Long Term Efficacy and Safety of Secukinumab in the Treatment of the Multiple Manifestations of Psoriatic Disease

Authors: K Reich,[1] RB Warren,[2] LC Coates,[3] Gabriele Di Comite[4]

Affiliations:

1. Translational Research in Inflammatory Skin Diseases, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Skinflammation® Center, Hamburg, and Dermatologikum Berlin, Berlin, Germany

2. Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester NIHR Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester, UK.

3. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom.

4. Novartis Pharma AG, Basel, Switzerland

Target Journal: Journal of the European Academy of Dermatology and Venereology

Corresponding Author:
Gabriele Di Comite
Novartis Pharma AG
Asklepio 8-1.001.17
Postfach
CH-4002 Basel
Switzerland
gabriele.dicomite@novartis.com

Key words: Psoriasis, secukinumab, psoriatic arthritis, ankylosing spondylitis, interleukin-17A inhibitor

Current word count: 4041 (Introduction to end of Discussion), excluding tables, figures, and references

Number of tables: 3

Number of figures: 3

Funding: The development of review article was funded by Novartis Pharma AG

Conflict of interest

- **Kristian Reich:** Dr Reich has served as consultant and/or paid speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Amgen, Biogen-Idec, Celgene, Centocor, Covagen, Eli Lilly, Forward Pharma, GSK, Janssen-Cilag, Leo Pharma, Medac, MSD, Novartis, Pfizer, Vertex, Takeda, and Xenoport.

- **Richard Warren:** Dr Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, Leo, Novartis, Pfizer & UCB and consulting fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo, Lilly, Novartis, Pfizer, Sanofi & UCB. Dr Warren is funded by a National Institute for Health Research Clinician Scientist award. He is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

- **Laura Coates:** Dr Coates has served as consultant and/or paid speaker for Abbvie, Amgen, Celgene, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Prothena and UCB. Laura C Coates is funded by a National Institute for Health Research Clinician Scientist award. She is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

- **Gabriele Di Comite:** Employee of Novartis

Abstract

Psoriatic disease is a multifaceted disorder which develops in the skin, its appendages, and joints. Though characterised by different pathogenic background and clinical manifestations, skin plaque psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are related, sharing key inflammatory mechanisms and hence mode of management. Secukinumab is a fully human monoclonal antibody that selectively binds and neutralises interleukin-17A. It has been approved for use as a subcutaneous injection for the treatment of moderate-to-severe PsO, PsA, and AS. The current review highlights the long-term efficacy and safety profile of secukinumab in the treatment of plaque psoriasis and its multiple manifestations from its Phase 3 clinical trial programme. The long-term extension of pivotal trials has shown sustainable efficacy and safety of secukinumab up to 5 years in PsO, PsA, and AS and up to 2.5 years in moderate-to-severe nail and palmoplantar PsO through dedicated randomised controlled trials. The effect of secukinumab therapy in all these indications has corresponding effects on improvement in quality-of-life and daily activities. Overall secukinumab is an effective and safe treatment choice for patients suffering from psoriatic disease in its multiple clinical variants.

Introduction

Psoriatic disease is a systemic inflammatory disorder which develops in the skin, its appendages, and joints, that can be complicated by systemic comorbidities including cardiometabolic syndrome and inflammatory bowel disease (IBD).[1-4] Psoriasis (PsO) can affect any area of the skin but some localisations (scalp, nail, palms, soles, and joints) deserve special attention because their involvement is associated with a significant impact on quality-of-life (QoL), physical limitation, and are the most difficult manifestations to control even with systemic therapy.[5-8]

Approximately 80% of patients with plaque PsO develop nail disease in their lifetime, and this prevalence seems to increase in patients with concomitant psoriatic arthritis (PsA).[9] Similarly, up to 80% of patients with PsO are affected by scalp disease[5,10], while palmoplantar psoriasis (ppPsO) is reported in ~12–16% of all PsO patients.[8] PsA occurs in up to 42% (range 6–42%) of PsO patients and has a prevalence of 0.1–1.0 % in the overall population.[11-13] Patients with PsA may develop not only peripheral arthritis but also axial disease, dactylitis, and enthesitis, giving rise to a variety of possible clinical manifestations. The presence of one or more of those critical manifestations is associated with significant impairment in physical activities and QoL. In addition, patients face stigmatisation and psychological stress, which lead to disruption of psychosocial well-being and social relationships.[14, 15]

The ultimate goal of psoriatic disease management is to clear (or significantly improve) skin disease, control those manifestations associated with major burden, improve QoL, and prevent further disability.[16-19] Secukinumab, is a fully human monoclonal antibody that selectively neutralises interleukin (IL)-17A, a cornerstone cytokine involved in the development of all manifestations of psoriatic disease. This article reviews the main results of

the Phase 3 clinical trial programme of secukinumab across the multiple manifestations of psoriatic disease, including skin plaques, nail, scalp and ppPsO, PsA, and ankylosing spondylitis (AS) (**Fig. 1**).[20-25]

Efficacy

Skin and appendages

Secukinumab in plaque psoriasis

Two pivotal Phase 3 studies, ERASURE (N=738) and FIXTURE (N=1306), demonstrated the efficacy of secukinumab (300/150 mg) compared with placebo and etanercept (50 mg) up to 1 year of treatment in moderate-to-severe PsO patients.[21]

In ERASURE, a significantly greater proportion of patients on secukinumab 300 mg achieved Psoriasis Activity and Severity Index (PASI) 75 and Investigator's global assessment (IGA) 0/1 compared with placebo (P<0.001 for all comparisons) at Week 12 (primary endpoint). Efficacy was sustained up to Week 52, with 80.5% and 74.4% patients in the secukinumab 300 mg group achieving PASI 75 and IGA 0/1 response. The FIXTURE study showed that PASI 75, IGA 0/1, and Dermatology Life Quality Index (DLQI) responses of 0 or 1 at Week 12 were significantly higher with secukinumab 300 mg than with placebo (P<0.001) or etanercept (P<0.001 for all comparisons).[21] Furthermore, at Week 52, 84.3% and 79.7% of patients in the secukinumab 300 mg group achieved a PASI 75 and IGA 0/1 response compared with 72.5% and 56.8% of patients in the etanercept group, respectively. Secukinumab also notably reduced patient-reported itching, pain, and scaling compared with placebo.[26]

In the 52-week, randomised double-blind Phase 3b CLEAR study (N=676), 79.0% and 44.3% of patients receiving secukinumab 300 mg achieved a PASI 90 response (primary endpoint) and PASI 100 response at Week 16 compared with 57.6% and 28.4% of patients

receiving ustekinumab (P<0.0001 for both comparisons).[27] Similar results were observed at Week 52 (secukinumab versus ustekinumab: PASI 90: 76% vs 61%, P<0.0001; PASI 100: 46% vs 36%, P=0.0103).[28] Secukinumab efficacy was sustained up to 104 weeks with 74.7%, 47.4%, and 68.8% patients achieving PASI 90/100 and IGA mod 2011 0/1 response rates, respectively.[29]

The SCULPTURE trial compared 1 year of treatment with secukinumab at fixed-interval dosing (N=217; N=203) (every 4 weeks) versus retreatment-as-needed (N=217, 300 mg; N=206, 150 mg) in moderate-to-severe PsO.[30] Subjects who completed 52 weeks of the study entered a long-term extension which was double-blinded for 2 years and open-label for another 2 years. A total of 122 patients (as observed) in the secukinumab 300 mg fixed interval cohort completed 5 years of treatment. Secukinumab treatment demonstrated sustained efficacy as measured by PASI 75/90/100 responses at Year 1 (88.9%, 68.5%, and 43.8%, respectively) and Year 5 (88.5%, 66.4%, and 41.0% **(Fig. 2A**). [31] A similar response to 5 years has been recently shown from a long-term extension of the ERASURE and FIXTURE trials.[32] Secukinumab treatment also lead to marked improvements in patients' QoL as indicated by a DLQI 0/1 response of 72.7% at Year 1 and 65.5% at Year 5.[31]

In recent years, a growing body of effectiveness and safety evidence has been generated from secukinumab real-world use through independent and company sponsored registries and post-marketing phase 4 studies. Differences among those observational studies in terms of design, patient population and country specific regulation are so broad that comparison of outcomes require a detailed critical appraisal which goes beyond the purpose of this publication. A meta-analysis of 43 phase 4 studies which have been published on the use of secukinumab in PsO, has been submitted and is currently under evaluation for publication. Data from the largest cohorts published to date show that the rate of PASI 90 response at 1 year ranges

between 40% and 66% in the overall population, with response rate increasing to 61-76% in the subgroup of biologic-naïve patients.[33-36]

In terms of long-term drug survival, two large independent cohorts, respectively with 330 and 324 patients, have shown a rate of persistence on secukinumab treatment at 18 months of 79 and 90% respectively.[37,38] The Danish registry DERMBIO has reported a rate of persistence on treatment with secukinumab at 3 years around 80% among patients naïve to previous biologics and between 30-50% according to the number of previous lines of biologics.[39] Considering the heterogeneity in terms of severity, comorbidities and treatment history of patients treated in real-world compared to clinical trials, the overall real world evidence in effectiveness, QoL and safety of secukinumab in PsO seems to confirm the findings from phase 3 studies.

