Wk 52
Immunogenicity	There is a potential for immunogenicity, although the incidence of immunogenicity may not have been reliably determined because of limitations with the type of assay used to detect anti-secukinumab antibodies. Using an electrochemiluminescence-based bridging immunoassay, less than 1% of subjects treated with secukinumab developed anti-drug antibodies during 52 weeks of treatment.[8] About 50% of subjects who developed antibodies had antibodies classified as neutralizing. Neutralizing antibodies were not associated with loss of efficacy. Comparison of the incidence of anti-secukinumab antibodies with incidences of antibody formation with other agents may be misleading.

Drug Interactions

Drug-Drug Interactions	• Live Vaccines – Avoid in patients treated with secukinumab • Non-live Vaccines – May be given to patients treated with secukinumab. Clinical effectiveness of meningococcal and influenza vaccines have not been assessed in patients receiving secukinumab. (In healthy volunteers, secukinumab did not interfere with the immune response to these vaccines.[37]) • CYP450 Substrates – Secukinumab could normalize the formation of CYP450 enzymes (which may be increased during chronic inflammation). Consider monitoring for therapeutic effect (e.g., warfarin) or drug concentration (e.g., cyclosporine) of CYP450 substrates and adjusting their dose if indicated.

Risk Evaluation

As of 8 March 2016

Sentinel Event Advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike / Sound-alike Error Potential

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Secukinumab	None	None	None	Siltuximab Canakinumab Ustekinumab Eculizumab Sacubitril-valsartan
COSENTYX	None	None	None	Covaryx HS Cerebyx Chantix

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Superior PASI90 Efficacy

- The FDA has typically considered at least 75% improvement in the Psoriasis Area and Severity Index (PASI75) to be a measure of treatment success, as it reflects achievement of at least "mild" psoriatic disease.
- The European Medicines Agency now defines the threshold of treatment success as at least 90% improvement in PASI (PASI90).
- The American Academy of Dermatology considers PASI90 to be a measure of optimal response.
- Secukinumab was shown to be significantly better than etanercept (42%–54% vs. 21%; FIXTURE trial[2]) and ustekinumab (79.0% vs. 57.6%; CLEAR trial[16]) for PPsO using PASI90 response, a more difficult to achieve response than that used in prior TNFI trials.
- Secukinumab is the first agent to be allowed by the FDA to include PASI90 response claims in the prescribing information.

Other IL-17 Inhibitors and Association with Suicide

- Brodalumab is an investigational fully human anti-IL-17RA (receptor) monoclonal antibody that has shown efficacy in the treatment of psoriasis. Brodalumab has been associated with suicidal thoughts and behaviors in preliminary analyses of phase III trial results.[38] Causality has not been established.
- Ixekinumab is another IL-17A inhibitor approved by the FDA on 22 March 2016.
- Neither secukinumab nor ixekinumab has been associated with suicidal ideation or behavior.

Storage

- Store product at 2°C to 8°C (36°F to 46°F).
- Product should be allowed to reach room temperature before administration (15–30 minutes).
- Administer dose within 1 hour after removal from refrigerator.

Postmarketing Surveillance

- None. Secukinumab is not marketed elsewhere in the world.

Pharmacokinetics

- In PPsO patients, mean half-life ranged from 22 to 31 days.
- Apparent clearance of secukinumab increases with increasing body weight.
- Because of its large molecular size (~150 kDa), nondegraded secukinumab is unlikely to be eliminated by the kidneys.
- CYP enzyme metabolism or biliary secretion is generally not a substantial route of elimination for IgG antibodies such as secukinumab.

Dosing and Administration

Refer to prescribing information for complete information on dosing and administration.

Plaque Psoriasis

- The recommended dosage is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Each 300-mg dose is given as two subcutaneous injections of 150 mg.
- For some patients, a dose of 150 mg may be acceptable.

Psoriatic Arthritis

- For patients with psoriatic arthritis and coexistent moderate to severe plaque psoriasis, use the dosing and administration recommendations for plaque psoriasis.
- For other patients with psoriatic arthritis, administer secukinumab with or without a loading dose by subcutaneous injection.
    - With a loading dosage: 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
    - Without a loading dose: 150 mg every 4 weeks.
    - If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg.
- Secukinumab may be administered with or without methotrexate.

Ankylosing Spondylitis

- Administer secukinumab with or without a loading dosage by subcutaneous injection.
    - With a loading dose: 150 mg at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter.
    - Without a loading dose: 150 mg every 4 weeks.

