Pharmacology & Therapeutics 229 (2022) 107925

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

# Secukinumab for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis: Physical and pharmacological properties underlie the observed clinical efficacy and safety

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ARTICLE INFO

Available online 23 June 2021

Editor name: J.P. Hardwick

*Keywords:*
Secukinumab
Biologics
IL-17
Psoriasis
Psoriatic arthritis
Axial spondyloarthritis

ABSTRACT

Psoriasis, psoriatic arthritis, and axial spondyloarthritis are systemic inflammatory diseases, each commonly manifesting as a spectrum of symptoms, complications, and comorbidities that arise differently in individual patients. Drugs targeting inflammatory cytokines common to the pathogenesis of each of these conditions have been developed, although their specific actions in the different tissues involved are variable. For a drug to be effective, it must be efficiently delivered to and locally bioactive in disease-relevant tissues. Detailed clinical data shed light on the therapeutic effects of individual biologics on specific domains or clinical manifestations of disease and assist in guiding treatment decisions. Pharmacologic, molecular, and functional properties of drugs strongly impact their observed safety and efficacy, and an understanding of these properties provides complementary insight. Secukinumab, a fully human monoclonal IgG1/κ antibody selectively targeting interleukin (IL)-17A, has been in clinical use for >6 years in the treatment of moderate to severe psoriasis, psoriatic arthritis, and both radiographic (also known as ankylosing spondylitis) and nonradiographic axial spondyloarthritis. In this review, we discuss pharmacokinetic and pharmacodynamic data for secukinumab to introduce clinicians to the pharmacological properties of this widely used drug. Understanding how these properties affect the observed clinical efficacy, safety, and tolerability of this drug in the treatment of IL-17A–mediated systemic inflammatory diseases is important for all physicians treating these conditions.



*Abbreviations:* AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; CV, coefficient of variation; $C_{max}$, maximum concentration; FLS, fibroblast-like synoviocytes; $IC_{50}$, half maximal inhibitory concentration; $IC_{90}$, 90% maximal inhibitory concentration; IgG, immunoglobulin G; IIV, interindividual variability; IL, interleukin; IL-17A/F, IL-17A homodimer, IL-17F homodimer, and IL-17AF heterodimer; IL-17AF, IL-17AF heterodimer; IL-17R, IL-17 receptor; IV, intravenous; $K_D$, equilibrium dissociation constant; mAb, monoclonal antibody; NFKBIZ, NF-κB inhibitor ζ; NOAEL, no-observed-adverse-effect level; nr-axSpA, nonradiographic axial spondyloarthritis; PASI, Psoriasis Area and Severity Index; PD, pharmacodynamic; PK, pharmacokinetic; PsA, psoriatic arthritis; PsO, psoriasis; q2w, every 2 weeks; q4w, every 4 weeks; SC, subcutaneous; TNF-α, tumor necrosis factor alpha; Th17, helper T-cell subtype 17.

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https://doi.org/10.1016/j.pharmthera.2021.107925

**Contents**



## 1. Introduction

Psoriasis (PsO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) manifest in patients as a spectrum of clinical symptoms, physical manifestations, and comorbidities (Carvalho et al., 2016; Coates et al., 2017; Erol et al., 2018; Menter et al., 2008; Ogdie et al., 2014), so it is essential to select therapies that comprehensively address the multiple disease domains that affect their function and quality of life. Dysregulation of cytokine signaling is common to these diseases, generally leading to an increase in inflammation and joint damage (Griffiths & Barker, 2007; Sieper & Poddubnyy, 2017; Veale & Fearon, 2018). A number of targeted biologic therapies inhibiting tumor necrosis factor alpha (TNF-α), interleukin (IL)-12/23, IL-23, and IL-17A cytokine signaling are approved to treat some or all of these diseases (Gossec et al., 2020; Menter et al., 2019; van der Heijde et al., 2017). These selective biologic therapies have largely replaced conventional, broad-acting systemic immunosuppressants, such as methotrexate and cyclosporine. However, not all biologic therapies are similarly efficacious in each of these diseases, depending on the target they inhibit. For example, IL-12/23 and IL-23 inhibition are effective in treating PsO but not axSpA (Baeten et al., 2018; Deodhar, Gensler, et al., 2019), possibly due to differential involvement of cytokine pathways and/or differential hierarchy of biological effects exerted by those cytokines in axial and skin disease (Siebert, Millar, & McInnes, 2019).

Although clinical data guide treatment decisions, the pharmacological properties of biologics provide complementary insight into the potential clinical efficacy and safety profiles of these drugs. Pharmacokinetic (PK) properties of a biologic, such as steady-state concentrations, clearance, distribution volume and associated tissue access, and therapeutic index, define clinical treatment characteristics. These include, but are not limited to, dose level, frequency of dosing, total dose administered, tissues affected, and safety and tolerability. Pharmacodynamic (PD) properties, including target specificity, binding affinity (frequently reported as the equilibrium dissociation constant [$K_D$]), and ligand efficacy, can explain the strength and specificity of a drug for its target as well as any off-target effects that may contribute to adverse events. Specific biochemical properties of a therapeutic antibody, as well as properties of the molecular target, can contribute to immunogenicity, injection-site reactions, and the overall safety and tolerability profile.

Elevated expression of the inflammatory cytokine IL-17A is a feature of the pathogenesis of the PsO-PsA-axSpA disease cluster and represents a common therapeutic target across these indications (Blauvelt & Chiricozzi, 2018). IL-17A induces keratinocyte-mediated inflammation in psoriatic lesions (Krueger et al., 2012; Krueger & Brunner, 2018), as well as enthesitis and inflammation in synovial tissue in peripheral and axial joints in PsA and axSpA (McGonagle, McInnes, Kirkham, Sherlock, & Moots, 2019; Nograles, Brasington, & Bowcock, 2009). IL-17A is produced by several cell types, including αβ T cells such as helper T-cell subtype 17 (Th17), γδ T cells, and innate lymphoid cells (Blauvelt & Chiricozzi, 2018). Cellular targets of IL-17A include keratinocytes, endothelial cells, fibroblasts, neutrophils, chondrocytes, osteoclasts, and osteoblasts (Blauvelt & Chiricozzi, 2018). The varied sources and cellular targets of IL-17A may help explain some of the heterogeneity across disease states, as the abundance of specific pathogenic cells may differ in affected tissues in individual patients. The monoclonal antibody (mAb) secukinumab, first approved in 2015 by the US Food and Drug Administration and European Commission for the treatment of patients with moderate to severe PsO, is a selective IL-17A inhibitor with many years of documented clinical data in psoriatic and related inflammatory diseases including PsO (Bagel et al., 2017; Gottlieb et al., 2017; Hueber et al., 2010; Langley et al., 2014; Reich et al., 2018; Thaci et al., 2015), PsA (Kivitz et al., 2019; McInnes et al., 2015; Mease et al., 2015; Nash et al., 2018; van der Heijde et al., 2020), and axSpA (Baeten et al., 2015; Deodhar, Blanco, et al., 2020; Marzo-Ortega et al., 2017). The spectrum of axSpA manifestations includes nonradiographic axSpA (nr-axSpA), characterized by inflammatory back pain with no definitive evidence of radiographic damage in the sacroiliac joints, and radiographic axSpA, also known as ankylosing spondylitis (AS), in which patients have radiographic sacroiliitis (Rudwaleit et al., 2009). In this review, we highlight the pharmacological, molecular, and functional properties of secukinumab that underlie its efficacy and tolerability in the treatment of PsO, PsA, and axSpA.

## 2. Statement of literature search

A variety of techniques were used to identify references included in this work. Publications known to the authors and relevant to the pharmacological properties and history of the secukinumab clinical development program were included. Additionally, a series of PubMed keyword searches were conducted between June 2019 and March 2021 to identify relevant references and those providing important context. Search terms were related to research questions addressed herein; example searches included "(anti-interleukin 17 OR anti-IL-17 OR interleukin 17 inhibitor OR IL-17 inhibitor) AND biologic*," "(interleukin 17 OR IL-17) AND biologic* AND affinity," "(Cosentyx OR secukinumab OR AIN457) AND (pharmacokinetic* OR pharmacodynamic*," "(Cosentyx OR secukinumab OR AIN457) AND (psoriasis OR psoriatic arthritis OR ankylosing spondylitis OR nonradiographic axial spondyloarthritis)." Publications relevant to pharmacological properties of secukinumab and related discussions were included, and irrelevant references were excluded from consideration. This review also includes relevant unpublished data from the preclinical development of secukinumab.

## 3. PK properties of secukinumab and clinical implications

### 3.1. Overview of PK properties of secukinumab

Secukinumab is a fully human immunoglobulin G (IgG)1/κ mAb developed in 2001 (Novartis data on file) using the HuMAb platform (Medarex, Inc). HuMab is a transgenic mouse strain carrying a portion of the human immunoglobulin heavy- and light-chain repertoire (Fishwild et al., 1996). Human IgG1-based drugs interacting with soluble targets have well-characterized PK properties; this isotype was selected for the development of secukinumab due to its high stability in blood, long half-life within the body, and widespread clinical use and because IL-17A is a soluble cytokine (Lobo, Hansen, & Balthasar, 2004; Wang, Wang, & Balthasar, 2008). Furthermore, because endogenous IgG1 is abundant in human serum (Vidarsson, Dekkers, & Rispens, 2014), exogenous IgG1 resulting from treatment does not significantly alter the overall level of this IgG subtype in the body. Effector functions of IgG1 are of no concern, as secukinumab targets a soluble protein as opposed to a receptor expressed on the cell surface.