Secukinumab in nail psoriasis

The 2.5 year safety and efficacy of secukinumab in moderate-to-severe nail PsO patients (N=198) was investigated in TRANSFIGURE, the only long-term double-blind, randomised, placebo-controlled, Phase 3 trial specifically dedicated to this patient pool. The primary endpoint of the study (change in NAil Psoriasis Severity Index [NAPSI] from baseline) was met at 16 weeks and the improvement continued to 2.5 years (−73.3% and −63.6% with secukinumab 300 mg and 150 mg, respectively; **Fig. 2B**).[40] A sustained decrease in total mean NAPPA (Nail Assessment in Psoriasis and Psoriatic Arthritis) QoL scores from baseline to 2.5 years was also observed (−52.4% and −18.1%, for 300 mg and 150 mg, respectively). A total of 70.2% and 71.0% of patients achieved a weighted NAPPA-PBI (Patient Benefit Index) global score of ≥2 (at least moderate benefits) with secukinumab 300 mg (N=66) and 150 mg (N=67), respectively, indicating sustained benefits with secukinumab treatment in this patient population.[41]

Secukinumab in palmoplantar psoriasis

GESTURE, long-term double-blind, randomised, placebo-controlled trial specifically dedicated to patients with moderate-to-severe ppPsO, assessed efficacy and safety of secukinumab in 205 patients. The primary endpoint, ppIGA 0/1 response at Week 16, established the efficacy of secukinumab versus placebo.[42] Efficacy was sustained over 2.5 years with 59.2% and 52.5% of patients in the secukinumab 300 and 150 mg groups achieving ppIGA 0/1, respectively (multiple imputation [MI] analysis; **Fig. 2C**). At the end of Year 2.5, the mean ppPASI score had decreased by 87.2% and 80.4% from Baseline in the secukinumab 300 and 150 mg groups, respectively, and 45.5% vs 23.9% of patients achieved a DLQI 0/1 response. Consistently, after 2.5 years 16.7% and 17.9% of patients in the secukinumab 300 and 150 mg were experiencing no difficulty in hand and feet functionality, as measured through the Palmoplantar QoL Instrument (ppQLI), a clinical score dedicated to assessing the impact of palmoplantar skin lesions on daily personal and social activities performed with hands and feet and on symptoms.[43,44]

Secukinumab in scalp psoriasis

In a 24-week, double-blind, Phase 3b study by Bagel et al, the efficacy and safety of secukinumab in patients with moderate-to-severe scalp PsO (N=102) patients were evaluated.[45] Efficacy was assessed by a 90% improvement of Psoriasis Scalp Severity Index (PSSI 90) score from baseline to Week 12 (secukinumab 300 mg versus placebo, 52.9% versus 2.0%; $P<0.001$) and IGA modified 2011 scalp responses of 0 or 1 (secukinumab 300 mg vs placebo, 56.9% vs 5.9%; $P<0.001$). Complete clearance of scalp PsO at Week 12 was achieved by a significantly higher proportion of patients treated with secukinumab 300 mg than with placebo (35.3% vs 0%; $P<0.001$). Efficacy was further enhanced up to Week 24 where 58.8%, 47.1%, and 62.7% of patients receiving secukinumab achieved PSSI 90, PSSI 100, and IGA modified 2011 scalp responses of 0 or 1, respectively. Patients required a

median time of 3.29 weeks for a 50% reduction in PSSI score. Feldman et al observed that secukinumab-treated patients reported greater reductions in scalp pain (−1.98 vs 0.61), itching (−4.07 vs −0.04), and scaling (−5.76 vs −0.95) than placebo at Week 12 (all *P*<0 .001). The mean change from baseline in Scalpdex total scores was greater with secukinumab treatment as compared with placebo (−39.62 vs −7.91); results were also significant for symptom (−34.42 vs −1.64), emotional (−35.94 vs −5.1), and functional scales (−42.27 vs −10.28) (all *P*<0 .001).[14]

Musculoskeletal domains

Secukinumab in Psoriatic Arthritis

PsA presentation can be highly variable depending on the domains of musculoskeletal disease affected and the underlying pathogenic process; signs and symptoms are generally related to synovitis, spondylitis, enthesitis, or dactylitis.[11,46] The FUTURE 1 study assessed the 5-year efficacy and safety of secukinumab in active PsA. A total of 606 patients were randomised to secukinumab (10 mg/kg intravenously followed by 150 mg or 75 mg subcutaneously every 4 weeks) or matching placebo, of which 476 patients (78.5%) completed 2 years of treatment.[47] At Week 24, the American College of Rheumatology criteria for 20% (ACR20) and 50% improvement response (ACR50) were significantly higher for patients in both 150 mg and 75 mg secukinumab dose groups compared with placebo (ACR20: 50.0% and 50.5%, respectively, vs 17.3%; *P*<0.001 and ACR50: 34.7% and 30.7% vs 7.4%; *P*<0.001).[48] Efficacy was sustained at 2 years with 66.8%, 39.0%, and 22.4% of patients in the secukinumab 150 mg group achieving ACR20, ACR50, and ACR70 responses, respectively. At Week 104, 84.3% of patients in the secukinumab 150 mg showed no radiographic disease progression (observed data).[47]

Clinical responses were sustained or further improved through 5 years of treatment. The proportion of patients achieving ACR20, ACR50, and ACR70 were 67.9%, 52.7%, and

37.4%, respectively **(Fig. 3A)**. A total of 82.6% and 73.7% of patients treated with secukinumab 150 mg showed resolution of dactylitis and enthesitis (MI data) at Year 2, and 94.0% and 82.7%, respectively, at Year 5.[49] Secukinumab showed sustained efficacy across multiple domains of PsA, including signs and symptoms, disease activity, skin symptoms, dactylitis, and enthesitis.

FUTURE 2 was a Phase 3, double-blind, placebo-controlled study to determine the efficacy and safety of subcutaneous secukinumab in patients with active PsA (N=397). The efficacy endpoint, ACR20, at Week 24 was achieved by a significantly higher proportion of patients receiving secukinumab 300 mg (54%; $P<0{\cdot}0001$), 150 mg (51%; $P<0{\cdot}0001$), and 75 mg (29%; $P=0{\cdot}0399$) vs placebo (15%). ACR50 was achieved by 35%, 35%, 18%, and 7% of patients in the secukinumab 300 mg, 150 mg, 75 mg, and placebo groups, respectively. The percentage of patients achieving resolution of dactylitis and enthesitis in the pooled secukinumab group was 47% and 40%, respectively, at Week 24.[25] Minimal disease activity (MDA) responses with secukinumab 300 and 150 mg, achieved at Week 16 (28% and 23% respectively), were continued up to 2 years with a higher proportion of patients achieving MDA at Weeks 52 (78% with 300 mg and 74% with 150 mg) and 104 (85% with 300 mg and 62% with 150 mg).[50]

In FUTURE 1 and FUTURE 2, QoL was assessed by the change from baseline in the physical component summary score (PCS) of the Medical Outcomes Study 36-Item Short Form health survey (SF-36).[25,46,51,52] In addition, the change from baseline in the HAQ-DI score was also used to assess the physical function. In FUTURE 2, least-square mean (standard error, SE) change in the SF-36 PCS score from baseline (secukinumab 300, 36·9 [8·0] and secukinumab 150, 36·2 [8·1]) was 7.25 (0.74), and 6.39 (0.73), respectively, at Week 24.[25] Similar results were also obtained in FUTURE 1 at 2 years with a mean (SE) improvement of 4.89 (0.59) in the SF-36 PCS score with secukinumab 150 mg.[53] This was

accompanied by sustained improvements in the HAQ-DI scores indicating an improved physical function.

In PsA, little evidence has been published to date on the use of secukinumab in real world. EuroSpA is a research collaboration network among 16 registries being run in 16 individual countries, which includes more than 60000 patients with PsA or Axial SpA treated with different DMARDS and biologics, as of end of 2017.[54] EuroSpA data presented at EULAR 2019 from more than 1500 PsA patients treated with secukinumab (80% had experienced biologics and had a mean disease duration of 10 years) showed that DAS28CRP, SDAI and DAPSA28 remission at 6 months were achieved by 35%, 12% and 12%, respectively. The overall retention rate was 86%, with significant differences across the registries and higher remission and retention rates for biologic-naïve compared with non-naïve patients.[55]

Secukinumab in Ankylosing Spondylitis

AS is a chronic inflammatory disorder involving the sacroiliac joint and the spine which is frequently associated with skin PsO.[56] MEASURE 1 was a 2-year Phase 3 study (followed by a 3-year extension) that evaluated the efficacy and safety of secukinumab in patients with AS.[57-59] The Assessment of SpondyloArthritis International Society 20 (ASAS20) response rates at Week 16 were 61% with secukinumab 150 mg, 60% with secukinumab 75 mg, and 29% with placebo (P<0.001 for both comparisons with placebo).[59] Secukinumab continued to improve AS signs and symptoms over 3 and 5 years of therapy; ASAS 20/40 response rates were 79.5%/60.9%[60] and 78.6%/65.2%,[61] respectively, in patients treated with secukinumab 150 mg **(Fig. 3B)**. In a subgroup analyses, secukinumab was effective both in tumour necrosis factor (TNF) inhibitor-naïve patients and in patients intolerant of/refractory to TNF inhibitors.[62]

The secukinumab 150 mg treatment regimen was associated with clinically significant improvements compared with placebo in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, change from baseline = −2.3 vs −0.6; *P*<0.0001), SF-36 PCS score (5.6 vs 1.0; *P*<0.0001), and Ankylosing Spondylitis Quality of Life (ASQoL, (–3.6 vs –1.0; *P*<0.0001). Clinically significant improvements were also observed in the EQ-5D, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Work Productivity and Activity Impairment-General Health scores with secukinumab vs placebo at Weeks 16 and 52, indicating an overall benefit in QoL.[63] In the extension study, sustained improvements in study outcomes were observed over 5 years. The mean change from baseline in the BASDAI score and Bath Ankylosing Spondylitis Functional Index was −3.5±2.08 and −3.1±2.26, respectively.[61]

The long-term (3 year) efficacy and safety results of the Phase 3 MEASURE 2 study were also consistent with the findings from MEASURE 1. ASAS 20/40 response rates for secukinumab 150 mg were 70.1%/60.9%, resulting in improved physical function and a retention rate of >85%.[64]

Other Phase 3 studies including MEASURE 3 open-label extension, SURPASS (completion by Year 2021), PREVENT (in patients with active non-radiographic axial spondyloarthritis; core study to be completed in 2021) and MAXIMISE (in patients with axial manifestations of PsA; completed in June 2019) will further ascertain the role of secukinumab in axial arthritis.

