Secukinumab immunogenicity over 52 weeks in patients with psoriatic arthritis and ankylosing spondylitis

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Conflict of Interest

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Short running header (max 4 words)

Secukinumab immunogenicity in PsA/AS

Abstract

Objectives: Secukinumab, a fully human anti–interleukin-17A monoclonal antibody, is efficacious for the treatment of psoriatic arthritis (PsA) and ankylosing spondylitis (AS). This study examined the immunogenicity of secukinumab in patients with PsA and AS exposed to secukinumab for up to 52 weeks.

Methods: Antibody bridging assays were used to assess the immunogenicity of secukinumab in patients with PsA (FUTURE 1–3 studies, and AS (MEASURE 1–4 studies). Evaluations were at Baseline (BL) and at Weeks 16 (AS only), 24 and 52. Treatment-emergent anti-drug antibodies (TE-ADA) were defined as a positive ADA signal in ≥ 1 post-treatment sample in patients negative at baseline. Positive samples were analyzed for drug-neutralizing potential and impact of TE-ADA on secukinumab pharmacokinetics, immunogenicity-related adverse events, and on efficacy through Week 52 was assessed.

Results: Of 1414 treated PsA and 1164 treated AS patients with samples available for immunogenicity evaluation, five (0.35%) and eight (0.69%), respectively, developed TE-ADA. All but one PsA patient were biologic naïve; two of the five PsA and one of the eight AS patients received concomitant methotrexate, and two of the eight AS patients received concomitant sulfasalazine. Associations between TE-ADA and secukinumab dose, frequency or administration mode were not observed. Other than one PsA patient, all TE-ADA were non-neutralizing. No TE-ADA were associated with any adverse events. All TE-ADA were associated with normal secukinumab pharmacokinetics and none were associated with loss of secukinumab efficacy.

Conclusions: Secukinumab treatment was associated with a low (<1%) incidence of immunogenicity in PsA and AS patients.

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INTRODUCTION

Interleukin (IL)-17A has been implicated in many aspects of the pathophysiology and resulting key clinical features of spondyloarthropathies including synovial inflammation, joint erosion, enthesitis, new bone formation, and epidermal inflammation,(1-4) and represents a rational therapeutic target for active psoriatic arthritis (PsA) and ankylosing spondylitis (AS). Secukinumab, a fully human anti–interleukin-17A monoclonal antibody (mAb), has shown efficacy in the treatment of moderate to severe plaque psoriasis,(5-8) PsA,(9-11) and AS,(12-15) demonstrating a rapid onset of action and sustained responses with a favorable safety profile.

It is known that mAb therapies may be associated with immunogenicity and the production of treatment-emergent anti-drug antibodies (TE-ADA). In turn, TE-ADA can cause immunogenicity-related adverse events (AEs), including acute complications such as infusion-related reactions, allergic reactions, and anaphylaxis, as well as non-acute reactions such as delayed hypersensitivity and autoimmunity.(16) Furthermore, TE-ADA can affect drug pharmacokinetics, and impact clinical response, potentially decreasing efficacy, as has been observed with biologic agents.(16-19)

The low incidence of immunogenicity of secukinumab in patients with moderate to severe plaque psoriasis has been assessed previously in the psoriasis phase 3 program in which TE-ADA occurred in <1% patients treated for up to 52 weeks.(20) The objective of this new analysis was to examine the immunogenicity of secukinumab in patients with PsA and AS, who were treated with secukinumab for up to 52 weeks.

METHODS

Study design

The immunogenicity of secukinumab, as indicated by TE-ADA, was assessed across Phase 3 clinical trials in patients with PsA or AS (9-15) who were exposed to secukinumab for up to 52 weeks. TE-ADA were evaluated at baseline and at Weeks 16 (AS only), 24 and 52.

The Phase III PsA secukinumab studies included in this analysis were FUTURE 1–3 (NCT01392326; NCT01752634; and NCT01989468, respectively). (9-11)

In FUTURE 1, (10) patients were randomly assigned in a 1:1:1 ratio to one of two secukinumab dose groups or a placebo group. Patients in the secukinumab groups received an intravenous (i.v.) dose of 10 mg/kg at Baseline and Weeks 2 and 4, followed by subcutaneous (s.c.) secukinumab at a dose of either 150 mg or 75 mg every 4 weeks thereafter. Patients in the placebo group were treated according to the same i.v.-to-s.c. administration schedule.

In FUTURE 2,(9) patients were randomly assigned in a 1:1:1:1 ratio to receive s.c. secukinumab 300 mg, 150 mg, 75 mg, or placebo once a week from Baseline to Week 4 and then every 4 weeks thereafter.