Special Populations (Adults)

Elderly	• Insufficient data to determine whether patients aged 65 years and older respond differently from younger patients. • Pharmacokinetic analyses showed that the elderly and younger patients have similar clearance rates.
Pregnancy	• Category B. Weigh risks versus benefits.
Lactation	• Whether secukinumab is excreted in human milk or absorbed systemically after ingestion is unknown. Use caution.
Renal Impairment	• No formal trials were conducted.
Hepatic Impairment	• No formal trials were conducted.
Pharmacogenetics/genomics	• No studies were found.

Projected Place in Therapy

- PPsO, PsA and AS are chronic inflammatory diseases primarily affecting the skin, peripheral joints or spine and sacroiliac joints, respectively.
    - The chronic plaque subtype of psoriasis is a common, immune-mediated disease that has varying prevalence (0.91 to 8.5 percent) across the world, with the prevalence being higher in locations farther from the equator than those closer.[39] The age of disease onset is bimodal; one peak occurs between the ages of 30 and 39 years and the second peak occurs between the ages of 50 and 69 years. The incidence of psoriasis seems to have increased from 50.8 cases per 100,000 during the period from 1970 to 1974 to 100.5 cases per 100,000 during the period from 1995 to 1999, although improvements in diagnosis may account for at least part of the increase. Risk factors for plaque psoriasis include genetics (PSORS1 and HLA-Cw6 in the major histocompatibility genes, IL-12/23–related genes, and others), smoking, obesity, exposure to certain drugs (e.g., beta blockers, lithium, antimalarials), alcohol, infections and vitamin D deficiency. TNFI therapy has been associated with paradoxical development of psoriatic lesions. Increased concentrations of the cytokine IL-17A have been detected in lesions and blood of individuals with psoriasis.[40]

  - PsA is a chronic, progressive, inflammatory, oligoarticular, autoimmune spondyloarthropathy that affects approximately 1% of adults in the US.[41] PsA is one variant of spondyloarthritis (SpA), a group of disorders characterized by enthesitis (inflammation around sites where ligaments and tendons insert into bone), an asymmetric, oligoarticular pattern of peripheral arthritis mainly involving the lower extremities, radiographic sacroiliitis, and association with the human leukocyte antigen (HLA)-B27. Estimates of the prevalence of PsA vary widely. In one US interview survey, 0.25% (95% CI 0.18%–0.31%) of 27,220 randomly selected persons had PsA.[42] Of 601 interviewed with psoriasis, 11% (95% CI 9%–14%) had PsA, and the prevalence depended on the extent of skin lesions. PsA is often preceded by psoriatic skin lesions and typically affects joints of the fingers, toes and spine. In addition to peripheral and axial synovitis, manifestations of PsA may include enthesitis, dactylitis, anterior uveitis, iritis and skin and nail involvement. Inflammatory bowel disease–like gastrointestinal symptoms may also occur. Patients with the comorbidity of PsA and psoriasis are more likely to report that the condition affects their job and that they are unemployed, relative to those with psoriasis alone.[43]
  - AS, a chronic inflammatory disease primarily of the axial skeleton, is the most common variant of SpA. Estimates of the prevalence of AS vary from 0.03 to 1.8 percent across Europe, North America and China.[44] Clinical manifestations of AS include back pain, progressive spinal stiffness, inflammation of the hip and shoulders, peripheral arthritis, enthesitis, anterior uveitis, psoriasis and inflammatory bowel disease. AS occurs in 4 to 10 percent of patients with inflammatory bowel disease, and about 6.5 percent of SpA patients develop new-onset inflammatory bowel disease.[45] The onset of AS symptoms usually occurs before the age of 30 years. The disease often progresses, impairing physical function, employment and quality of life.[44] Some patients progress to complete spinal fusion with hyperkyphosis.
- Practice guideline recommendations relevant to secukinumab were found for nail psoriasis and psoriatic arthritis only.
  - *Nail Psoriasis, Medical Board of the National Psoriasis Foundation (2015)*[46]: Secukinumab was reviewed (one trial); however, none of the recommendations included secukinumab.
  - *Psoriatic Arthritis*
    - *European League Against Rheumatism (EULAR, 2016)*[47]: Secukinumab may be considered in patients with peripheral arthritis and an inadequate response to at least one csDMARD and for whom TNFIs are inappropriate.
    - *Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA, 2015)*[48]: *Strongly recommend* IL-17 inhibitors for plaque psoriasis skin manifestations. *Conditionally recommend* IL-17 inhibitors for (1) peripheral arthritis in patients who have an inadequate response to csDMARDs or biologics (e.g., TNFIs, IL-12/23 inhibitor); (2) axial PsA in biologic-naïve patients or inadequate responders to biologics; and (3) enthesitis, dactylitis, and nail psoriasis. There were no recommendations for the use of IL-17 inhibitors for peripheral arthritis in DMARD-naïve patients because of a lack of evidence. Secukinumab was not yet approved by the FDA at the time the treatment recommendations were written.
- UpToDate recommendations relevant to secukinumab are as follows:
  - *Moderate or Severe PPsO*[49]: Topical glucocorticoids, vitamin D analogs (e.g., calcipotriene and calcitriol), tar, and retinoids (tazarotene) with or without systemic therapy are beneficial in patients with moderate disease. Severe disease requires phototherapy or systemic therapies. In patients who have contraindications to phototherapy, failed phototherapy or no access to phototherapy, treatment with a systemic agent is recommended. Systemic therapy may also be preferable to phototherapy for some patients depending on financial means or time limitations. Systemic agents include retinoids, methotrexate, cyclosporine, apremilast, TNFIs, ustekinumab and secukinumab.
  - *PsA*[50]: In inadequate responders to trials of two different TNFIs, secukinumab is an alternative to ustekinumab. When there is substantial skin involvement, treatments effective for both PPsO and PsA are necessary. Agents that treat both skin and joint manifestations and have radiologic benefit are TNFIs, ustekinumab, and secukinumab.
  - *AS*[51]: Secukinumab may be an option for AS patients who have an inadequate response to other therapies, including TNFIs.
- The potential place in therapy of secukinumab based on the evidence would be in (1) patients with moderate to severe PPsO despite topical and systemic (mainly conventional) therapies; (2) patients with active PsA despite prior therapy with an NSAID, csDMARD or up to three prior TNFIs; and (3) patients with active AS despite concurrent treatment with maximum tolerated doses of NSAIDs (some of whom may receive up to one prior TNFI). The majority of patients in clinical trials did not receive prior biologic therapy including TNFIs. There have been no studies evaluating secukinumab as a first-line therapy in patients naïve to conventional therapies.