EuroSpA data presented at EULAR 2019 from more than 1500 Axial SpA patients on secukinumab showed that BASDAI <4 was achieved by 49% of the patients at 6 months. Overall retention rate was 83%. Also, in this condition, significant differences across registries and higher remission and retention rates for biologic-naïve compared with non-naïve patients was observed.[65]

SAFETY

A pooled safety analysis from 9 Phase 2 and 10 Phase 3 randomised, double-blind clinical trials, supports the favourable long-term safety profile of secukinumab in patients with PsO. A total of 4674 patients were exposed to any secukinumab dose; total numbers of patients exposed at Years 2, 3, 4, and 5 were 3423, 1972, 1522, and 909, respectively. The exposure-adjusted incidence rates (EAIR) for infections and infestations at 1 year were comparable across all 3 drug groups (secukinumab, etanercept and ustekinumab) but numerically higher with placebo. One of the common adverse effects of interest in IL-17 inhibitors is mucocutaneous candidiasis, yet these infections usually do not lead to interruption of IL-17 inhibitors. Other adverse effects of interest – although rare – are neutropenia and inflammatory bowel disease.

The incidence of adverse events (AEs) of special interest for IL-17 inhibitors, mucocutaneous candidiasis,[66] did not increase over the 5 year period. The EAIR, at Year 1, for *Candida* infections were numerically higher with secukinumab (any dose: 3.1/100 PY, 95% CI: 2.56, 3.67) compared with etanercept (1.4/100 PY, 95% CI: 0.37, 3.47), ustekinumab (1.6/100 PY, 95% CI: 0.51, 3.70), and placebo (1.7/100 PY, 95% CI: 0.54, 3.90). However, the incidence of *Candida* infections with secukinumab (any dose) after year 1 progressively decreases, with EAIR of 2.0 at Year 2 and EAIR 0.3 at Year 5.[67] The majority of cases were mild-to-moderate in intensity and did not lead to study discontinuation.

Epidemiological studies have associated PsO and PsA with IBD and data suggests that IBD is 2–4 fold more prevalent in PsO patients than the general population.[68-70] In another pooled analysis of 21 clinical studies with secukinumab, there were 14, 5 and 1 cases of ulcerative colitis (UC), Crohn's disease (CD) and IBD unclassified (IBDU) (EAIRs: 0.13, 0.05 and 0.01) respectively amongst 5181 PsO patients; 3, 3 and 2 cases of UC, CD and IBDU

(EAIRs: 0.08, 0.08 and 0.05) respectively amongst 1380 PsA patients and 4, 8 and 1 cases of UC, CD and IBDU (EAIRs: 0.2, 0.4 and 0.1) respectively amongst 1380 AS patients.[71] Overall, secukinumab demonstrated a comparable pooled safety profile to that of placebo, etanercept, and ustekinumab over the course of 1 year. No new safety signals were identified for up to 5 years of treatment and there were no increases in yearly AE rates from Year 1. Secukinumab's safety profile was consistent with that established in previous Phase 2/3 studies.

Discussion:

Psoriatic disease is a systemic inflammatory disease that includes multiple manifestations. A subset of T cells, so called T17cells, play a vital role in sustaining the inflammatory cascade in psoriatic skin plaques. IL-17A, the principal effector cytokine of T17 cells, stimulates keratinocytes to release inflammatory molecules that mediate skin damage and recruit neutrophils, monocytes, Th17 cells, and other cell types on site. [72] The central role of IL-17A is also related to the synergistic activity that this cytokine shows with many different upstream cytokines and tissue-related factors, establishing a self-reinforcing cycle orchestrated by IL-17A itself. [73-81]

Recent advances have shown that much of the IL-17A released in PsO is produced by innate immune cells, including γδ-T cells, Type 3 innate lymphoid cells (ILC3), mast cells, and neutrophils.[72,82-86] IL-23 provides an efficient mechanism to induce IL-17A production in T17 and innate cells. However, additional pathways can promote IL-23-independent production of IL-17A in innate cell populations.[82,84,87-89] This is likely due to the release of IL-17A by innate immune cells in an IL-23-independent manner. Synovial and innate immune cells in the joints seem to be the main source of IL-17A in patients with arthritis.[72,90-94] Innate immunity seems to also play a role in nail and ppPsO.[94-96] Interestingly, these manifestations

are strongly associated with the development of arthritis.[94,97,98] This suggests a common mechanism of disease, where innate immunity might be the central factor.

Phase 3 clinical studies demonstrate that IL-17A inhibition with secukinumab provides significant rates of skin clearance in patients with moderate-to-severe PsO with a favourable safety profile. Efficacy results were sustained up to 5 years. Meaningful effectiveness was also observed in challenging-to-treat variants of PsO including nail, scalp, and ppPsO, and in PsA and AS, with improving disease activity, symptoms, dactylitis, and enthesitis. The treatment effectiveness translated into improved QoL in all studies. In the 52-week, randomised, double-blind, placebo-controlled CARIMA trial in patients with moderate-to-severe plaque PsO without clinical cardiovascular (CV) disease, secukinumab demonstrated improved endothelial function, suggesting a possible beneficial effect on CV risk.[99] Biologics with different mechanisms of action (MoA) are available in clinical use for patients with plaque psoriasis, PsA and AS. Direct head-to-head (H2H) trials and large meta-analysis studies can help compare the differences among diverse MoA compounds.

A recent network meta-analysis (NMA) including 77 trials (N=34816) from 11 biologic and 4 non-biologic therapies in moderate-to-severe PsO shows that three approved IL-17 inhibitors (secukinumab 300 mg, ixekizumab 80 mg and brodalumab 210 mg), and IL-23 inhibitors (guselkumab 100 mg and risankizumab 150 mg) are more efficacious than tildrakizumab (another IL-23 inhibitor), ustekinumab (in-label dose; IL-12/23 inhibitor), all TNFi and non-biologic treatments at each level of PASI response.[100,101]

The superiority of IL17 and IL23 inhibitors versus biologics with alternative mechanisms of action in PsO at 1 year has been directly shown through various head-to-head (H2H) trials, with secukinumab and ixekizumab compared to the anti-TNF etanercept;[21,28,102] guselkumab and risankizumab compared to the anti-TNF adalimumab;[103,104] and secukinumab,

ixekizumab and risankizumab to ustekinumab.[21,28,102,105] The ECLIPSE head-to-head (H2H) trial (N=1048) has shown guselkumab (100mg) to be superior to secukinumab (300mg) at Week 48 in PASI90, with a respective response rate of 84.5% vs 70.0%.[106] On the other hand, the IXORA-R trial (ixekizumab vs guselkumab; top-line results announced, yet to be published) shows that IL-17 inhibition with ixekizumab is superior to guselkumab in achieving fast PASI response.[107,108] A H2H trial comparing risankizumab versus secukinumab in terms of PASI90 at Week 16 and 48 weeks is ongoing and results are expected in 2020.[109]

Similarly, a recent indirect comparison of 24 clinical trials with 17 biologic and non-biologics for the treatment of PsA suggest that anti-TNF drugs (infliximab, golimumab, etanercept and adalimumab) and secukinumab are the most effective treatments in inducing ACR20 clinical response, with ixekizumab and ustekinumab showing moderate efficacy only. In PsA, the efficacy of IL-23 inhibitors is still being explored through phase 3 studies.[110] The SPIRIT-H2H trial (N=566) in patients with active PsA has shown the IL-17 inhibitor ixekinumab to be non-inferior to the TNF-inhibitor adalimumab at Week 52 in ACR50 (51% vs 47%) (95% CI [-4.3%, 12.1%]) (For non-inferiority with -12.0% margin).[110] The ongoing H2H EXCEED trial compares efficacy and safety of secukinumab (300 mg) vs adalimumab (40 mg) in PsA. Data will be available in 2020.[111]

The efficacy of different biologics in AS has been recently reviewed by the American College of Rheumatology and new recommendations for treatment have been published. Consistently with PsA evidence, anti-TNF and anti-IL17 biologics are recommended as the most efficacious therapies in AS which is active despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Anti-TNF are conditionally recommended over IL-17 drugs based on longer experience and familiarity.[112] Interestingly, the IL-23/IL-12 inhibitor ustekinumab and the IL-23 inhibitors risankizumab and tildrakizumab have proven to be

ineffective in AS. The ongoing H2H SURPASS trial is aimed at comparing efficacy and safety of secukinumab (300/150 mg) vs adalimumab (40 mg) in AS. Data will be available in 2022.[113]

IL-23 independent sources of IL-17A in the joints are likely to be the reason for the lack of efficacy of IL-12/23 and IL-23 inhibitors in AS and the suboptimal efficacy of IL-12/23 inhibitors reported in PsA (efficacy of IL-23 inhibitors in PsA is still to be demonstrated).[114] Consistently, it has been shown that inhibition of IL-23 is associated with the persistence of significant amounts of IL-17A at the site of inflammation and in the circulation.[87]

In summary, psoriatic disease is a chronic systemic disorder comprising myriad of manifestations across the skin, its appendages and joints. The aim of the treatment in a patient with psoriatic disease should be an effective control of the multiple manifestations of his disease, ultimately leading to a significant improvement in QoL and prevention of further progressive irreversible damage. Its Phase 3 clinical trial programme shows that secukinumab provides an effective treatment across the multiple manifestations of psoriatic disease, with rates of skin clearance in the highest range among all biologics, along with other IL-17 inhibitors and IL-23 inhibitors, and the highest rates of efficacy in PsA and AS along with anti-TNF inhibitors.