In FUTURE 3, (11) patients were randomized (1:1:1) to one of two secukinumab dose groups (secukinumab 300 mg or 150 mg) or placebo. Patients in the secukinumab groups received s.c. secukinumab at a dose of 300 mg (2 × 1.0 mL autoinjector) or 150 mg (1.0 mL autoinjector + 1.0 mL placebo autoinjector) at Baseline, Weeks 1, 2, 3, and 4, and every 4 weeks thereafter. Patients in the placebo group (2 × 1.0 ml placebo autoinjector) were treated according to the same administration schedule as the active drug. Patients were stratified at randomization based on previous anti-TNF therapy use as anti-TNF-naïve or anti-TNF-IR; at least 60% of patients in each treatment arm (secukinumab 300 mg, secukinumab 150 mg, and placebo) were anti-TNF naïve

At Week 16 in all three FUTURE studies, patients were classified as responders (≥ 20% improvement from Baseline in tender and swollen joint counts) or non-responders. In FUTURE 1, placebo-treated patients were randomly assigned again in a 1:1 ratio to receive s.c. secukinumab 150 mg or 75 mg every 4 weeks from Week 16 (non-responders) or Week 24 (responders). In FUTURE 2 and FUTURE 3, placebo-treated patients were randomly assigned again in a 1:1 ratio to receive s.c. secukinumab 300 mg or 150 mg every 4 weeks from Week 16 (non-responders) or Week 24 (responders).

The Phase III studies in patients with AS included in this analysis were MEASURE 1–4 (NCT01358175; NCT01649375; NCT02008916; and NCT02159053, respectively). (12-15)

In MEASURE 1,(12) patients randomized to secukinumab received a 10 mg/kg i.v. infusion at Baseline and Weeks 2 and 4, followed by s.c. injections of 150 mg (secukinumab i.v.–150 mg) or 75 mg (i.v.–75 mg) every 4 weeks from week 8; patients in the placebo group were treated using the same i.v.-to-s.c. schedule. Placebo-treated patients were randomly reassigned (1:1) to receive secukinumab 150 or 75 mg s.c. every 4 weeks from Week 16 (non-responders) or week 24 (responders), with response based on Assessment of SpondyloArthritis International Society 20 (ASAS20) response criteria.

In MEASURE 2,(12) patients were randomized to receive s.c. secukinumab 150 mg, 75 mg or placebo at Baseline, Weeks 1, 2 and 3 and every 4 weeks from Week 4. At week 16, placebo-treated subjects were re-randomized to receive s.c. secukinumab 150 or 75 mg every 4 weeks, irrespective of the clinical response.

In MEASURE 3, (15) patients were randomized (1:1:1) to one of two secukinumab dose groups (300 mg or 150 mg) or a placebo group. Patients in the secukinumab groups received an i.v. dose of 10 mg/kg at Baseline and Weeks 2 and 4, followed by s.c. secukinumab in the form of prefilled syringes (PFS) at a dose of either 300 mg (i.v.–300 mg) or 150 mg (i.v.–150 mg) every 4 weeks starting at Week 8. Patients in the placebo group were treated according to the same i.v.-to-s.c. administration schedule. At week 16, all patients in the placebo group were re-randomized to receive either secukinumab 300 mg or 150 mg (1:1) s.c. every 4 weeks.

In MEASURE 4, (14) patients with AS were randomly assigned (1:1:1) to one of three treatment groups: s.c. secukinumab 150 mg with loading dose; s.c. secukinumab 150 mg without loading dose, or placebo. All patients received s.c. secukinumab 150 mg or placebo at Baseline and Weeks 1, 2, 3, and every 4 weeks starting at Week 4. At Week 16, all placebo patients were switched to s.c. secukinumab 150 mg every 4 weeks. Thus, starting at Week 16, patients in all three arms received secukinumab 150 mg every 4 weeks.

All studies were double-blind and placebo-controlled, and full details of the study designs have been described in detail previously.(9-15) All studies were approved by the institutional review board or ethics committee at each participating site and were conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval numbers for the main institutions are included in Supplementary Table 1. All patients provided written informed consent.

Assay methods

Blood sample and antidrug antibody analysis

Blood samples were obtained pre-dose at Baseline and throughout the studies. For this analysis, immunogenicity in patients with PsA and AS exposed to secukinumab was evaluated at Baseline and at Weeks 16 (AS only), 24 and 52.

ADA assessment followed the standard, sequential three-tiered approach that is commonly used to assess ADA of therapeutic antibodies (screening, confirmation and titration).(20, 21) In tier 1, patient-derived samples were analysed for ADA in a screening assay (summarized in Figure 1A); in tier 2, positive samples were retested in a confirmatory assay where specificity was assessed by performing the assay in the presence of excess secukinumab; in tier 3, confirmed ADA-positive samples were quasi-quantified via titration to obtain a titre value.

In the first step (the screening assay), the assay signal of patient-derived samples, is evaluated against a pre-defined and validated assay signal cut-point. If the signal is above this cut-point, the sample is considered screening positive, but not yet ADA positive. In the second step, the screening positive samples are then tested in the so called confirmatory assay as it confirms specificity of the signal observed in the first assay. The confirmatory assay is based on the same analytical principle as the screening assay. However, before being analyzed in the assay, the patient-derived screening positive samples are pre-incubated with an excess of the drug. In the case of a specific signal, the addition of drug to the sample will prevent the ADA from being detected and the assay signal will decrease. The inhibition of the assay signal is compared against a pre-defined and validated cut-point. If the inhibition of the signal exceeds this confirmatory cut-point, then the sample is considered as ADA positive. In the third step, the ADA response is semi-quantified by determining a titer. The assay for titer determination is again based on the same assay principle as screening and confirmatory assay. In this assay however, the patient-derived samples are diluted sequentially leading to a decrease in signal with increasing

dilution factor. The reported titer corresponds to the dilution at which the assay signal reaches the pre-defined and validated titer cut-point of the assay.