The PK properties of secukinumab are well characterized and directly relevant to the observed clinical efficacy of secukinumab across all indications. The serum half-life is 25 to 27 days in patients with PsO, PsA, or AS (Bruin, Loesche, Nyirady, & Sander, 2017; Novartis data on file). The absolute bioavailabilities of subcutaneous (SC) secukinumab in patients with PsO, PsA, and AS are 73%, 85%, and 79%, respectively (Bruin et al., 2017; Novartis data on file). These values compare favorably with other SC IgG therapeutics (Berger, Jolles, Orange, & Sleasman, 2013) and are comparable or higher than other IgG antibodies targeting soluble cytokines (AbbVie, 2020; Eli Lilly, 2020; Janssen, 2019; Janssen, 2020; UCB, 2019; Vena & Cassano, 2007). Secukinumab has straightforward linear PK properties, with no dose dependence of clearance (Bruin et al., 2017). A 2-compartment model describes time-concentration profiles for secukinumab 300 mg SC and 150 mg SC at weeks 0, 1, 2, 3, and 4 followed by every 4 weeks until week 48 (Bruin et al., 2017). Typical serum secukinumab time-concentration profiles resulting from therapeutic regimens at both the 300-mg and 150-mg dose levels are presented in Fig. 1 (Bruin et al., 2017). The time to reach maximum serum concentration after SC dosing is approximately 6 days for both the 300-mg and 150-mg doses (Bruin et al., 2017). Secukinumab displays no target- or tissue-mediated disposition (Roman, Madkan, & Chiu, 2015), consistent with IL-17A as a soluble target. The impact of intravenous (IV) loading regimens on clinical response was evaluated in proof-of-concept studies in different indications, and dose-finding studies and phase 3 clinical trials in PsA and AS. A typical IV loading regimen during the first month was 10 mg/kg, which is a total dose of 800 mg for an 80-kg patient, at weeks 0, 2, and 4. Such an IV regimen showed time-concentration profiles with maximum concentration ($C_{max}$) values reaching nearly 400 μg/mL after the third infusion, compared with approximately 100 μg/mL after the fifth 300-mg SC dose at week 4 (Fig. 1), and an overall approximately 2.5-fold higher serum exposure during the first 8 weeks than with the standard therapeutic regimen at the 300-mg SC dose. In the approved indications, the 10 mg/kg IV loading regimens did not lead to faster onset of response or greater clinical response during maintenance therapy than SC dosing.

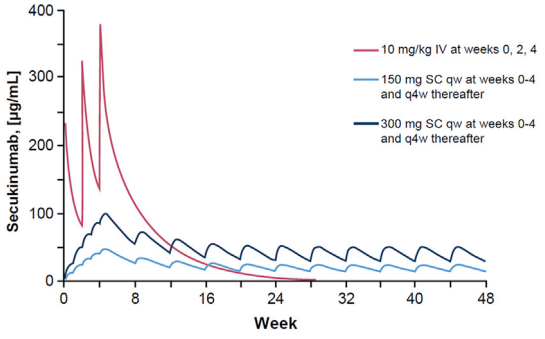


**Fig. 1.** Predicted pharmacokinetics of secukinumab in humans following different SC or IV dosing regimens.
IV, intravenous; qw, weekly; q4w, every 4 weeks; SC, subcutaneous.

The favorable PK properties of secukinumab allow for consistent and flexible dosing across indications, thereby addressing the needs of most patients by allowing modifications of the dosing regimen to achieve optimal clinical responses in diverse populations. Proof-of-concept and dose-ranging studies found that secukinumab serum concentrations increase in a roughly proportional manner to dose within the therapeutic range (Papp et al., 2013). Importantly, secukinumab maintains similar PK properties across patients with different diseases (Deodhar et al., 2019), and secukinumab has no appreciable sensitivity to racial background (Frieder, Kivelevitch, & Menter, 2018), as substantiated by the similar dosages from posology studies conducted in Asian patient populations. With initial weekly dosing changing to monthly administration after week 4, mean steady-state trough serum levels of approximately 35 μg/mL of secukinumab at the 300-mg dose level and a 2-fold lower concentration of secukinumab at the 150-mg dose level are reached at week 24 and remain stable thereafter for ≥5 years from initiation of treatment (Table 1) (Reich et al., 2019).

A decreased dosing interval for secukinumab 300 mg from every 4 weeks (q4w) to every 2 weeks (q2w) is currently being explored for hard-to-treat patients or those with inadequate response to the q4w dosing regimen. In a recent study in patients with PsO and body weight ≥ 90 kg, patients achieving 75% improvement in the Psoriasis Area and Severity Index (PASI75) but not PASI90 at week 16 received either q2w or q4w administration of secukinumab 300 mg SC (Reich et al., 2020). Sustained efficacy responses from week 16 through week 32 were numerically higher in the secukinumab q2w group than the secukinumab q4w group. Achievement of PASI90 was numerically greater among patients who received uptitration to secukinumab q2w compared with those continuing to receive the q4w regimen. Safety was comparable between the groups taking secukinumab 300 mg q2w and q4w. Although most patients in either group achieved PASI90, these numerical benefits from increased dosing frequency likely result from proportionally increased serum concentrations of secukinumab.

Another recent study compared secukinumab 300 mg q4w and q2w dosing regimens for the treatment of moderate to severe PsO in patients weighing ≥90 kg (Augustin, Patekar, et al., 2020). The secukinumab 300 mg q2w dose regimen was found to be superior to secukinumab 300 mg q4w with respect to the primary endpoint of PASI90 response at week 16, with numerical benefits for secukinumab 300 mg q2w vs q4w in the secondary endpoint of Investigator's Global Assessment (modified 2011) score of 0 or 1 at week 16. Efficacy responses beyond week 16 were higher in the secukinumab q2w vs q4w group through 1 year. Furthermore, patients who received dose escalation from q4w to q2w after PASI90 nonresponse at week 16 achieved greater efficacy responses than patients who continued to receive the q4w regimen. Safety was comparable between the secukinumab dosing groups. To accommodate uptitration in real-world clinical practice and for improved patient convenience, 2-mL injection devices will become available in addition to the standard 2 × 1-mL prefilled syringes or autoinjectors for delivery of secukinumab 300 mg.

### 3.2. Secukinumab clearance and distribution in the skin and joints

Clearance and distribution volume of secukinumab are important PK parameters. To achieve efficacy in the skin and joints, secukinumab must reach and maintain therapeutic levels in these different target tissues. A population PK analysis of 1233 patients with PsO from 5 phase 3 studies of secukinumab estimated the clearance and distribution

**Table 1**
Secukinumab serum exposure (trough concentrations) and clinical efficacy data.[a]

| Property | | Dose | Time | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Week 4 | Week 12 or 16 | Week 24 | Week 52 | Week 104 | Week 260 |
| Typical serum trough concentrations (μg/mL)[b,c] | | PsO | | | | | | |
| | | 150 mg | 44.1 | 23.2 (week 12) | 18.9 | 16.9 | 19.1 | 19.8 |
| | | 300 mg | 85.2 | 45.2 (week 12) | 36.4 | 34.4 | 35.9 | 33.8 |
| | | PsA | | | | | | |
| | | 75 mg | 24.4 | 12.1 (week 16) | 10.5 | 11.7 | 9.88 | 8.17 |
| | | 150 mg | 47.6 | 21.2 (week 16) | 19.6 | 18.6 | 18.9 | 16.6 |
| | | 300 mg | 96.8 | 43.1 (week 16) | 38.6 | 34.0 | 37.8 | 28.2 |
| | | AS | | | | | | |
| | | 75 mg | 26.1 | 12.3 (week 16) | 11.6 | 10.7 | 9.22 | 14.0[b] |
| | | 150 mg | 54.0 | 23.4 (week 16) | 20.5 | 20.5 | 19.5 | 17.7 |
| | **Clinical response, % of patients** | | | | | | | |
| Skin | PASI75 (Bissonnette et al., 2018; Mrowietz et al., 2015) | 150 mg | 27.9 | 84.4 (week 12) | 80.3 | 62.1 | – | – |
| | | 300 mg | 42.9 | 90.1 (week 12) | 88.0 | 78.2 | 80.9 | 88.5 |
| | PASI90 (Bissonnette et al., 2018; Mrowietz et al., 2015) | 150 mg | 6.7 | 49.3 (week 12) | 66.5 | 45.8 | – | – |
| | | 300 mg | 13.7 | 64.2 (week 12) | 74.1 | 59.7 | 64.5 | 66.4 |
| | PASI100 (Bissonnette et al., 2018; Mrowietz et al., 2015) | 150 mg | 0.4 | 16.2 (week 12) | 29.1 | 21.2 | – | – |
| | | 300 mg | 2.3 | 25.7 (week 12) | 36.1 | 36.6 | 43.4 | 41.0 |
| Peripheral joints | ACR20 (McInnes et al., 2015; McInnes et al., 2017) | 75 mg | 28.3 | 33.3 (week 16) | 29.3 | 50.5 | 50.3 | – |
| | | 150 mg | 49.0 | 56.0 (week 16) | 51.0 | 64.0 | 64.4 | 70.0 |
| | | 300 mg | 37.0 | 57.0 (week 16) | 54.0 | 64.0 | 69.4 | 66.7 |
| | ACR50 (McInnes et al., 2015; McInnes et al., 2017) | 75 mg | 3.1 | 18.3 (week 16) | 18.2 | 30.3 | 28.2 | – |
| | | 150 mg | 14.0 | 37.0 (week 16) | 35.0 | 39.0 | 36.0 | 45.0 |
| | | 300 mg | 20.8 | 36.8 (week 16) | 35.0 | 44.0 | 50.6 | 36.4 |
| Axial joints[d] | ASAS20 (Baeten et al., 2015) | 75 mg | 38.4 | 41.1 (week 16) | 46.6 | 53.4 | 76.8 | 71.4 |
| | | 150 mg | 52.8 | 61.1 (week 16) | 61.1 | 62.5 | 79.7 | 67.9 |
| | ASAS40 (Baeten et al., 2015) | 75 mg | 16.4 | 26.0 (week 16) | 34.2 | 34.2 | 55.4 | 61.9 |
| | | 150 mg | 34.7 | 36.1 (week 16) | 45.8 | 48.6 | 54.2 | 57.1 |

ACR, American College of Rheumatology; AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, psoriasis.
[a] All values correspond to on-label use of secukinumab at the indicated doses; Novartis data on file unless otherwise cited.
[b] Concentrations as observed in the SCULPTURE and SCULPTURE extension studies in PsO, in FUTURE 2 in PsA, and in MEASURE 2 in AS.
[c] In the 75-mg arm of MEASURE 2, some patients were uptitrated to 150 mg, leading to a higher mean concentration.
[d] Using observed data at weeks 104 and 260.

volume of secukinumab for a typical patient weighing 90 kg (Bruin et al., 2017). Overall serum clearance was low and estimated to be 0.19 L/day with an interindividual variability (IIV) of 32% coefficient of variation (CV). The total distribution volume was also low, with a central compartment volume of 3.61 L (IIV, 30% CV) and a peripheral compartment volume of 2.87 L (IIV, 18% CV); this is close to the total blood volume of an adult patient and indicates that the distribution into peripheral tissue is limited. Both clearance and distribution volume of secukinumab were found to vary with body weight in an allometric relationship; differences in serum concentrations between individuals are mainly caused by differences in body weights (Bruin et al., 2017).