Acknowledgment

The authors thank Aafrin Khan, of Product Life Sciences, Novartis Business Services, India for providing medical writing support which was funded by Novartis Pharma AG in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

List of Tables and Figures

B. ***ASAS40 response rates through 5 years of treatment– Results from MEASURE 1***

ASAS40, Assessment of Spondyloarthritis International Society 40; N, total number of patients; n, number of patients

Data shown are as observed through 5 Years

Secukinumab 75 mg arm includes patients who had their dose escalated to 150 mg after Week 168 (n = 82) where n is number of evaluable patients

Table 1: Summary of Phase 3 secukinumab studies – Skin and appendages

Study/Author	Patients population studied/Study duration	Comparator	Efficacy parameters	PROs used	Final conclusion
ERASURE[21]	Moderate-to-severe plaque PsO/52 weeks	Placebo	PASI and IGA mod 2011	DLQI	Secukinumab is superior to placebo in treating moderate-to-severe plaque PsO
FIXTURE[21]	Moderate-to-severe plaque PsO/52 weeks	Placebo and Etanercept	PASI and IGA mod 2011	DLQI	Secukinumab is superior to etanercept in treating moderate-to-severe plaque PsO
CLEAR[28]	Moderate-to-severe plaque PsO/52 weeks	Ustekinumab	PASI and IGA mod 2011	DLQI, EQ-5D-3L, WPAI-PSO, HAQ-DI*	Secukinumab demonstrated sustained superior efficacy in comparison with ustekinumab in clearing skin through Week 104, greater improvement in QoL, and a favourable and comparable safety profile.
SCULPTURE[31]	Moderate-to-severe plaque PsO/5 years	None	PASI and BSA score	DLQI, HAQ-DI*	Secukinumab 300 mg treatment delivered high and sustained levels of skin clearance and improved QoL in patients with moderate-to-severe PsO, with almost 100% of PASI response rates maintained from Year 1 to Year 5
TRANSFIGURE[40,41]	Moderate-to-severe nail PsO/2.5 years	Placebo to Week 16	NAPSI, PASI, and IGA mod 2011	NAPPA-QoL, NAPPA-PBI, EQ-5D, DLQI,	Secukinumab demonstrated meaningful efficacy, with significant sustained QoL improvements for up to 2.5 years in difficult-to-treat nail PsO

				SGA using VAS	
GESTURE[42]	Moderate-to-severe palmoplantar PsO/2.5 years	Placebo to Week 16	ppIGA and ppPASI	DLQI, EQ-5D, SGA using VAS, ppQLI	Secukinumab provides a strong and sustained response over 2.5 years in challenging to treat palmoplantar PsO
SCALP[45]	Moderate-to-severe scalp PsO/24 weeks	Placebo	PSSI and IGA mod 2011 scalp	NA	Secukinumab is efficacious and well-tolerated for patients with extensive moderate-to-severe scalp PsO

* For subjects with confirmed diagnosis of PsA

DLQI, Dermatology Life Quality Index; EQ-5D, EuroQoL 5-Dimension Health Questionnaire; EQ-5D-3L, EuroQoL5-Dimension Health Questionnaire 3-level version;

HAQ-DI, Health Assessment Questionnaire-Disability Index; IGA mod 2011, Investigator's Global Assessment, 2011 modified version;

NAPPA-QOL, Nail Assessment in Psoriasis and Psoriatic Arthritis-Quality of Life; NASPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; ppIGA, palmoplantar IGA; ppPASI, palmoplantar PASI; ppQLI, palmoplantar Quality of Life Index; PsA, psoriatic arthritis; PsO, psoriasis; PSSI, Psoriasis Scalp Severity Index; QoL, quality of life; SGA, Subject`s Global Assessment; WPAI-PSO, Work Productivity and Activity Impairment Questionnaire-Psoriasis; VAS, Visual Analogue Scale

Table 2: Summary of Phase 3 secukinumab studies – Musculoskeletal apparatus

Study/Author	Number of patients/Study duration	Drug/Comparator	Efficacy parameters	PROs used	Final conclusion
PsA					
FUTURE 1[46,47]	606/104 weeks	Intravenous secukinumab/Placebo	ACR20, ACR50, PASI, DAS28, incidence of dactylitis and enthesitis, SHS to assess radiographic progression	SF-36-PCS, HAQ-DI	Secukinumab provided sustained improvements in PsA at 2 years, with very little or no radiographic progression (≤0.5 increase in vdH-mTSS from Baseline) in 80% patients
FUTURE 2[25]	397/52 weeks	Secukinumab/Placebo	ACR20, ACR50, PASI, DAS28-CRP, incidence of dactylitis and enthesitis	SF-36-PCS, HAQ-DI	Subcutaneous secukinumab 300 mg and 150 mg improved the signs and symptoms of PsA at 52 weeks
FUTURE 3[115]	414/52 weeks	Auto-injected secukinumab/Placebo	ACR20, ACR50, PASI, DAS28-CRP, incidence of dactylitis and enthesitis	SF-36-PCS, HAQ-DI, FACIT-Fatigue, SIAQ	Self-administration of subcutaneous secukinumab provided sustained improvements at 52 weeks across multiple clinical domains in patients with active PsA
FUTURE 5[116]	996/112 weeks (ongoing). Week 24	Secukinumab with or without loading dose/Placebo	ACR20, vdH-mTSS, PASI, DAS28-CRP, resolution of	HAQ-DI	Subcutaneous secukinumab 300 mg and 150 mg with and without loading dose significantly improved clinical signs and symptoms and

	results have been reported		dactylitis and enthesitis		inhibited radiographic structural progression versus placebo at Week 24 in patients with PsA
AS					
MEASURE 1[57,58,117]	371/2 and 3 year results have been published	Intravenous secukinumab/Placebo	ASAS20, ASAS40, ASAS5/6, BASDAI score, radiography by mSASSS, BASFI, BASMI and ASDAS-CRP	SF-36, ASQoL	Secukinumab improved AS signs and symptoms through 2 years of therapy, with no unexpected safety findings. The symptoms and physical function continued to remain improved at 3 years
MEASURE 2[64,118]	219/5 year study; 2 and 3 year results have been published	Subcutaneous secukinumab/Placebo	ASAS20, ASAS40, ASAS5/6, BASDAI score, hsCRP (in the 2 years study) and ASDAS-CRP (in the 3 years study)	SF-36, ASQoL, EQ-5D, FACIT-fatigue	Secukinumab provided sustained improvement through 2 years in the signs and symptoms of AS which were maintained through 3 years of follow up
MEASURE 3[119]	226/3 year study; 1 year results have been published	Intravenous secukinumab followed by subcutaneous secukinumab/Placebo	ASAS20, ASAS40, ASAS5/6, BASDAI score, hsCRP	SIAQ	Secukinumab (300 mg and 150 mg dose groups) provided rapid, significant and sustained improvement over 52 weeks in the signs and symptoms of patients with AS.

ACR20, American College of Rheumatology criteria for 20% improvement; ACR50, American College of Rheumatology criteria for 50% improvement; AS, ankylosing spondylitis; ASAS5/6 response; ≥20% improvement in five of the six ASAS response domains; ASAS20,

Assessment of Spondyloarthritis International Society 20; ASAS40, Assessment of Spondyloarthritis International Society 40; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy—Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCS, mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; PASI, Psoriasis Area and Severity Index; PCS, physical component summary; PRO, patient reported outcome; PsA, psoriatic arthritis; SF-36, 36-Item Short Form health survey; SIAQ, Self-Injection Assessment Questionnaire; SHS, modified total Sharp/van der Heijde score; vdH-mTSS, van der Heijde-modified total Sharp score

Table 3: Summary of safety for secukinumab and comparators (up to 1 year) and long-term safety of secukinumab up to 5 years

	Year 1					Year 2		Year 3		Year 4		Year 5	
	SEC		ETN	UST	PBO	SEC		SEC		SEC		SEC	
	Any dose n=4674	300 mg n=1773	50 mg (n=323)	45/90 mg (n=336)	n=1090	Any dose n=3423	300 mg (n=1188)	Any dose n=1972	300 mg n=572	Any dose n=1522	300 mg (n=397)	Any dose n=909	300 mg n=263
Duration of exposure (patient-years)	4093.5	1467.4	296.9	318.1	301.2	2631.3	859.6	1,659.6	423.0	1392.2	377.5	291.6	90.0
Total AEs (EAIR)	254.1	275.6	245.7	252.2	355.8	169.9	168.1	159.8	160.2	104.1	111.9	12.0	13.9
Non-fatal SAEs, (EAIR)	8.6	8.9	6.9	8.2	9.1	7.6	7.3	7.4	8.8	5.8	6.8	0.7	1.1
AE of Special Interest, n (EAIR)													
Ulcerative Colitis	3 (0.08)	2 (0.14)	1 (0.34)	0	0	4 (0.15)	2 (0.23)	2 (0.12)	1 (0.24)	1 (0.07)	1 (0.27)	0	0
Crohn's disease	2 (0.05)	0	0	0	0	1 (0.04)	0	0	0	0	0	0	0

Candida Infection	124 (3.08)	91 (3.73)	4 (1.35)	5 (1.58)	5 (1.67)	51 (1.96)	38 (2.55)	23 (1.40)	19 (2.26)	21 (1.52)	12 (1.61)	1 (0.34)	1 (0.65)
Neutropenia	124 (3.16)	43 (3.03)	20 (7.05)	2 (0.63)	5 (1.79)	61 (2.43)	11 (1.33)	38 (2.44)	7 (1.76)	11 (0.85)	3 (0.85)	1 (0.37)	1 (1.20)

AE, adverse event; EAIR, exposure-adjusted incidence rate; ETN, etanercept; N, total number of patients; n, number of patients; PBO, placebo,

SAE, serious AE;

SEC, secukinumab; UST, ustekinumab

References

1 Boehncke WH, Schon MP. Psoriasis. *Lancet* 2015; **386**: 983-94.

2 Lebwohl M. Psoriasis. *Ann Intern Med* 2018; **168**: Itc49-itc64.

3 Lee JY, Kang S, Bae JM *et al.* Psoriasis increases the risk of concurrent inflammatory bowel disease: A population-based nationwide study in Korea. *Indian J Dermatol Venereol Leprol* 2018.

4 Egeberg A, Thyssen JP, Burisch J *et al.* Incidence and risk of inflammatory bowel disease in patients with psoriasis - a nationwide 20-year cohort study. *J Invest Dermatol* 2018.

5 Wozel G. Psoriasis treatment in difficult locations: scalp, nails, and intertriginous areas. *Clin Dermatol* 2008; **26**: 448-59.

6 Handa S. Newer trends in the management of psoriasis at difficult to treat locations: scalp, palmoplantar disease and nails. *Indian J Dermatol Venereol Leprol* 2010; **76**: 634-44.

7 Sanchez-Regana M, Aldunce Soto MJ, Belinchon Romero I *et al.* Evidence-based guidelines of the spanish psoriasis group on the use of biologic therapy in patients with psoriasis in difficult-to-treat sites (nails, scalp, palms, and soles). *Actas Dermosifiliogr* 2014; **105**: 923-34.