- The quality of the body of evidence for secukinumab is high for short-term (≤24 weeks) efficacy in PPsO, PsA and AS, moderate for efficacy / effectiveness and safety up to 52 weeks in PPsO, PsA and AS, low for short-term efficacy in nail psoriasis and palmoplantar psoriasis, and low for long-term (>52 weeks) efficacy / effectiveness and safety in PPsO, PsA and AS. Evidence is of moderate quality for the superiority of secukinumab over etanercept or ustekinumab in PPsO. There is some uncertainty about the magnitude of benefit that secukinumab may have over US-approved etanercept. US Veterans were not represented in the clinical trials; therefore, whether secukinumab will provide the same magnitude of benefits and similar safety profile during actual clinical use in the VHA is uncertain.
- In general, most patients with moderate to severe PPsO (who are candidates for systemic therapy or phototherapy), active PsA or active AS may be treated initially with the conventional systemic agents and / or TNFIs, depending on the specific condition. Secukinumab offers a moderately to highly efficacious and well tolerated alternative second- or third-line therapy for patients who have a contraindication, nonresponse, inadequate response, loss of response, or intolerance to TNFIs. In PPsO and PsA patients for whom TNFIs are inappropriate or inadequate, ustekinumab may be preferable over secukinumab as a treatment alternative because of greater long-term safety experience. In PPsO, ustekinumab also has a lower VA drug cost but is less effective than secukinumab (NNT of 4.7 for PASI90 response rate at 16 weeks). In AS, secukinumab is the only biologic available as an alternative to TNFIs. Secukinumab has not been compared with ustekinumab for indications other than PPsO and it has not been compared with a US-approved etanercept product. There have been no trials evaluating secukinumab in treatment-naïve patients for the approved indications. The long-term effectiveness and safety of secukinumab beyond 52 weeks is uncertain; during long-term therapy patients should be monitored for maintenance of beneficial effects and potential rare, serious adverse effects (e.g., infections and infestations, neutropenia, malignancy, thyroid disease / cancer; paradoxical autoimmune diseases including IBD; suicidal behavior). Patient-centered individualization of therapy should be a priority when selecting appropriate medications for PPsO, PsA and AS.

Revised September 2016 (corrected number of thyroid cancer cases from 3 to 2). Originally prepared April 2016. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager – Formulary, Pharmacy Benefits Management Services (10P4P)

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Appendix A: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.