Secukinumab administered SC is rapidly distributed to psoriatic lesions, as shown by open-flow microperfusion, a unique method used to directly measure the local concentration of secukinumab in the interstitial fluid of nonlesional and lesional skin (Dragatin et al., 2016). Seven days after a single SC injection of secukinumab 300 mg in patients with PsO, secukinumab was found at a concentration of 8.3 μg/mL in nonlesional and 6.8 μg/mL in lesional skin interstitial fluid, corresponding to 39% and 32% of the serum secukinumab concentrations at that time point, respectively (Dragatin et al., 2016). This is consistent with tissue distribution of other IgG therapeutics after IV administration (Choy et al., 2000) and indicates that human antibodies of the IgG isotype administered by SC dosing eventually partition into the skin interstitial fluid. Based on the secukinumab half-life and 4-week dosing interval during maintenance, a 2-fold accumulation of secukinumab at steady state was observed in serum (Bruin et al., 2017), which suggests that skin interstitial fluid concentrations at steady state are also approximately 2-fold higher than after a single dose. The fast and efficient distribution of secukinumab into the skin may, therefore, contribute to the rapid onset of action seen in the treatment of patients with PsO. Furthermore, it was demonstrated that dermal levels of IL-17A at baseline were significantly higher in lesional than nonlesional psoriatic skin with means of 9.8 vs 0.8 pg/mL in lesional and nonlesional skin, respectively. IL-17A was not detectable in the skin of healthy participants (less than the lower limit of quantitation: $< 0.64$ pg/mL) (Kolbinger et al., 2017). Similarly, dermal interstitial fluid levels of the IL-17AF heterodimer at baseline were significantly higher in lesional than nonlesional psoriatic skin, with means $\pm$ SD of 117 $\pm$ 91 pg/mL and 6.8 $\pm$ 6.7 pg/mL in lesional and nonlesional skin, respectively (Novartis data on file). In a study of transcriptomic changes in lesional skin of patients with PsO treated with secukinumab, 80 genes were differentially regulated within 4 days of the first injection of secukinumab; importantly, mRNA levels of NF-κB inhibitor ζ (*NFKBIZ*) encoding for the signaling node IκB-ζ were decreased and found to correlate with PASI scores (Bertelsen et al., 2020). IκB-ζ activates inflammatory cytokines and chemokines, including but not limited to IL-6 and CXCL1. Likewise, *IL6* and *CXCL1* transcript levels, as well as *CXCL8, IL1, MMP1, DEFB4A, and DEFB4B*, were significantly reduced at this early timepoint (Bertelsen et al., 2020). In the open-flow microperfusion study introduced above, proteome assessment of psoriatic lesions revealed changes to the level of several proteins after a single 300-mg SC dose of secukinumab (Kolbinger et al., 2017). β-defensin 2, an antimicrobial peptide encoded by *DEFB4A* and produced by keratinocytes, was identified as a serum biomarker for IL-17A–driven skin pathology and a biomarker of PD response to secukinumab treatment (Kolbinger et al., 2017). Two weeks after administration of a single 300-mg SC dose of secukinumab to patients with PsO, tape stripping identified a $>$ 3-fold change in the epidermal levels of 32 proteins; a $>$ 10-fold decrease was confirmed for several dysregulated proteins, including matrix metalloproteinase-8, myeloperoxidase, IL-8, matrix metalloproteinase-9, and IL-1β ($P < .05$ for all comparisons) (Loesche et al., 2016).

Clinical responses must be considered within distinct tissue compartments across different diseases. For secukinumab to effectively improve joint symptoms of PsA or axSpA, including tenderness, swelling, stiffness, and long-term joint damage and erosion, it must reach synovial tissue in the joints and/or entheseal tissue. Secukinumab is efficacious in treating joint manifestations in patients with PsA and AS (Baeten et al., 2015; Mease et al., 2015). Although the local concentration in joints has not been measured for secukinumab, IgG has been measured in synovial fluid reaching approximately 20% to 30% of serum levels depending on dose (Choy et al., 2000); this is similar to the observed secukinumab distribution to the skin interstitial fluid (Dragatin et al., 2016). Secukinumab partitions into the skin interstitial fluid to a similar extent as endogenous IgG molecules (Dragatin et al., 2016) and has PK properties consistent with other IgG therapeutics (Bruin et al., 2017). Therefore, it is likely that secukinumab levels in the joints are approximately 30% of serum levels.

In preclinical studies, secukinumab has shown efficacy in reduction of human IL-17A–induced joint inflammation in a DBA/1 mouse model. Briefly, inflammation rapidly develops in mice when NIH-3T3 cells expressing human IL-17A are injected unilaterally into joints. Mice pretreated with secukinumab developed significantly less inflammation in injected joints than mice receiving a control IgG (Fig. 2). Furthermore, histological analysis of the synovial lining of affected knee joints in these mice indicates that secukinumab completely inhibits IL-17A–mediated influx of inflammatory cells (Novartis data on file). These results suggest that secukinumab reaches therapeutically relevant levels in the synovium in this mouse model. Entheseal tissue is not routinely biopsied, and mAb levels in entheses have not been as well studied as in other tissues, such as the skin. However, clinical improvement of enthesitis following inhibition of IL-17A signaling suggests sufficient distribution of therapeutics to entheses.

Differences in the speed of onset of action of secukinumab in alleviating skin symptoms vs joint symptoms have been observed. In general, secukinumab more rapidly and strongly improves the skin vs the joints in patients with psoriatic disease (Table 1). Differences in target expression, signaling strength, and pathway relevance among different target tissues may explain these different clinical responses in skin and joints. For example, a gene expression analysis in patients with PsA indicated a more pronounced IL-17A gene signature in skin than in synovium, compared with roughly equal gene signatures for TNF-α in both tissues (Belasco et al., 2015). This suggests that IL-17A may be a more critical mediator of inflammation in the skin than TNF-α and is supported by a direct comparison of secukinumab and adalimumab in patients with PsA (McInnes et al., 2020). Furthermore, in studies of pediatric patients with PsO receiving either secukinumab or etanercept, although direct comparisons could not be made due to differences in trial design, secukinumab resulted in improved skin clearance (Magnolo et al., 2020; Paller et al., 2008).

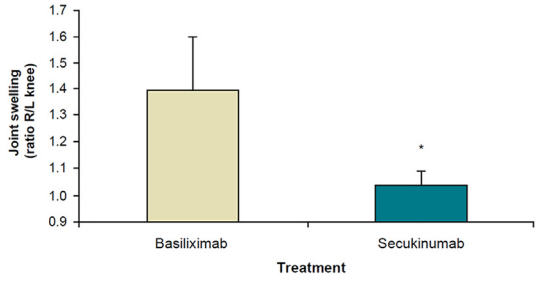


**Fig. 2.** Secukinumab inhibits swelling in knee joints of DBA/1 mice injected with NIH-3T3 cells producing human IL-17A.[a]
IL, interleukin.
[a] DBA/1 mice were administered 2 intraparietal doses of 20 mg/kg secukinumab or isotype control (basiliximab, anti-human CD25) 24 h and 2 h prior to injection into the right knee joint of 50,000 NIH-3T3 cells secreting human IL-17A. Swelling measured 3 days after cell injection is expressed as the ratio between the right (treated) and left (untreated) joint. The results presented represent the mean ± SEM ($n = 8$).
* $P < .0001$.

Clinical trials comparing the efficacy of drugs targeting IL-17A with those targeting TNF-α in PsA may further illuminate the relative mechanistic importance of these 2 cytokines in managing the different musculoskeletal and skin manifestations of PsA. In a randomized, double-blind, controlled study comparing the efficacy of secukinumab with that of the anti–TNF-α mAb adalimumab in biologic-naive patients with PsA (EXCEED), secukinumab demonstrated numerically higher clinical responses in joint symptoms, with significantly improved efficacy in the skin compared with adalimumab (McInnes et al., 2020). Similarly, the phase 3b/4, open-label study comparing the anti–IL-17A mAb ixekizumab with adalimumab in patients with PsA (SPIRIT-H2H; NCT03151551) suggests that ixekizumab resulted in greater improvement in a combined articular and cutaneous endpoint compared with adalimumab in patients with PsA (Mease et al., 2020; Smolen et al., 2020). Direct comparisons between these 2 clinical studies are limited by differences in study designs and patient populations.