8 Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. *Dermatol Ther* 2018; **31**: e12589.

9 Manhart R, Rich P. Nail psoriasis. *Clin Exp Rheumatol* 2015; **33**: S7-13.

10 Wozel G, Klein E, Mrowietz U *et al.* Scalp psoriasis. *J Dtsch Dermatol Ges* 2011; **9**: 70-4.

11 Mease PJ, Armstrong AW. Managing patients with psoriatic disease: the diagnosis and pharmacologic treatment of psoriatic arthritis in patients with psoriasis. *Drugs* 2014; **74**: 423-41.

12 Gladman DD, Antoni C, Mease PJ *et al.* Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis* 2005; **64 Suppl 2**: ii14-7.

13 Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. *Rheum Dis Clin North Am* 2015; **41**: 545-68.

14 Feldman SR, Green L, Kimball AB *et al.* Secukinumab improves scalp pain, itching, scaling and quality of life in patients with moderate-to-severe scalp psoriasis. *J Dermatolog Treat* 2017; **28**: 716-21.

15 Augustin M, Radtke MA. Quality of life in psoriasis patients. *Expert Rev Pharmacoecon Outcomes Res* 2014; **14**: 559-68.

16 Mrowietz U, Steinz K, Gerdes S. Psoriasis: to treat or to manage? *Exp Dermatol* 2014; **23**: 705-9.

17 Dauden E, Blasco AJ, Bonanad C *et al.* Position statement for the management of comorbidities in psoriasis. *J Eur Acad Dermatol Venereol* 2018.

18 Dauden E, Castaneda S, Suarez C *et al.* Clinical practice guideline for an integrated approach to comorbidity in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2013; **27**: 1387-404.

19 Golbari NM, Porter ML, Kimball AB. Current guidelines for psoriasis treatment: a work in progress. *Cutis* 2018; **101**: 10-2.

20 Papp KA, Langley RG, Sigurgeirsson B *et al.* Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol* 2013; **168**: 412-21.

21 Langley RG, Elewski BE, Lebwohl M *et al.* Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; **371**: 326-38.

22 Paul C, Reich K, Gottlieb AB *et al.* Secukinumab improves hand, foot and nail lesions in moderate-to-severe plaque psoriasis: subanalysis of a randomized, double-blind, placebo-controlled, regimen-finding phase 2 trial. *J Eur Acad Dermatol Venereol* 2014; **28**: 1670-5.

23 Armstrong AW, Vender R, Kircik L. Secukinumab in the Treatment of Palmoplantar, Nail, Scalp, and Pustular Psoriasis. *J Clin Aesthet Dermatol* 2016; **9**: S12-s6.

24 Paul C, Lacour JP, Tedremets L *et al.* Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). *J Eur Acad Dermatol Venereol* 2014.

25 McInnes IB, Mease PJ, Kirkham B *et al.* Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; **386**: 1137-46.

26 Strober B, Sigurgeirsson B, Popp G *et al.* Secukinumab improves patient-reported psoriasis symptoms of itching, pain, and scaling: results of two phase 3, randomized, placebo-controlled clinical trials. *Int J Dermatol* 2016; **55**: 401-7.

27 Thaci D, Blauvelt A, Reich K *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *Journal of the American Academy of Dermatology* 2015; **73**: 400-9.

28 Blauvelt A, Reich K, Tsai TF *et al.* Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol* 2017; **76**: 60-9.e9.

29 A Blauvelt LP, K Reich, TF Tsai, S Tyring, K Kingo, M Ziv, A Pinter, R Vender, A Lacombe, S Xia, V Bhosekar, I Gilloteau, A Guana, D Thaçi. Continuous Treatment With Secukinumab 300 mg Demonstrates Sustained Efficacy in Clearing Skin and Improving Patient-Reported Outcomes in Moderate to Severe Plaque Psoriasis: Two Year Results From the CLEAR Study. In: *26th European Academy of Dermatology and Venereology Congress*. Geneva, Switzerland. 2017.

30 Mrowietz U, Leonardi CL, Girolomoni G *et al.* Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). *Journal of the American Academy of Dermatology* 2015; **73**: 27-36.

31 Bissonnette R, Luger T, Thaci D *et al.* Secukinumab Demonstrates High Sustained Efficacy and a Favorable Safety Profile in Patients with Moderate to Severe Psoriasis through 5 Years of Treatment (SCULPTURE Extension Study). *J Eur Acad Dermatol Venereol* 2018.

32 Richard Langley BS, Jacek Szepietowski, Tsen-Fang Tsai, Ana de Vera, Pascal Charef, Isabelle Gilloteau, Ruquan You, Isabelle Hampele. Secukinumab is Associated with Sustained Improvement in Patients' Quality of Life up to Year 5: Results of a Randomized Extension of the Phase III ERASURE and FIXTURE Trials. In: *6th congress of the SPIN – Skin Inflammation & Psoriasis International Network*. Paris, France. 2019.

33 Papp K, Gooderham M, Alavi A *et al.* Secukinumab Treatment Results in Improvement of Disease Characteristics in Patients with Moderate to Severe Psoriasis: 24 Month Follow-up Data from the PURE Registry. In: *2019 AAD Annual Meeting*. Washington, DC. March 1-5, 2019; Poster #10084.

34 Ortiz-Salvador JM, Saneleuterio-Temporal M, Magdaleno-Tapial J *et al.* A prospective multicenter study assessing effectiveness and safety of secukinumab in a real-life setting in 158 patients. *J Am Acad Dermatol* 2019; **81**: 427-32.

35 Notario J, Deza G, Vilarrasa E *et al.* Treatment of patients with plaque psoriasis with secukinumab in a real-life setting: a 52-week, multicenter, retrospective study in Spain. *Journal of Dermatological Treatment* 2019; **30**: 424-9.

36 Yanofsky H, Siddha S, Adam D *et al.* Secukinumab demonstrates significant improvement of disease activity and health related quality of life at 1 year in Canadian psoriasis patients in a real world setting. In: *AAD Annual Meeting*. Washington, DC. March 1-5, 2019; Poster #8375.

37 Torres T, Balato A, Conrad C *et al.* Secukinumab drug survival in patients with psoriasis: A multicenter, real-world, retrospective study. *J Am Acad Dermatol* 2019; **81**: 273-5.

38 Megna M, Di Costanzo L, Argenziano G *et al.* Effectiveness and safety of secukinumab in Italian patients with psoriasis: an 84 week, multicenter, retrospective real-world study. *Expert Opin Biol Ther* 2019; **19**: 855-61.

39 Egeberg A, Bryld LE, Skov L. Drug survival of secukinumab and ixekizumab for moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2019; **81**: 173-8.

40 Reich K, Sullivan J, Arenberger P *et al.* Effect of secukinumab on the clinical activity and disease burden of nail psoriasis: 32-week results from the randomized placebo-controlled TRANSFIGURE trial. *Br J Dermatol* 2018.

41 K Reich PA, U Mrowietz, S Jazayeri, M Augustin, A Parneix, P Regnault, R You, J Frueh. Secukinumab Shows High and Sustained Efficacy in Nail Psoriasis: 2.5-Year Results From the TRANSFIGURE Study. In: *Psoriasis From Gene to Clinic 8th International Congress*. London, UK. 2017.

42 Gottlieb A, Sullivan J, van Doorn M *et al.* Secukinumab shows significant efficacy in palmoplantar psoriasis: Results from GESTURE, a randomized controlled trial. *J Am Acad Dermatol* 2017; **76**: 70-80.

43 Farley E, Masrour S, McKey J *et al.* Palmoplantar psoriasis: a phenotypical and clinical review with introduction of a new quality-of-life assessment tool. *J Am Acad Dermatol* 2009; **60**: 1024-31.

44 Alice B Gottlieb JS, Alex Kubanov, Ruquan You, Pascaline Regnault, Jennifer Frueh. Secukinumab Shows High and Sustained Efficacy in Subjects with Moderate to Severe Palmoplantar Psoriasis: 2.5-Year Results from the GESTURE Study. In: *Psoriasis From Gene to Clinic 8th International Congress*. London, United Kingdom. 2017.

45 Bagel J, Duffin KC, Moore A *et al.* The effect of secukinumab on moderate-to-severe scalp psoriasis: Results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. *J Am Acad Dermatol* 2017; **77**: 667-74.

46 Mease PJ, McInnes IB, Kirkham B *et al.* Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N Engl J Med* 2015; **373**: 1329-39.

47 Kavanaugh A, Mease PJ, Reimold AM *et al.* Secukinumab for Long-Term Treatment of Psoriatic Arthritis: A Two-Year Followup From a Phase III, Randomized, Double-Blind Placebo-Controlled Study. *Arthritis Care Res (Hoboken)* 2017; **69**: 347-55.

48 Mease PJ, McInnes IB, Kirkham B *et al.* Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *New England Journal of Medicine* 2015; **373**: 1329-39.

49 Mease PJ, Reimold A, Tahir H *et al*. Secukinumab Provides Sustained Improvements in the Signs and Symptoms in Psoriatic Arthritis: Final 5-year Efficacy and Safety Results from a Phase 3 Trial. In: *ACR/ARHP (2018) American College of Rheumatology/ARHP - 2018 Annual Scientific Meeting*. 2018.

50 Coates LC, Mease PJ, Gossec L *et al.* Minimal Disease Activity among Active Psoriatic Arthritis Patients Treated with Secukinumab: 2-year Results from the FUTURE 2 Study. *Arthritis Care Res (Hoboken)* 2018.

51 Kavanaugh A, McInnes IB, Mease PJ *et al.* Efficacy of Subcutaneous Secukinumab in Patients with Active Psoriatic Arthritis Stratified by Prior Tumor Necrosis Factor Inhibitor Use: Results from the Randomized Placebo-controlled FUTURE 2 Study. *J Rheumatol* 2016; **43**: 1713-7.

52 McInnes IB, Mease PJ, Ritchlin CT *et al.* Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. *Rheumatology (Oxford)* 2017; **56**: 1993-2003.

53 Kavanaugh A, Mease PJ, Reimold AM *et al.* Secukinumab for Long-Term Treatment of Psoriatic Arthritis: A Two-Year Followup From a Phase III, Randomized, Double-Blind Placebo-Controlled Study. *Arthritis Care and Research* 2017; **69**: 347-55.

54 Hetland M, Østergaard M, Askling J *et al.* FRI0450 Commonalities and differences in data collection across european spondyloarthritis registries. *Annals of the Rheumatic Diseases* 2017; **76**: 656-7.

55 Michelsen B, Brahe CH, Jacobsson LTH *et al.* SAT0391 REMISSION AND DRUG RETENTION RATES OF SECUKINUMAB IN 1549 PATIENTS WITH PSORIATIC ARTHRITIS TREATED IN ROUTINE CARE – POOLED DATA FROM THE OBSERVATIONAL EUROSPA RESEARCH COLLABORATION NETWORK. *Annals of the Rheumatic Diseases* 2019; **78**: 1281-2.

56 Shah R, Perry L, Deodhar A. The role of secukinumab in the treatment of ankylosing spondylitis. *Immunotherapy* 2015; **7**: 1241-7.

57 Braun J, Baraliakos X, Deodhar A *et al.* Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis* 2017; **76**: 1070-7.

58 Baraliakos X, Kivitz AJ, Deodhar AA *et al.* Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clin Exp Rheumatol* 2018; **36**: 50-5.

59 Baeten D, Sieper J, Braun J *et al.* Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *New England Journal of Medicine* 2015; **373**: 2534-48.

60 Baraliakos X, Kivitz AJ, Deodhar AA *et al.* Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the Phase 3 MEASURE 1 trial. *Clinical and Experimental Rheumatology* 2018; **36**: 50-5.

61 Baraliakos X BJ, Deodhar AA, Poddubnyy D, Kivitz AJ, Tahir H, van Den Bosch F, Delicha EM, Talloczy Z, Fierlinger A. Long-Term Evaluation of Secukinumab in Ankylosing Spondylitis: 5 Year Efficacy and Safety Results from a Phase 3 Trial. In: *2018 ACR/ARHP Annual Meeting*: Arthritis Rheumatol. 2018; 70 (suppl 10). . 2018.

62 Blair HA, Dhillon S. Secukinumab: A Review in Ankylosing Spondylitis. *Drugs* 2016; **76**: 1023-30.

63 Deodhar AA, Dougados M, Baeten DL *et al.* Effect of Secukinumab on Patient-Reported Outcomes in Patients With Active Ankylosing Spondylitis: A Phase III Randomized Trial (MEASURE 1). *Arthritis Rheumatol* 2016; **68**: 2901-10.

64 Marzo-Ortega H, Sieper J, Kivitz A *et al.* Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis with high retention rate: 3-year results from the phase III trial, MEASURE 2. *RMD Open* 2017; **3**: e000592.

65 Michelsen B, Brahe CH, Askling J *et al.* FRI0404 POOLED 6-MONTH TREATMENT OUTCOMES AND DRUG RETENTION RATES IN 1556 PATIENTS WITH AXIAL SPONDYLOARTHRITIS TREATED WITH SECUKINUMAB IN ROUTINE CLINICAL PRACTICE IN 12 EUROPEAN COUNTRIES IN THE EUROSPA RESEARCH COLLABORATION. *Annals of the Rheumatic Diseases* 2019; **78**: 888-9.

66 Kamata M, Tada Y. Safety of biologics in psoriasis. *J Dermatol* 2018; **45**: 279-86.

67 Deodhar A, Mease PJ, McInnes IB *et al.* Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Research & Therapy* 2019; **21**: 111.

68 Augustin M, Reich K, Glaeske G *et al.* Co-morbidity and age-related prevalence of psoriasis: Analysis of health insurance data in Germany. *Acta Derm Venereol* 2010; **90**: 147-51.

69 Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. *J Eur Acad Dermatol Venereol* 2009; **23**: 561-5.

70 Makredes M, Robinson D, Jr., Bala M *et al.* The burden of autoimmune disease: a comparison of prevalence ratios in patients with psoriatic arthritis and psoriasis. *J Am Acad Dermatol* 2009; **61**: 405-10.

71 Schreiber S, Colombel JF, Feagan BG *et al.* Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. *Ann Rheum Dis* 2019; **78**: 473-9.

72 Keijsers RR, Joosten I, van Erp PE *et al.* Cellular sources of IL-17 in psoriasis: a paradigm shift? *Exp Dermatol* 2014; **23**: 799-803.

73 Noack M, Miossec P. Selected cytokine pathways in rheumatoid arthritis. *Semin Immunopathol* 2017; **39**: 365-83.

74 Bosteen MH, Tritsaris K, Hansen AJ *et al.* IL-17A potentiates TNFalpha-induced secretion from human endothelial cells and alters barrier functions controlling neutrophils rights of passage. *Pflugers Arch* 2014; **466**: 961-72.

75 Johansen C, Bertelsen T, Ljungberg C *et al.* Characterization of TNF-alpha- and IL-17A-Mediated Synergistic Induction of DEFB4 Gene Expression in Human Keratinocytes through IkappaBzeta. *J Invest Dermatol* 2016; **136**: 1608-16.

76 Murakami M, Hagforsen E, Morhenn V *et al.* Patients with palmoplantar pustulosis have increased IL-17 and IL-22 levels both in the lesion and serum. *Exp Dermatol* 2011; **20**: 845-7.

77 Tohyama M, Hanakawa Y, Shirakata Y *et al.* IL-17 and IL-22 mediate IL-20 subfamily cytokine production in cultured keratinocytes via increased IL-22 receptor expression. *Eur J Immunol* 2009; **39**: 2779-88.

78 Simanski M, Rademacher F, Schroder L *et al.* IL-17A and IFN-gamma synergistically induce RNase 7 expression via STAT3 in primary keratinocytes. *PLoS One* 2013; **8**: e59531.

79 Croes M, Oner FC, van Neerven D *et al.* Proinflammatory T cells and IL-17 stimulate osteoblast differentiation. *Bone* 2016; **84**: 262-70.

80 Hau CS, Kanda N, Tada Y *et al.* Lipocalin-2 exacerbates psoriasiform skin inflammation by augmenting T-helper 17 response. *J Dermatol* 2016; **43**: 785-94.

81 Chen X, Takai T, Xie Y *et al.* Human antimicrobial peptide LL-37 modulates proinflammatory responses induced by cytokine milieus and double-stranded RNA in human keratinocytes. *Biochem Biophys Res Commun* 2013; **433**: 532-7.

82 Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol* 2010; **10**: 479-89.

83 Lin AM, Rubin CJ, Khandpur R *et al.* Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol* 2011; **187**: 490-500.

84 Housseau F, Wu S, Wick EC *et al.* Redundant Innate and Adaptive Sources of IL17 Production Drive Colon Tumorigenesis. *Cancer Res* 2016; **76**: 2115-24.

85 Siegemund S, Schutze N, Schulz S *et al.* Differential IL-23 requirement for IL-22 and IL-17A production during innate immunity against Salmonella enterica serovar Enteritidis. *Int Immunol* 2009; **21**: 555-65.

86 Villanova F, Flutter B, Tosi I *et al.* Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44+ ILC3 in psoriasis. *J Invest Dermatol* 2014; **134**: 984-91.

87 Sofen H, Smith S, Matheson RT *et al.* Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. *J Allergy Clin Immunol* 2014; **133**: 1032-40.

88 Patel DD, Lee DM, Kolbinger F *et al.* Effect of IL-17A blockade with secukinumab in autoimmune diseases. *Ann Rheum Dis* 2013; **72 Suppl 2**: ii116-23.

89 Yoshiga Y, Goto D, Segawa S *et al.* Invariant NKT cells produce IL-17 through IL-23-dependent and -independent pathways with potential modulation of Th17 response in collagen-induced arthritis. *Int J Mol Med* 2008; **22**: 369-74.

90 Paulissen SM, van Hamburg JP, Davelaar N *et al.* Synovial fibroblasts directly induce Th17 pathogenicity via the cyclooxygenase/prostaglandin E2 pathway, independent of IL-23. *J Immunol* 2013; **191**: 1364-72.

91 Ciccia F, Guggino G, Rizzo A *et al.* Type 3 innate lymphoid cells producing IL-17 and IL-22 are expanded in the gut, in the peripheral blood, synovial fluid and bone marrow of patients with ankylosing spondylitis. *Ann Rheum Dis* 2015; **74**: 1739-47.

92 Kenna TJ, Brown MA. The role of IL-17-secreting mast cells in inflammatory joint disease. *Nat Rev Rheumatol* 2013; **9**: 375-9.

93 Appel H, Maier R, Wu P *et al.* Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. *Arthritis Res Ther* 2011; **13**: R95.

94 McGonagle D, Palmou Fontana N, Tan AL *et al.* Nailing down the genetic and immunological basis for psoriatic disease. *Dermatology* 2010; **221 Suppl 1**: 15-22.

95 McGonagle D. Enthesitis: an autoinflammatory lesion linking nail and joint involvement in psoriatic disease. *J Eur Acad Dermatol Venereol* 2009; **23 Suppl 1**: 9-13.

96 Bissonnette R, Nigen S, Langley RG *et al.* Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. *J Eur Acad Dermatol Venereol* 2014; **28**: 1298-305.

97 Wilson FC, Icen M, Crowson CS *et al.* Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum* 2009; **61**: 233-9.

98 Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. *Reumatologia* 2017; **55**: 131-5.

99 von Stebut E, Reich K, Thaci D *et al.* Impact of secukinumab on endothelial dysfunction and other cardiovascular disease parameters in psoriasis patients over 52 weeks. *J Invest Dermatol* 2018.

100 Puig L. Guselkumab for the treatment of adults with moderate to severe plaque psoriasis. *Expert Rev Clin Immunol* 2019; **15**: 589-97.

101 Sawyer LM, Malottki K, Sabry-Grant C *et al.* Assessing the relative efficacy of interleukin-17 and interleukin-23 targeted treatments for moderate-to-severe plaque

psoriasis: A systematic review and network meta-analysis of PASI response. *PLoS One* 2019; **14**: e0220868.