### 3.3. Therapeutic index

Secukinumab has a large therapeutic index, defined as the window between the effective human serum exposure (as $C_{max}$ or area under the curve) and the exposure at the no-observed-adverse-effect level (NOAEL). NOAEL is defined as the dose with a level of drug exposure in animal toxicology studies at which there is no biologically or statistically significant increase in the frequency or severity of any adverse effects compared with placebo. In cynomolgus monkeys, the NOAEL for secukinumab was found to be at the highest SC dose administered (150 mg/kg), leading to high human exposure multiples. Using 2-compartment PK models based on PK data from several studies in humans and observed toxicokinetics data from SC toxicology studies in the cynomolgus monkey, human exposure multiples were calculated for the 300-mg SC dosing regimen used in the main phase 3 studies in PsO (Table 2). Monthly 300-mg SC maintenance doses of secukinumab—corresponding to 3 to 4 mg/kg for patients with a body weight range of 75 to 100 kg—result in a 120-fold lower average serum secukinumab concentration at steady state than the corresponding serum concentration after weekly dosing at the NOAEL in the cynomolgus monkey (exposure multiple; Table 2). For the 300-mg SC q2w regimen, the human exposure multiple based on the average secukinumab concentration at steady state during maintenance is 60-fold lower than the average serum concentration at the NOAEL, thus still providing a high safety margin. During the first-month induction phase with weekly dosing, the average human serum concentration is 60-fold lower than in cynomolgus monkeys. Similar human exposures are obtained based on maximum concentrations during induction and maintenance (Table 2). The mean human profile for the 300-mg dosage is shown in Fig. 1.

## 4. PD properties of secukinumab and clinical implications

### 4.1. IL-17A as a pharmacological target

The IL-17 cytokine family consists of 6 different members (IL-17A-F); functional cytokines are secreted as dimers, which signal by promoting the association of cell surface receptors of the IL-17 receptor (IL-17R) family (Pappu, Ramirez-Carrozzi, & Sambandam, 2011). Of these IL-17 cytokine isoforms, IL-17A and IL-17F share the greatest amount of sequence homology (approximately 50%). Both isoforms function comparably in inflammation and host defense (Brembilla, Senra, & Boehncke, 2018) and are the only isoforms for which heterodimerization (IL-17AF) has been described (Pappu et al., 2011). Homodimeric IL-17A is known to stimulate keratinocytes, fibroblasts, endothelial cells, epithelial cells, and other cell types to produce an

**Table 2**
Comparative systemic exposure in cynomolgus monkey and humans.

| Dose regimen | $C_{av,ind}/C_{av,main}$ (μg/mL)[a] | $C_{max,ind}/C_{max,main}$ (μg/mL)[b] | Induction | | Maintenance | |
|---|---|---|---|---|---|---|
| | | | $C_{av,ss}$ of 4824 μg/mL[c] | $C_{max,ss}$ of 5455 μg/mL[c] | $C_{av,ss}$ of 4824 μg/mL[d] | $C_{max,ss}$ of 5455 μg/mL[d] |
| | Human serum levels (μg/mL) | | At NOAEL of 150 mg/kg SC in cynomolgus monkey | | | |
| | | | Human exposure multiple | | | |
| 300 mg SC at weeks 0–4, then 300 mg SC q4w starting at week 8 | 80.1/40.1 | 98.6/49.3 | **60** | **55** | **120** | **110** |

NOAEL, no-observed-adverse-effect level; q4w, every 4 weeks; SC, subcutaneous.
[a] $C_{av,ind}$ is the average secukinumab concentration after the fifth dose in the induction phase; $C_{av,main}$ is the average secukinumab concentration during maintenance (q4w dosing interval) at steady state.
[b] $C_{max,ind}$ is the maximum secukinumab concentration after the fifth dose in the induction phase; $C_{max,main}$ is the maximum secukinumab concentration during maintenance (q4w dosing interval) at steady state.
[c] $C_{av,ind}$ and $C_{max,ind}$ in patients were compared with $C_{av,ss}$ and $C_{max,ss}$, respectively, at the NOAEL of 150 mg/kg SC in the 13-week toxicology study in cynomolgus monkey.
[d] Predicted $C_{av,\ maint}$ and $C_{max,maint}$ in patients were compared with $C_{av,ss}$ and $C_{max,ss}$, respectively, at the NOAEL of 150 mg/kg SC in the 13-week toxicology study in cynomolgus monkey to calculate the exposure multiple during maintenance; τ (dosing interval) is 7 days in the cynomolgus toxicology study and 28 days in patients in the maintenance phase.

array of inflammatory and immune-mediating molecules, including cytokines, chemokines, and antimicrobial peptides (Iwakura, Ishigame, Saijo, & Nakae, 2011). The potency of IL-17A toward the induction of IL-6 secretion was found to be approximately equal in keratinocytes (Teunissen, Koomen, de Waal Malefyt, Wierenga, & Bos, 1998) and rheumatoid arthritis synovial fibroblasts (Chabaud, Fossiez, Taupin, & Miossec, 1998). In these experimental systems, human IL-17A was found to be the most potent IL-17A/F cytokine, followed by IL-17AF and IL-17F with approximately 10- and 100-fold lower potency, respectively, vs IL-17A (Huppertz, Hennze, Curcic, & Kolbinger, 2013; Wright et al., 2008).

The IL-17A receptor complex consists primarily of 2 IL-17R family subunits: IL-17RA and IL-17RC (Gaffen, 2009). However, it has recently been shown that IL-17A can also signal through a complex of IL-17RA and IL-17RD, although additional research is required to understand the role and functional consequences of this receptor complex in IL-17A signaling (Su et al., 2019). Many cytokines activate the same intracellular signaling networks, and these signaling pathways are tightly regulated within the cell. Directly targeting cytokines with biologics is a preferable mechanism of action compared with targeting receptors such as IL-17RA or downstream intracellular signaling networks if high selectivity is desired. The selectivity and affinity of secukinumab for IL-17A are favorable for targeting this individual signaling pathway with minimal cross talk.

### 4.2. Secukinumab binding to IL-17A

Secukinumab has a high affinity for human IL-17A. Surface plasmon resonance measurements determined a $K_D \pm$ SD for unmodified, recombinant human IL-17A (0.060 ± 0.016 nM; Table 3) and for N-terminally amyloid precursor protein hexapeptide–tagged human IL-17A (0.090 ± 0.025 nM). These measurements were acquired using clinical batches of secukinumab and high-quality protein preparations produced in mammalian cells (Novartis data on file). Importantly, the epitope for secukinumab on IL-17A is spatially separated from the IL-17A N-terminus, and thus, N-terminal tags are unlikely to sterically interfere with secukinumab binding (Fig. 3). Earlier studies using different batches of secukinumab (including research batches not intended for human exposure) as well as C-terminally tagged, mammalian IL-17A and untagged IL-17A produced from *Escherichia coli* had suggested a $K_D$ of approximately 0.2 nM (Novartis, 2020). However, subsequent determination of the epitope showed that the C-terminal tag may affect binding affinity of secukinumab (Fig. 3).

Secukinumab binds to IL-17A more potently than to IL-17AF ($K_D \pm$ SD = 2.4 ± 0.2 nM [N-terminal amyloid precursor protein hexapeptide–tag on the IL-17F chain]) or IL-17F ($K_D$ not determinable, binding only observed at μM concentrations; Table 3). Importantly, the calculated maximum concentration of secukinumab at steady state in skin interstitial fluid resulting from SC administration of 300 mg q4w is approximately 120 nM, which is roughly 2000-fold higher than the $K_D$ of secukinumab binding to IL-17A and 50-fold higher than the $K_D$ for IL-17AF.

This rank order of affinities is supported by functional studies. In an in vitro assay using primary human fibroblast-like synoviocytes (FLS), secukinumab potently neutralized the IL-17A/F–dependent induction of IL-6 release in the presence of a fixed concentration of TNF-α (0.060 nM). IL-17A/F cytokine concentrations were selected to induce a similar IL-6 release by FLS. Secukinumab neutralized IL-6 release co-stimulated by TNF-α and 0.03 nM IL-17A (half maximal inhibitory concentration [$IC_{50}$] ± SD = 0.14 ± 0.02 nM), 1 nM IL-17AF ($IC_{50} \pm$ SD = 3.3 ± 0.2 nM), and 33 nM IL-17F ($IC_{50} \pm$ SD = 1800 ± 170 nM; Fig. 4). At steady state, the calculated maximum concentration of secukinumab in the skin is roughly 25-fold higher than the $IC_{90}$ for the neutralization of IL-17A ($IC_{90} \pm$ SD = 4.8 ± 1.6 nM) and roughly equal to the $IC_{90}$ for IL-17AF ($IC_{90} \pm$ SD = 122 ± 38 nM).

A large molar excess of secukinumab over IL-17A/F cytokine appears to be required to achieve full target engagement and saturating increases in systemic total IL-17A levels (Bruin et al., 2017). In contrast, systemic total IL-17AF levels do not change during secukinumab treatment, which indicates that secukinumab does not bind strongly to IL-17AF; the same is true for IL-17F (Novartis data on file). Although in vitro binding affinities and in vitro neutralization potencies of secukinumab for IL-17A/F isoforms indicate activity against IL-17A and IL-17AF (Table 3, Fig. 4), the observed levels of total (free and secukinumab-bound) IL-17A/F isoforms in patient serum suggest that, at concentrations achieved during therapy, secukinumab is selective for IL-17A, no binding and neutralization of IL-17F are expected, and only limited binding to IL-17AF is likely.

**Table 3**
Measured affinities of secukinumab for IL-17A, IL-17AF, and IL-17F.[a]

| Species, $K_D$, nM (SD) | IL-17A | IL-17AF | IL-17F |
|---|---|---|---|
| Human | 0.060 (0.016)[b]<br>0.090 (0.025)[c] | 2.4 (0.2)[c] | ND[c,d] |
| Cynomolgus monkey | 0.90 (0.16)[b]<br>1.2 (0.1)[c] | 4.3 (0.5)[c] | ND[c,d] |

IL, interleukin; ND, not determined.
[a] Novartis data on file.
[b] Data are from binding studies of secukinumab with untagged IL-17A constructs.
[c] Data are from binding studies of secukinumab with IL-17A/F constructs N-terminally tagged with amyloid precursor protein–derived hexapeptide.
[d] Binding of secukinumab to human and cynomolgus monkey IL-17F was only observed at micromolar concentrations as measured by surface plasmon resonance.

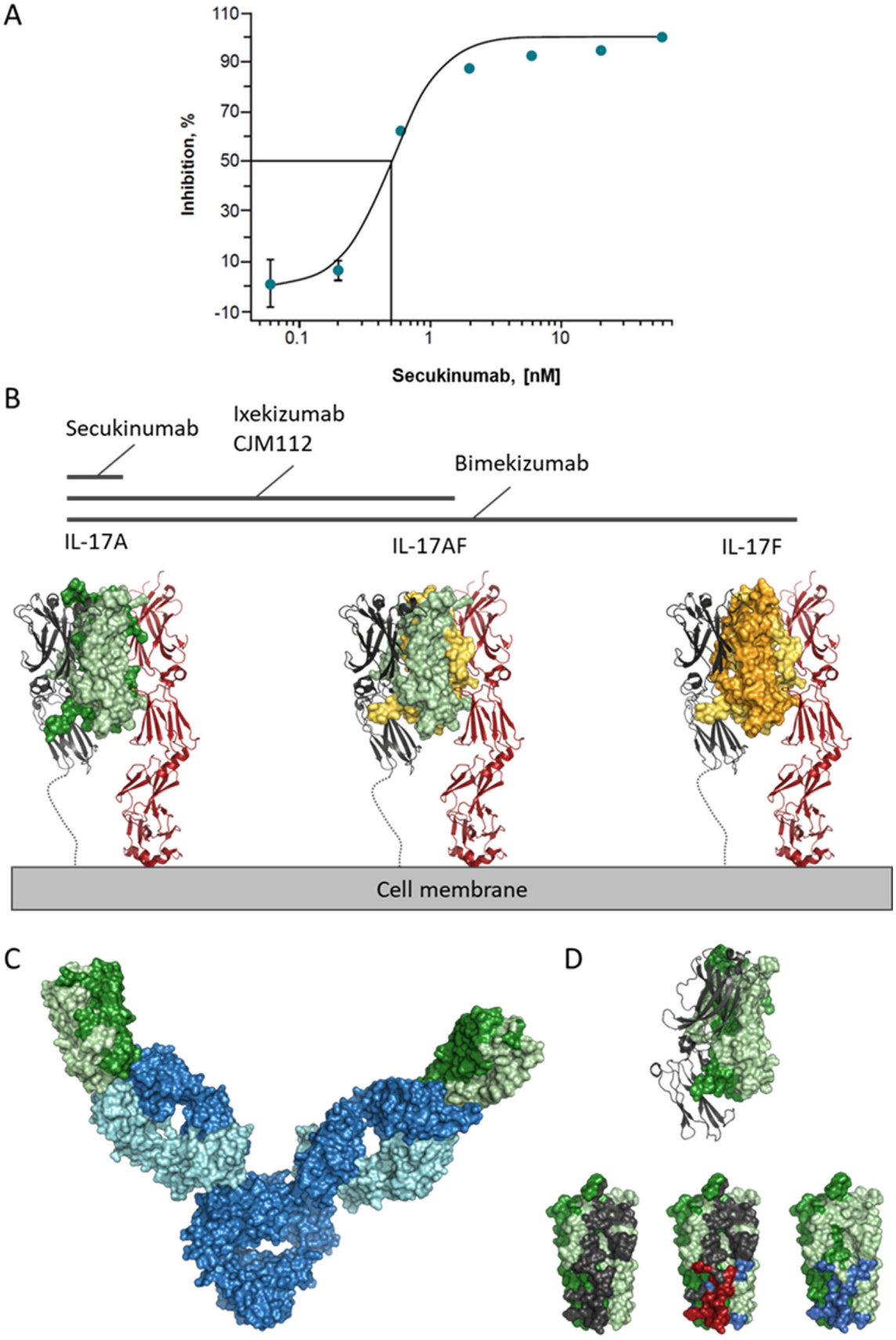


**Fig. 3.** Secukinumab competes with binding of IL-17RA to IL-17A. **(A)** Competition ELISA assay confirms inhibition of IL-17A binding to IL-17RA by secukinumab. **(B)** Models of the IL-17A, IL-17AF, and IL-17F signaling complexes, based on published x-ray analyses (Ely et al., 2009; Goepfert et al., 2020; Goepfert, Lehmann, Wirth, & Rondeau, 2017; Liu et al., 2013) and relevant clinical selectivity of current anti–IL-17A therapeutic antibodies. **(C)** Three-dimensional model of secukinumab (dark–/light-blue surface) in complex with 2 IL-17A molecules (dark–/light-green surface) generated from the crystal structure of the secukinumab Fv fragment with IL-17A (Novartis data on file). **(D)** Secukinumab competes with binding of IL-17RA to IL-17A. Top panel: crystal structure of the human IL-17A homodimer (dark–/light-green surface) in complex with the extracellular region of IL-17RA (black ribbon), based on 4HSA.PDB (Ely et al., 2009). Bottom panel: Left: footprint (black surface) of IL-17RA on the IL-17A homodimer (dark–/light-green surface); Right: footprint of secukinumab (blue surface) on the IL-17A homodimer; Center: the red surface patch shows the binding interface common to IL-17RA and secukinumab, responsible for the direct competition between secukinumab and the IL-17A receptor.
4HSA. PDB, Protein Data Bank entry for the structure of IL-17A in complex with IL-17 receptor A; ELISA, enzyme-linked immunosorbent assay; Fv, variable domain; IL, interleukin.

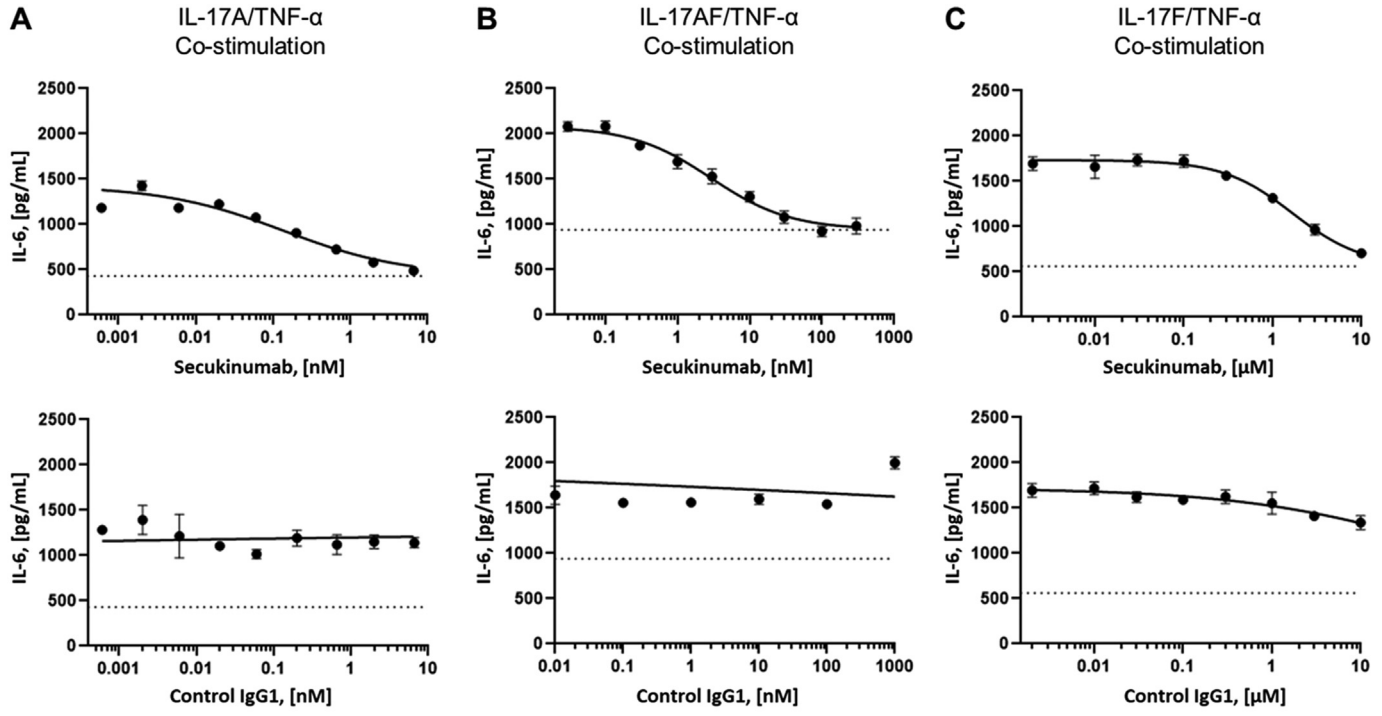


**Fig. 4.** Neutralization of (**A**) human IL-17A–, (**B**) IL-17AF–, and (**C**) IL-17F–dependent IL-6 secretion by human FLS co-stimulated with respective IL-17A/F cytokines and TNF-α by secukinumab (top row) and control IgG1 (bottom row). Dashed lines represent the level of IL-6 induced by TNF-α alone.
FLS, fibroblast-like synoviocytes; IgG, immunoglobulin G; IL, interleukin; TNF-α, tumor necrosis factor α.
[a] Primary human FLS were co-stimulated overnight with IL-17A (0.030 nM)/TNF-α (0.060 nM) in the presence of increasing concentrations of secukinumab or control IgG1. TNF-α alone induced an IL-6 release of 431 pg/mL.
[b] Primary human FLS were co-stimulated overnight with IL-17AF (1 nM)/TNF-α (0.060 nM) in the presence of increasing concentrations of secukinumab or control IgG1. TNF-α alone induced an IL-6 release of 941 pg/mL.
[c] Primary human FLS were co-stimulated overnight with IL-17F (33 nM)/TNF-α (0.060 nM) in the presence of increasing concentrations of secukinumab or control IgG1. TNF-α alone induced an IL-6 release of 562 pg/mL.