102 Griffiths CE, Reich K, Lebwohl M *et al.* Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015; **386**: 541-51.

103 Blauvelt A, Papp KA, Griffiths CE *et al.* Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol* 2017; **76**: 405-17.

104 Machado A, Torres T. Spotlight on risankizumab and its potential in the treatment of plaque psoriasis: evidence to date. *Psoriasis (Auckl)* 2018; **8**: 83-92.

105 Papp KA, Blauvelt A, Bukhalo M *et al.* Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. *N Engl J Med* 2017; **376**: 1551-60.

106 New Phase 3 data demonstrate superiority of TREMFYA® (guselkumab) vs Cosentyx® (secukinumab) in delivering PASI 90 responses in the treatment of moderate to severe plaque psoriasis at week 48. In. Content Lab - US n.d. [cited 2019 Feb 10]; Available from: https://www.jnj.com/new-phase-3-data-demonstrate-superiority-of-tremfya-guselkumab-vs-cosentyx-secukinumab-in-delivering-pasi-90-responses-in-the-treatment-of-moderate-to-severe-plaque-psoriasis-at-week-48.

107 A Study of Ixekizumab (LY2439821) Compared to Guselkumab in Participants With Moderate-to-Severe Plaque Psoriasis (IXORA-R). In: *ClinicalTrials.gov Identifier: NCT03573323*.

108 Lilly Announces Superiority of Taltz® (ixekizumab) versus TREMFYA® (guselkumab) in Delivering Total Skin Clearance at Week 12 in Topline Results from Head-to-Head (IXORA-R) Trial in People Living with Moderate to Severe Plaque Psoriasis. In; Published: Aug 13, 2019

109 Risankizumab Versus Secukinumab for Subjects With Moderate to Severe Plaque Psoriasis. ClinicalTrials.gov Identifier: NCT03478787.

110 McInnes IB, Nash P, Ritchlin C *et al.* Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/apremilast: a network meta-analysis. *J Comp Eff Res* 2018; **7**: 1107-23.

111 Efficacy of Secukinumab Compared to Adalimumab in Patients With Psoriatic Arthritis (EXCEED 1). ClinicalTrials.gov Identifier: NCT02745080.

112 Ward MM, Deodhar A, Gensler LS *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol* 2019; **71**: 1599-613.

113 Effect of Secukinumab on Radiographic Progression in Ankylosing Spondylitis as Compared to GP2017 (Adalimumab Biosimilar) (SURPASS). ClinicalTrials.gov Identifier: NCT03259074.

114 Sieper J, Poddubnyy D, Miossec P. The IL-23-IL-17 pathway as a therapeutic target in axial spondyloarthritis. *Nat Rev Rheumatol* 2019.

115 Nash P, Mease PJ, McInnes IB *et al.* Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). *Arthritis Res Ther* 2018; **20**: 47.

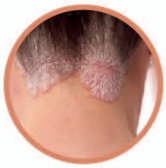
116 Mease PJ, van der Heijde D, Landewe R *et al.* Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. *Ann Rheum Dis* 2018; **77**: 890-7.

117 Baeten D, Sieper J, Braun J *et al.* Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. *N Engl J Med* 2015; **373**: 2534-48.

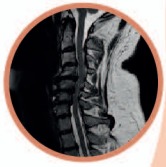
118 Marzo-Ortega H, Sieper J, Kivitz A *et al.* Secukinumab and Sustained Improvement in Signs and Symptoms of Patients With Active Ankylosing Spondylitis Through Two Years: Results From a Phase III Study. *Arthritis Care Res (Hoboken)* 2017; **69**: 1020-9.

119 Pavelka K, Kivitz A, Dokoupilova E *et al.* Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomized, double-blind phase 3 study, MEASURE 3. *Arthritis Res Ther* 2017; **19**: 285.

Scalp Psoriasis
SCALP

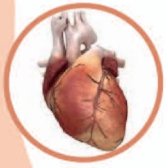


Ankylosing Spondylitis
MEASURE 1-4



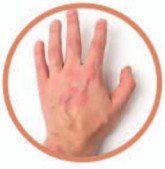
Plaque Psoriasis
ERASURE
FIXTURE
CLEAR
SCULPTURE