No appreciable binding to the other IL-17 cytokine family members IL-17C, IL-17D, and IL-17E (IL-25) and unrelated human cytokines, including IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-13, IL-18, IL-19, IL-20, IL-22, IL-23, TGF-β1, TGF-β2, and TNF-α, has been found for secukinumab (Novartis data on file). Additionally, secukinumab does not have any appreciable cross-species reactivity aside from IL-17A binding in nonhuman primates. Secukinumab binds weakly to rhesus monkey and marmoset IL-17A ($K_D \pm SD = 8.90 \pm 0.10$ nM and $1.55 \pm 0.35$ nM, respectively) and has no affinity for mouse or rat IL-17A (Novartis data on file) and binds strongly to cynomolgus monkey IL-17A ($K_D \pm SD = 0.90 \pm 0.16$ nM; Novartis data on file; Table 3).

Secukinumab effectively binds to free IL-17A in vitro and competitively inhibits IL-17A binding to the human IL-17 receptor IL-17RA (Fig. 3). This efficient binding of secukinumab to IL-17A directly competes with its binding to the human IL-17RA receptor (Novartis data on file; Fig. 3D) and is also supported by the binding epitope of secukinumab on human IL-17A, which sterically overlaps with the corresponding IL-17RA receptor-ligand interface (Ely, Fischer, & Garcia, 2009), confirming that secukinumab directly interferes with the binding of IL-17A to the IL-17RA receptor chain (Fig. 3). Secukinumab also directly competes with the binding of IL-17A to IL-17RC, potentially inhibiting IL-17RA–independent, IL-17RC–driven signaling pathways, although further research is needed to unravel the details of such pathways and their potential relevance to PsO, PsA, and axSpA (Goepfert, Lehmann, Blank, Kolbinger, & Rondeau, 2020).

Of note, the IL-17AF heterodimer appears to be assembled intracellularly by the combination of a single IL-17A monomer with a single IL-17F monomer, but this process does not appear to take place outside the cell, for example, by an exchange of monomers between IL-17A and IL-17F as shown in in vitro transfection experiments (Fig. 5). IL-17A and IL-17F protein can be simultaneously expressed by Th17 cells of healthy donors and patients with PsO (Fig. 6) (Pappu et al., 2011), suggesting that these IL-17A/IL-17F double-positive Th17 cells are one cellular source producing the IL-17AF heterodimer in vivo. Earlier studies have found that approximately 50% of Th17 cells expressing IL-17A also express IL-17F, although there appears to be a distinct subpopulation that expresses only IL-17F and not IL-17A (Yang et al., 2008). That

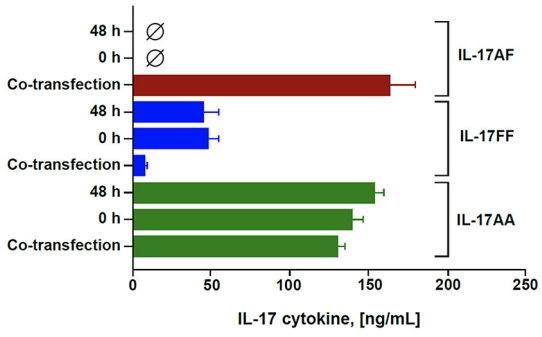


**Fig. 5.** IL-17AF heterodimer only formed upon co-transfection with IL-17A and IL-17F expression vectors.
ELISA, enzyme-linked immunosorbent assay; IL, interleukin.
HEK293FT cells were transfected with either IL-17A or IL-17F cDNA encoding plasmids alone or co-transfected with both plasmids. Twenty-four hours after transfection, cell culture supernatants from single transfected cells were collected, mixed in a 1:1 ratio, and directly frozen (0 h) or incubated for 48 h. IL-17A, IL-17AF, and IL-17F cytokine levels were determined in culture supernatant using specific ELISA assays, as described in Supplementary Methods.

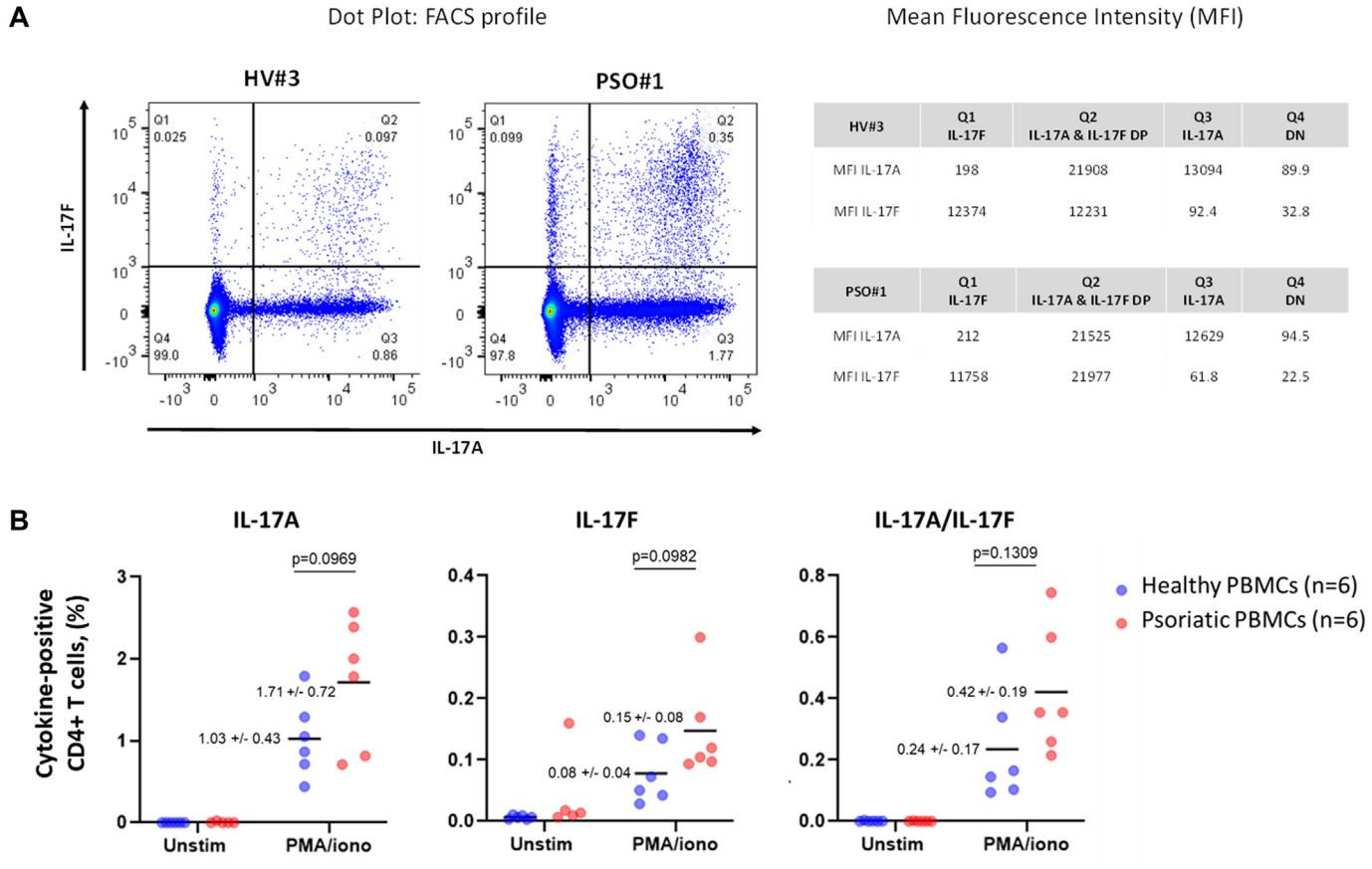


**Fig. 6.** IL-17A and IL-17F expression by $CD4^+$ T cells from healthy donors and patients with PsO. (**A**) Representative FACS profiles and MFIs of stimulated T cells from HV and PsO donors: Representative FACS dot plots and corresponding MFI table from PMA–/ionomycin-stimulated T cells of 1 healthy (HV#3) and 1 psoriasis patient (PsO#1). Percentages of each quadrant of the dot plots were extracted from each donor condition to generate study graphs. (**B**) Frequency of $CD4^+$ T cells producing IL-17A and IL-17F: $CD4^+$ T cells from patients with psoriasis display higher frequencies of IL-17A, IL-17F, and IL-17A/F than corresponding cells isolated from healthy donors. Solid line: mean of cytokine-positive CD4+ T cells (%); values show means ± SD.

DN, double negative; DP, double positive; FACS, fluorescence-activated cell sorting; HV, healthy volunteer; IL, interleukin; iono, ionomycin; MFI, mean fluorescence intensity of corresponding cytokine; PBMC, peripheral blood mononuclear cell; PMA, phorbol 12-myristate 13-acetate; PsO, psoriasis; Q1, CD4 T cells positive for IL-17F; Q2, CD4 T cells positive for both IL-17A and IL-17F; Q3, CD4 T cells positive for IL-17A; Q4, CD4 T cells negative for both IL-17A and IL-17F; unstim, unstimulated.

secukinumab significantly reduced *IL17A* and *IL17F* mRNA expression in skin biopsies of patients with PsO after 12 weeks of treatment (Krueger et al., 2019) indicates that over time, secukinumab may indirectly lead to a reduction of IL-17AF heterodimer and IL-17F homodimer levels and inhibition of IL-17AF and IL-17F function.

IL-17A is the main disease-driving IL-17A/F cytokine in PsO, while the role of IL-17F and that of IL-17AF appear to be more limited. This is supported by data in PsO, where the serum abundance of IL-17A, but not of IL-17F, correlates with clinical disease activity (ie, PASI responses), suggesting that IL-17A is indeed the major effector cytokine in this disease (Kolbinger et al., 2017). Additionally, IL-17A levels are significantly increased 10-fold in lesional skin compared with nonlesional skin (9.8 vs 0.8 pg/mL; $P < .01$), whereas IL-17F levels are increased by a factor of 2, although not with statistical significance (317.0 vs 163.0 pg/mL; $P > .05$) (Kolbinger et al., 2017). A more therapeutically important role of IL-17A over IL-17AF in PsO is supported by a recent proof-of-concept study comparing the anti–IL-17A/IL-17AF antibody CJM112 head-to-head with secukinumab in patients with PsO that revealed that additional neutralization of IL-17AF did not translate to increased clinical efficacy compared with secukinumab (Kaul et al., 2021). Recent data from phase 3 studies of patients with PsO treated with bimekizumab, a dual inhibitor of IL-17A and IL-17F, provide some detail on the relative contributions of IL-17A vs IL-17F or other targets in PsO disease modification as well as the safety of inhibiting these respective cytokines. (Adams et al., 2020; Reich, Warren, et al., 2021; Warren et al., 2021). In head-to-head comparison studies, bimekizumab resulted in a greater achievement of PASI100 among patients with PsO than did secukinumab (Reich, Warren, et al., 2021) or adalimumab (Warren et al., 2021), suggesting the increased benefit of inhibition of IL-17F in addition to IL-17A and the benefit of inhibiting both IL-17A and IL-17F vs TNF-α. However, 10%–19% of patients treated with bimekizumab in these studies experienced *Candida* infestations, compared with 3% of patients receiving secukinumab and no patients receiving adalimumab (Reich, Warren, et al., 2021; Warren et al., 2021). Notably, IL-17A and IL-17F are both involved in the immune response to *Candida* (Li, Casanova, & Puel, 2018; Mengesha & Conti, 2017).

Key pathological features of PsA and axSpA are known to be driven by IL-17A signaling. IL-17A signals through a number of different target cells in the joints (Blauvelt & Chiricozzi, 2018; Miossec, 2017; Zenobia & Hajishengallis, 2015), and IL-17A has been implicated in enthesitis, synovitis, bone destruction, and new bone formation in both PsA and axSpA (McGonagle et al., 2019). The demonstrated clinical efficacy of biologics targeting IL-17A for the treatment of PsA and axSpA provides the greatest evidence for the role of IL-17A in these inflammatory conditions. Both secukinumab and ixekizumab improve enthesitis, dactylitis, synovitis, and reduce chronic structural changes to bone over time among patients with PsA (Braun et al., 2018; Mease et al., 2015; Mease et al., 2017; Nash et al., 2017; Tahir et al., 2019; van der Heijde et al., 2018; van der Heijde et al., 2020). Similarly, both biologics have

proven effective at reducing axial symptoms and radiographic progression among patients with axSpA, highlighting the role of IL-17A in axial disease (Baeten et al., 2015; Braun et al., 2018; Deodhar, Blanco, et al., 2020; Deodhar, van der Heijde, et al., 2020; Dougados et al., 2020; van der Heijde, Cheng-Chung, et al., 2018). Early results of a phase 2b study of bimekizumab in patients with PsA demonstrate clinical responses in skin and joints similar to those observed in trials of secukinumab (Ritchlin et al., 2020). However, due to limited size of the patient population and lack of an active IL-17 comparator, superiority of dual IL-17A and IL-17F inhibition over IL-17A selective inhibition remains to be determined (Nash, 2020).

### 4.3. Comparisons with other approved biologics targeting IL-17A

Currently approved drugs targeting IL-17A include secukinumab, which selectively targets IL-17A ($K_D$, 0.060–0.090 nM; Table 3); ixekizumab, a humanized IgG4 mAb with roughly equal affinities for IL-17A ($K_D$, 0.0018 nM) and IL-17AF ($K_D$, < 0.003 nM) (Liu et al., 2016); and brodalumab, a mAb targeting IL-17RA ($K_D$, 0.239 nM) (Timmermann & Hall, 2019). Bimekizumab, a humanized IgG1 mAb selective for both IL-17A and IL-17F ($K_D$, 0.003 nM and 0.023 nM, respectively) (Adams et al., 2020), has shown strong clinical efficacy in PsO and is currently under review by the US Food and Drug Administration and European Medicines Agency as a potential treatment for moderate to severe PsO (Gordon et al., 2021; Reich, Papp, et al., 2021). To best compare the different clinical responses between different IL-17A inhibitors, head-to-head comparator studies are required. Indirect comparisons between trials suffer from several drawbacks, including demographic and clinical differences between patient populations, potential inconsistencies in assessment of outcomes, and different approaches to statistical analyses, among others. The only head-to-head clinical trial directly comparing biologics targeting the different soluble IL-17A/F isoforms (IL-17A, IL-17AF, and IL-17F) is BE RADIANT, evaluating bimekizumab vs secukinumab in patients with PsO (Reich, Warren, et al., 2021). Patients treated with bimekizumab were more likely than those receiving secukinumab to achieve PASI100 through 48 weeks, although bimekizumab was associated with greater oral candidiasis than secukinumab (19.3% vs 3.0% of patients) (Reich, Warren, et al., 2021). Although no randomized controlled, head-to-head studies have compared secukinumab with ixekizumab, real-world cohort studies comparing these two biologics have recently been published. One retrospective study of the first 59 and 29 patients with PsO treated with secukinumab and ixekizumab, respectively, found no significant differences in efficacy between these biologics (Herrera-Acosta, Garriga-Martina, Suárez-Pérez, Martínez-García, & Herrera-Ceballos, 2020). One cohort study found slightly higher drug survival among patients receiving ixekizumab than those receiving secukinumab, although clinical efficacy was not reported (Blauvelt et al., 2020). Another retrospective study of 245 patients receiving either biologic found higher efficacy outcomes among patients receiving secukinumab vs ixekizumab at week 12 despite a slightly lower drug survival rate for secukinumab (Caldarola et al., 2021).

Besides IL-17A/F isoform selectivity, one could consider differences among binding affinities as drivers of efficacy; this has been proposed (Paul, 2018) as a potential explanation for observed small differences in efficacy at week 12 in an indirect comparison study (Warren et al., 2018). However, affinity of a drug for its target is not the only parameter that defines the ultimate efficacy of that drug (Kenakin, 2009). The potency of a drug, as defined by the interplay between affinity/avidity and ligand efficacy, a quantitative term used to describe the ability of a ligand to produce a biological response once bound to the receptor (Kenakin, 2009), should also be considered and clearly distinguished from an in vitro binding affinity alone. For biologics, binding affinity for a target cytokine does not necessarily translate directly to potency at inhibiting the cytokine's ability to signal through its cognate receptor. In this respect, the corresponding target epitope is of critical importance. Additionally, tissue distribution, serum half-life, and the chosen dosing scheme also inform efficacy in the clinic. In patients, if an effective and safe dose of a given biologic is achievable, affinity does not directly translate to clinical efficacy; for example, 2 hypothetical antibodies with different affinities for the same target could achieve the same efficacy at different doses.

IL-17A is likely the main contributor to the pathogenesis of psoriatic disease compared with IL-17F or IL-17AF, although some contribution by IL-17F or IL-17AF is possible based on their similar biology to IL-17A. Comparing emerging clinical results for bimekizumab (IL-17A and IL-17F) with those for secukinumab (IL-17A), ixekizumab (IL-17A and IL-17AF), and brodalumab (IL-17RA) will likely shed more light on the relative importance of IL-17A vs IL-17F signaling in the pathophysiology of the indications studied, as well as the safety implications of inhibiting different IL-17A/F isoforms. For example, *Candida* infestations are higher in bimekizumab-treated patients with PsO (Gordon et al., 2021; Reich, Papp, et al., 2021) than for secukinumab- (Reich, Warren, et al., 2021) or ixekizumab-treated patients (Gordon et al., 2016), likely due to the role of both IL-17A and IL-17F in immune response to *Candida* (Li et al., 2018; Mengesha & Conti, 2017). Thus, selective inhibition of IL-17A but not IL-17F by secukinumab may provide advantages in frequency and severity of *Candida* infestations and potentially other infections compared with drugs inhibiting both isoforms.

## 5. Relationships to safety and immunogenicity

Because of the favorable PK and PD properties discussed here, secukinumab has been well tolerated in safety, general toxicology, and developmental and reproductive toxicology studies. The safety profile of secukinumab is favorable, with infrequent occurrences of infection or infestation, inflammatory bowel disease, uveitis, and liver enzyme changes (Baraliakos et al., 2019; Bissonnette et al., 2018; Deodhar, Mease, et al., 2019; Tahir et al., 2019). In toxicology studies of secukinumab, no antibody-dependent cellular cytotoxicity was observed, and secukinumab caused no hemolysis of human or cynomolgus monkey serum and plasma (Novartis data on file). Tissue cross-reactivity studies uncovered no nonspecific tissue binding of secukinumab (Novartis data on file). No reproductive target organ toxicity or embryo fetal development was observed in cynomolgus monkeys with secukinumab; in addition, no impact on fertility was seen with a surrogate anti-mouse IL-17A antibody in the mouse (Novartis data on file). Because inflammatory diseases treatable with secukinumab are known to have numerous comorbidities, patients receiving secukinumab may be receiving additional medication (Carvalho et al., 2016; Coates et al., 2016; Walsh, Song, Kim, & Park, 2018). It is therefore important that no drug-drug interactions have been observed for secukinumab. Secukinumab does not have significant PK interactions with drugs metabolized by the cytochrome P450 3A4 isoform in humans (Bruin et al., 2019). One advantage of secukinumab for physicians is that co-medication with low-molecular-weight drugs is possible, although caution should be taken in light of contraindications specific to the co-medications administered.