Palmoplantar Psoriasis
GESTURE

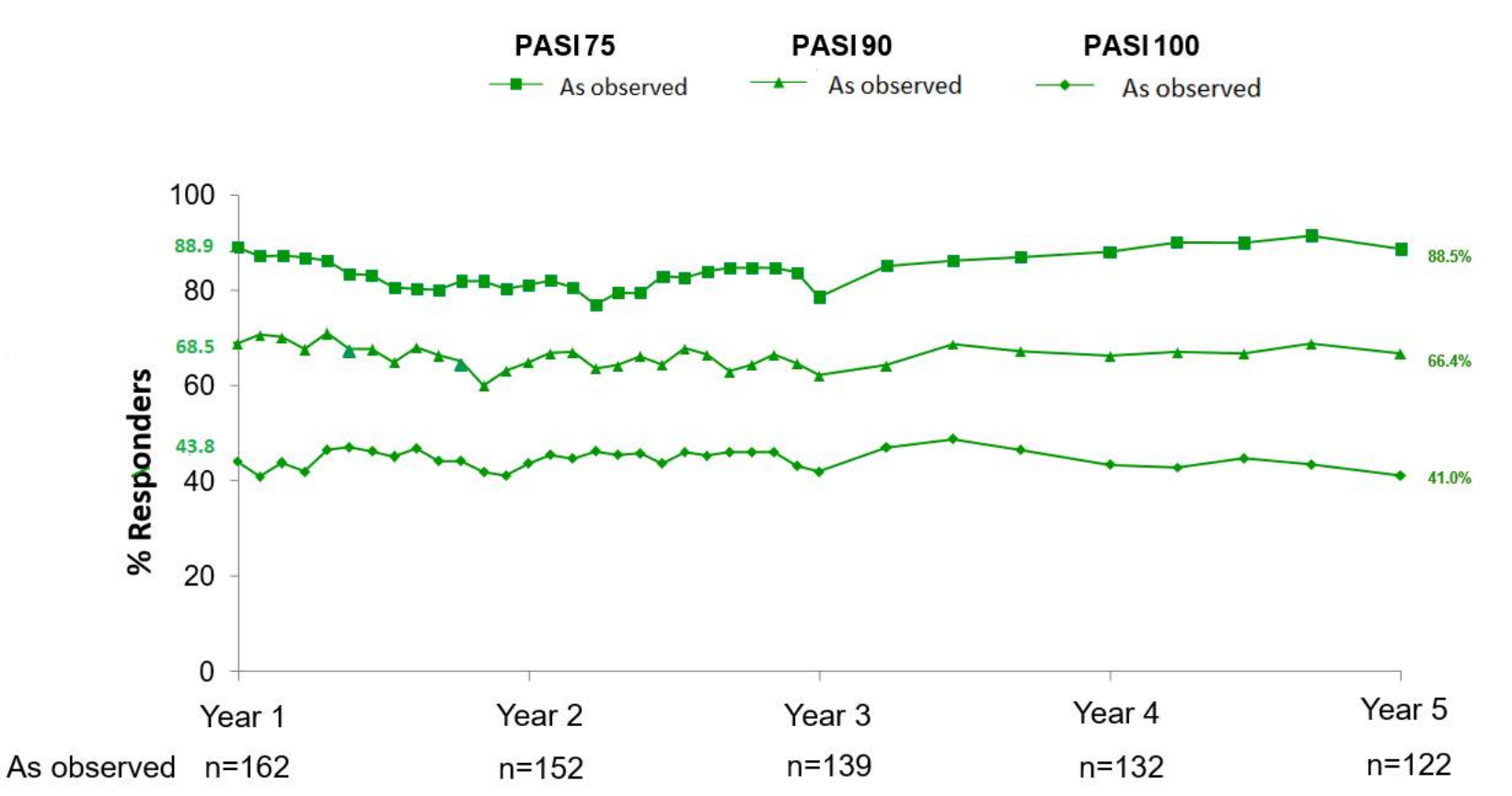


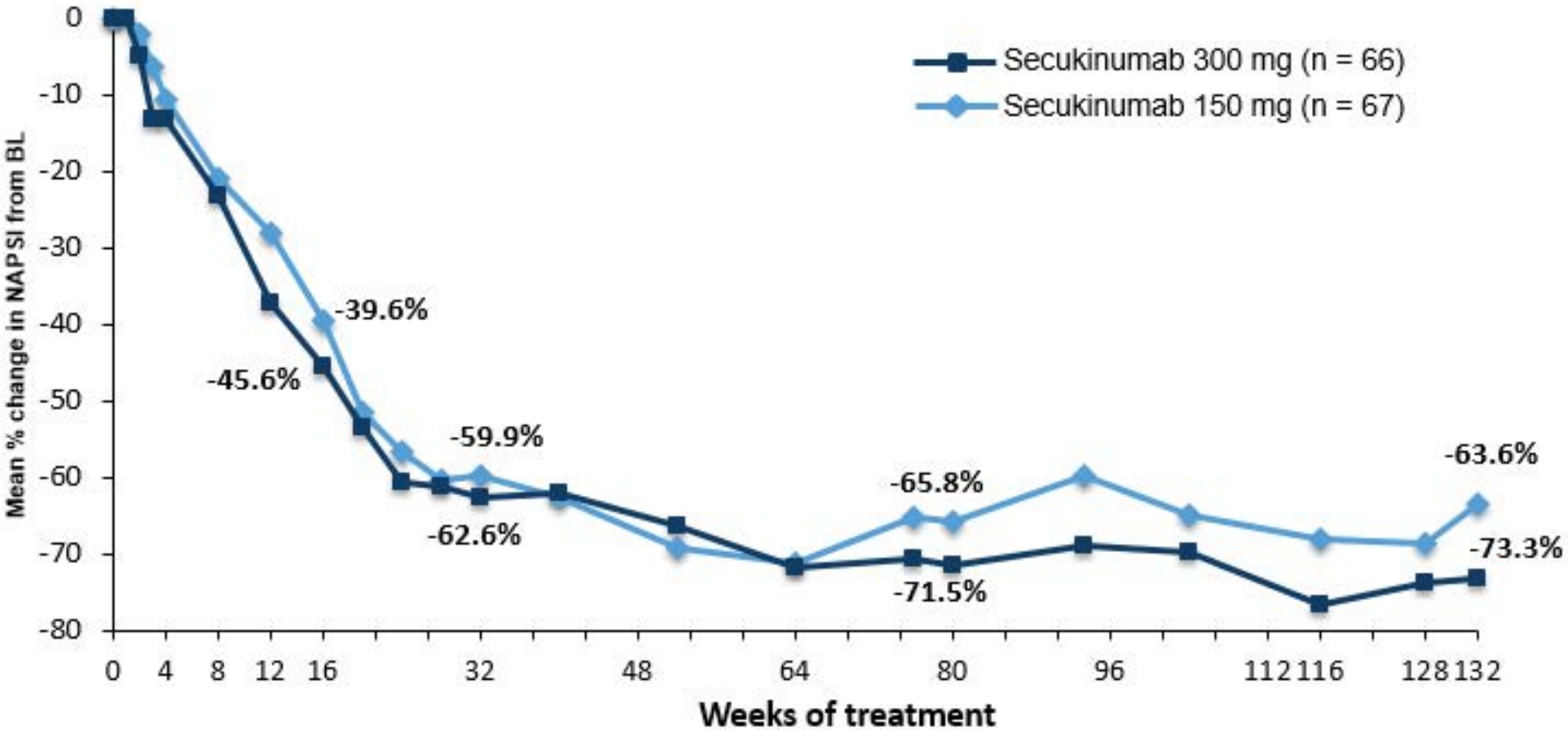
Cardiovascular Risk
CARIMA

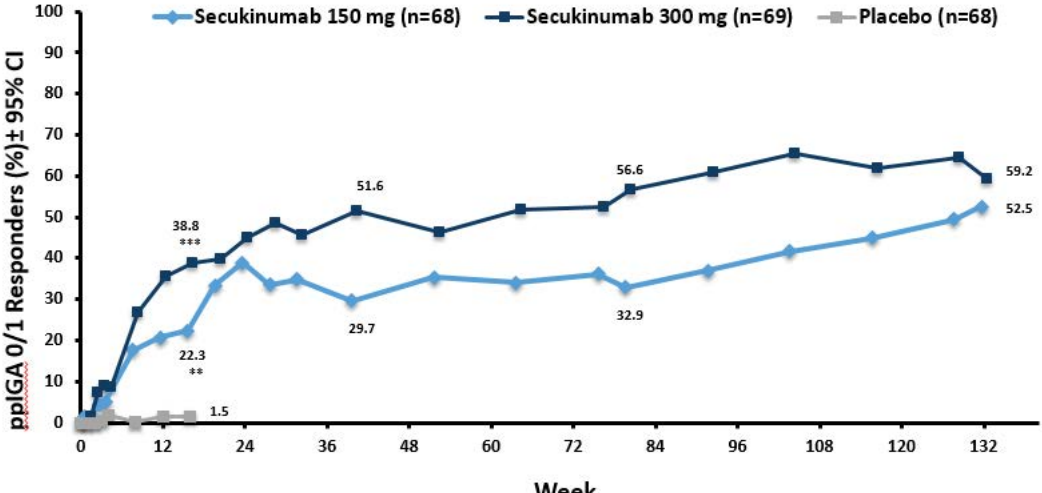
Nail Psoriasis
TRANSFIGURE

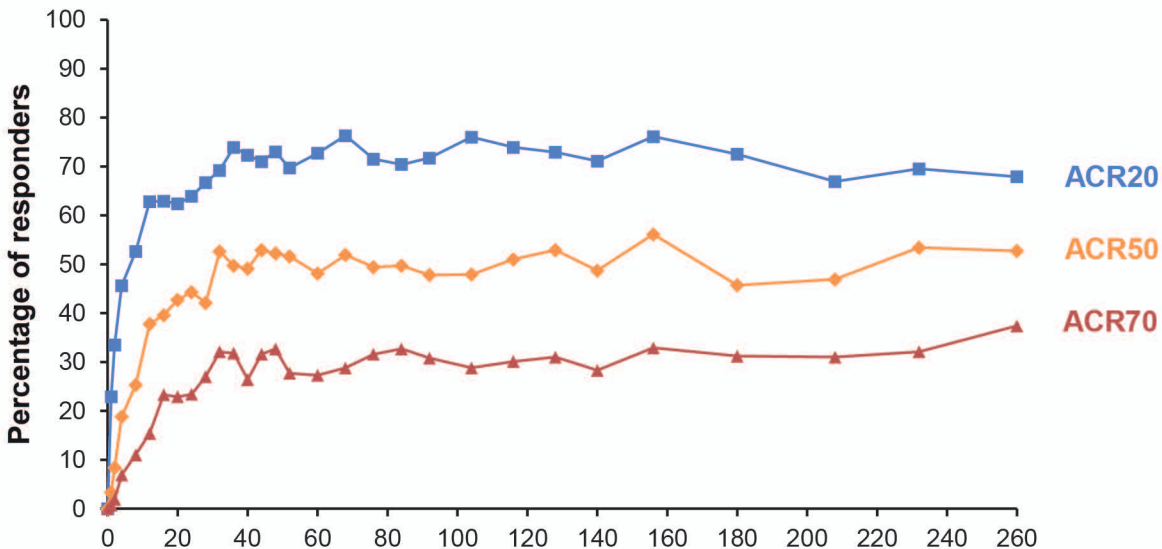


Psoriatic Arthritis
FUTURE 1-5

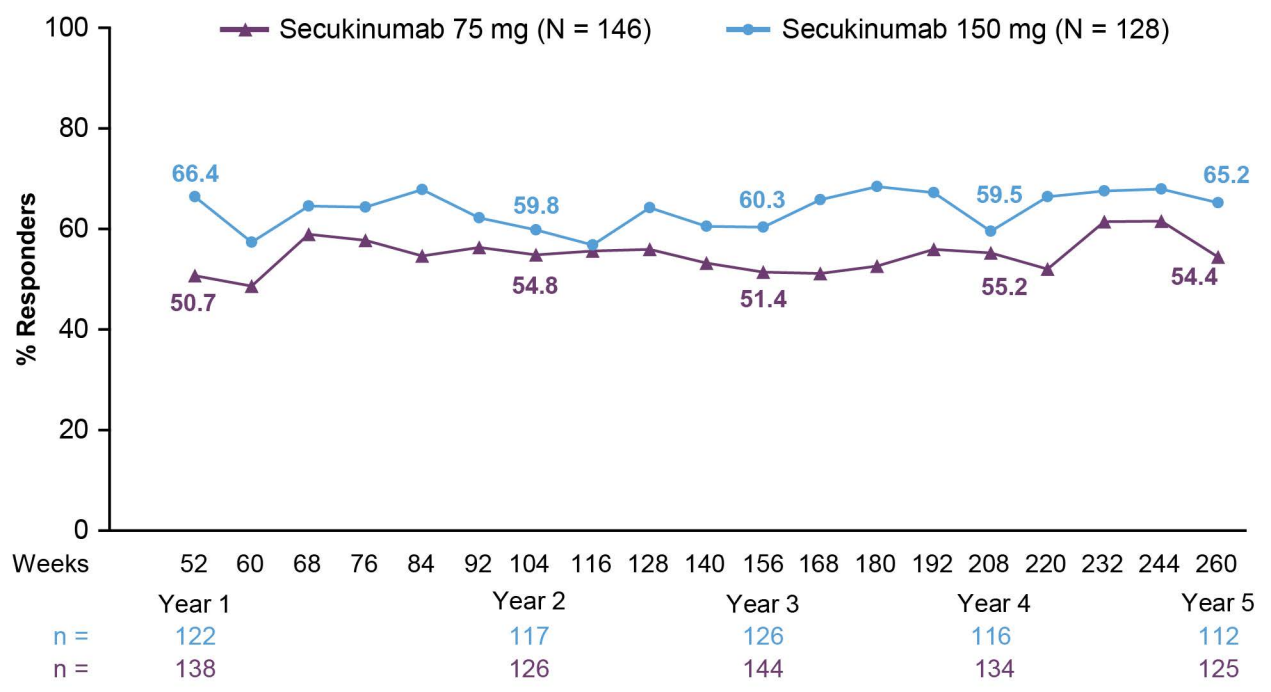

PASI 75
As observed
PASI 90
As observed
PASI 100
As observed
100
88.9
80
68.5
60
43.8
40
20
0
% Responders
88.5%
66.4%
41.0%
Year 1
Year 2
Year 3
Year 4
Year 5
As observed n=162
n=152
n=139
n=132
n=122


Secukinumab 300 mg (n = 66)
Secukinumab 150 mg (n = 67)
Mean % change in NAPSI from BL
0
-10
-20
-30
-40
-50
-60
-70
-80
-39.6%
-45.6%
-59.9%
-62.6%
-65.8%
-71.5%
-63.6%
-73.3%
0
4
8
12
16
32
48
64
80
96
112
116
128
132
Weeks of treatment


Secukinumab 150 mg (n=68)
Secukinumab 300 mg (n=69)
Placebo (n=68)
ppIGA 0/1 Responders (%)± 95% CI
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
84
96
108
120
132
Week
38.8
***
51.6
56.6
59.2
52.5
22.3
**
29.7
32.9
1.5



Dose received	1	52	104	156	180	208	232	260
150 mg	153	155	146	155	137	126	87	74
150 → 300 mg	0	0	0	0	1	19	44	57


Secukinumab 75 mg (N = 146)
Secukinumab 150 mg (N = 128)
% Responders
100
80
60
40
20
0
66.4
59.8
60.3
59.5
65.2
50.7
54.8
51.4
55.2
54.4
Weeks
52 60 68 76 84 92 104 116 128 140 156 168 180 192 208 220 232 244 260
Year 1
Year 2
Year 3
Year 4
Year 5
n = 122 117 126 116 112
n = 138 126 144 134 125