Other biochemical properties intrinsic to secukinumab contribute to its safety profile. Secukinumab, a fully human antibody, was generated from a hybridoma cell isolated from mice carrying portions of the human immunoglobulin repertoire; this is likely a significant contributor to the observed infrequent injection-site reactions and low immunogenicity. Injection-site reactions with secukinumab treatment are low to nonexistent in frequency compared with those observed for other biologics. The low immunogenicity prevalence leads to relatively few patients developing immunologic responses, including antidrug antibodies or neutralizing antibodies. Antidrug antibody incidence for secukinumab is <1% in studies across all indications at week 52 (Deodhar et al., 2020; Deodhar, Mease, et al., 2019), and this extends to treatment periods as long as 5 years (Reich et al., 2019). Furthermore, no increased antidrug antibodies were observed following treatment

interruption and restart of treatment in the SCULPTURE study (Mrowietz et al., 2015). The presence of antidrug antibodies does not universally correlate with loss of clinical efficacy. For example, immunogenicity was found to have no relationship to efficacy of guselkumab (Zhu et al., 2019), while efficacy of tildrakizumab is reduced in the presence of antidrug antibodies (Kimball et al., 2020). In vitro immunogenicity studies conducted using samples from healthy donors indicate that secukinumab has a low probability of inducing T-cell responses and that these responses are significantly higher for ixekizumab in the same healthy donors (Spindeldreher et al., 2018; Spindeldreher et al., 2020). This low immunogenicity potential may be explained by the observation that secukinumab has few T-cell epitopes (Spindeldreher et al., 2020).

## 6. Relationships to drug survival and rescue from secondary failure

Loss of response is a common feature of biologic drugs; switching between biologics is often used to reestablish treatment response in patients who experienced secondary failure or severe flare after initial clinical improvement (Costa et al., 2017; Leman & Burden, 2012; Mease et al., 2019). Multiple potential explanations underlie loss of response for patients on a biologic, including nonadherence, comorbidities, lower serum exposure in patients with higher body weight than in those with lower body weight, change in the immunopathology of the disease during the course of treatment, development of antidrug antibodies, medication- or bacterial infection–induced disease flares (eg, streptococcal pharyngitis), or fluctuation of underlying disease activity over time. As with any biologic, loss of treatment response has been observed for secukinumab. Based on PK data, it is unlikely that secondary failure of secukinumab results from either decreasing serum levels over time or immunogenicity. Steady-state trough levels are achieved after 24 weeks and maintained through 5 years of treatment (Bruin et al., 2017), and the formation of treatment-emergent antidrug antibodies is infrequent across indications (Deodhar, Gladman, et al., 2020; Deodhar, Mease, et al., 2019). Additionally, a meta-analysis of real-world studies determined the 12-month drug survival of secukinumab in patients with PsO to be 80% (Augustin, Jullien, Martin, & Peralta, 2020). Aside from loss to follow-up, the relatively infrequent discontinuation observed in the real world is primarily due to secondary nonresponse and less frequently due to adverse events (Megna et al., 2019; Torres et al., 2019; Yiu et al., 2020). Interestingly, a real-world study found that secukinumab has greater efficacy through 52 weeks in patients with PsO who are naive to biologics vs those with previous biologic experience (Chiricozzi et al., 2020); similar results have been found for patients with PsA treated with secukinumab (Michelsen et al., 2021).

Although small, retrospective cohort studies have recently demonstrated that a majority of patients who experienced loss of clinical response with secukinumab can subsequently respond to ixekizumab (Bokor-Billmann & Schäkel, 2019; Georgakopoulos, Phung, Ighani, & Yeung, 2018), it might be possible that patients would have potentially regained clinical response if treatment with secukinumab had continued or the dose had been increased. This possibility is supported by a detailed analysis of different clinical studies of secukinumab in the treatment of PsO that indicates that approximately half of patients experiencing a loss of response regained clinical response when secukinumab treatment was continued (Augustin, Thaci, et al., 2020). Taken together, these results suggest that decreased serum concentrations of secukinumab or treatment-emergent antidrug antibodies are likely not a major contributing factor for an observed loss of response to secukinumab over time.

One may speculate that the differences in IL-17A and IL-17AF selectivity, or different affinities for IL-17A or IL-17AF, could underlie rescue of secukinumab nonresponders with the higher-affinity antibody ixekizumab. This scenario is unlikely because anecdotal real-world observations of patients experiencing secondary failure with ixekizumab have shown that they improve with subsequent treatment with secukinumab (J.E.H, unpublished data, 2021).

Some caveats are important to understand when assessing rescue of response or drug survival. In particular, due to the often-immediate switching to other biologics upon loss of response in clinical practice, it is frequently not clear whether the loss of response that led to the switching of drugs would be permanent or transient. Furthermore, the timing of secukinumab's approval before ixekizumab's may have led to a bias in current real-world observations and reporting of rescue from loss of response of secukinumab because it has often been used first line. This potential bias may change with time, as different anti–IL-17A biologics are increasingly selected as first-line agents, allowing for a better understanding of whether rescue from loss of response by a given biologic is IL-17A/F selectivity related or dependent on which biologic was used first.

## 7. The near future: personalized medicine

The landscape of available biologics for the treatment of PsO, PsA, and axSpA, including both nr-axSpA and AS, continues to expand, and increasing amounts of data are available for each drug. In the near future, biologics may be prescribed in a systematic manner based on efficacy in the disease domains most affecting the lives of individual patients. Duration of disease and patient history may influence the clinical response, and early treatment may be beneficial for optimal response and prevention of disease progression—for example, from PsO to PsA. Distinct endotypes or disease domain manifestations of psoriatic disease or axSpA may respond differentially to drugs with different mechanisms of action. Machine learning can be applied to recognize endotypes and subpatterns of disease domain manifestations that may be most amenable to a given therapeutic intervention. Preliminary data obtained using the secukinumab phase 3 trial program in PsA are now being expanded to other clinical data sets to determine the impact of discrete responses for a given endotype to specific TNF-α inhibitors or IL-17A inhibitors (Novartis data on file). To realize effective, personalized treatment approaches for each patient, a thorough understanding of clinical and pharmacological data for biologics must be developed.

## 8. Conclusions

The high selectivity for IL-17A and PK/PD properties of secukinumab are important variables underlying its clinical efficacy and safety for treating adult and pediatric patients with PsO, adults with PsA, and adults with axSpA, including those with nr-axSpA and those with AS. The interplay between the PK and PD properties of secukinumab is well characterized and understood, and continuous dose optimization is applied to achieve ideal clinical responses in addressing specific patient needs. The favorable PK/PD profile of secukinumab leads to long-term drug survival and sustained efficacy over long treatment periods in clinical studies and real-world use. Secukinumab is safe for long-term treatment of PsO, PsA, and axSpA, and antidrug antibody responses and injection-site reactions with secukinumab have consistently been very low (< 1%) in all approved indications. No new safety signals have been identified in >34,000 patient-years in clinical trials and > 680,000 patient-years of cumulative exposure in the postmarketing setting across indications. Long-term clinical efficacy and safety data remain the most important information for physicians to consider when comparing different biologics for the treatment of individual patients with PsO, PsA, and axSpA, and secukinumab has shown a beneficial benefit-risk profile across the approved indications.

## Funding

Support for third-party writing assistance was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

## Conflict of interest statement

F. Kolbinger, C. Huppertz, T. Kuiper, J. M. Carballido, C. Calonder, B. Vogel, J.-M. Rondeau, and G. Bruin are employees of Novartis Pharma AG. F. Di Padova is Prime Force Consultant for Novartis Pharma AG. A. Deodhar has received research grants from AbbVie, Eli Lilly, GSK, Novartis, Pfizer, and UCB and consulting fees from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Gilead, GSK, Janssen, Novartis, Pfizer, and UCB. J. E. Hawkes has received personal fees/honoraria from AbbVie, Janssen, LearnSkin, LEO Pharma, Novartis, Pfizer, Sanofi, UpToDate, and VisualDx. I. B. McInnes has received personal fees from AbbVie, Bristol Myers Squibb, Celgene, Janssen, Lilly, Novartis, UCB, and LEO Pharma and grants from Bristol Myers Squibb, Janssen, UCB, AstraZeneca, and Boehringer Ingelheim. C. T. Ritchlin has received consulting fees from AbbVie, Amgen, Eli Lilly, Janssen, Pfizer, Novartis, Gilead, and UCB. D. Rosmarin has received honoraria as a consultant for AbbVie, Celgene, Concert, Dermavant, Dermira, Incyte, Janssen, Kyowa Kirin, Lilly, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharmaceuticals, and VielaBio; has received research support from AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Dermira, Galderma, Incyte, Janssen, Lilly, Merck, Novartis, Pfizer, and Regeneron; and has served as a paid speaker for AbbVie, Amgen, Celgene, Janssen, Lilly, Novartis, Pfizer, Regeneron, and Sanofi. G. Schett has received grant/research support from Bristol Myers Squibb, Celgene, GSK, Eli Lilly, and Novartis; is a consultant for AbbVie, Bristol Myers Squibb, Celgene, Janssen, Eli Lilly, Novartis, and UCB; and has received speakers bureau fees from AbbVie, Bristol Myers Squibb, Celgene, Janssen, Eli Lilly, Novartis, and Pfizer. P. Häusermann has served as a speaker and/or advisor for AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, and Sanofi.

## Acknowledgments

The authors thank Richard Karpowicz, PhD, of Health Interactions, Inc., Hamilton, NJ, USA, for providing medical writing support/editorial support, which was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). The authors also thank Carmen Barske, Marija Curcic, Robert Hennze, Erika Lötscher, and Camille Regairaz of the Novartis Institutes for BioMedical Research in Basel, Switzerland, for their excellent technical support.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pharmthera.2021.107925.

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