In this study, ADA were detected according to the assay approach described above using a Meso Scale Discovery (MSD) electrochemiluminescence assay (Meso Scale Discovery, Gaithersburg, MD, USA), which has been previously described in detail.(20) Validation of the MSD assay determined the limits of secukinumab ADA detection in serum samples from patients before and after treatment with secukinumab and was conducted according to FDA and EMA guidance and relevant white papers.(22-29) At baseline, before secukinumab exposure (and therefore in the absence of serum secukinumab), the MSD bridging assay was highly sensitive and able to detect 4 ng/mL of polyclonal anti-secukinumab positive control antibody. Drug tolerance (the ability of the analysis to detect ADA without interference from the drug under investigation) in the MSD assay was 53.8 µg/mL secukinumab. Therefore, after secukinumab exposure at serum secukinumab concentrations ≤53.8 µg/mL, the assay was sufficiently sensitive to detect concentrations down to 250 ng/mL of polyclonal anti-secukinumab positive control antibody.

TE-ADA were defined as ADA that developed following treatment with secukinumab in patients with no ADA detected before active treatment. Secukinumab immunogenicity was defined as a positive signal for TE-ADA in ≥ 1 post-treatment sample in patients who were negative at baseline. TE-ADA-positive samples were analyzed through Week 52 for the following: drug-neutralizing potential; impact of anti-drug antibodies on the pharmacokinetics of secukinumab; immunogenicity-related adverse events; and the impact of TE-ADA on the efficacy of secukinumab.

Neutralizing antibody assay

Serum samples from patients with confirmed TE-ADA were further analyzed for neutralizing ADA (antibodies that bind to secukinumab in such a way as to prevent it from binding to IL-17A, thereby neutralizing its activity). An enzyme-linked immunosorbent assay was used to determine the neutralizing potential of the ADA, based on the presence or absence of an IL-17A binding signal (Figure 1B).(21)

Pharmacokinetic profiles

Across all of the phase III studies, normal pharmacokinetic (PK) behavior in TE-ADA-positive patients was defined as secukinumab concentrations in individuals with TE-ADA at the various time points that were 1) within the observed range for all patients without ADA and 2) showed steady-state PK behavior at Weeks 24 and 52.

Definition of loss of response

Loss of response in patients with PsA was defined as an increase in disease activity leading to a failure to maintain > 20% reduction, compared to baseline, in both tender and swollen joint counts, on treatment after previously achieving such improvement for at least 2 consecutive visits prior to the first detection of ADA.

The definition of loss of response in patients with AS was based on the ASAS response criteria and was defined as an increase in disease activity leading to a failure to maintain ASAS20 (ASAS20 response defined as a relative improvement of ≥ 20% and an absolute improvement of ≥ 1 unit (on a 10-unit scale) in at least three of the four main ASAS domains [patient global assessment of disease activity, back pain, physical function, and inflammation], with no worsening of ≥ 20% and ≥ 1 unit [on a 10-unit scale] in the remaining domain) after previously achieving such improvement for at least 2 consecutive visits prior to the first detection of ADA. Impact on efficacy was assessed up to Week 52.

RESULTS

Antidrug antibody assay results

A total of 1414 of 1417 patients randomized in the three PsA trials and 1164 of 1166 patients randomized in the four AS trials and treated with secukinumab had samples analyzed for immunogenicity evaluation. Overall, five (0.35%) patients with PsA and eight (0.69%) patients with AS developed TE-ADA over 52 weeks (Figure 2).

For patients with PsA, one of 603 patients (0.17%) in FUTURE 1 and one of 397 (0.25%) patients in FUTURE 2 studies developed TE-ADA, as did three of 414 (0.72%) patients in FUTURE 3. Of the five patients with PsA who developed TE-ADA, two had received concomitant methotrexate and one of these two patients had also received corticosteroids.

In the AS studies, two of 371 patients in MEASURE 1 (0.54%), one of 220 patients in MEASURE 2 (0.45%) and one of 226 patients in MEASURE 3 (0.44%), and four of 347 patients in MEASURE 4 (1.15%) developed TE-ADA (Table 1). One of the eight patients with AS who developed TE-ADA received concomitant methotrexate; two out of these eight patients received concomitant sulfasalazine, and three of these eight patients received concomitant corticosteroids. In MEASURE 4, one patient experienced persistent immunogenicity with TE-ADA positive signals at Weeks 16 and 52. No boosted immunogenicity, i.e., increase of titer values over time, was observed. This patient had no abnormal PK, immunogenicity-related adverse effects, or loss of efficacy response.

As shown in Table 1, the frequency of TE-ADA did not appear to vary with increasing doses of secukinumab. At the time points that immunogenicity was measured, 96% of patients had secukinumab serum concentrations below the drug tolerance level of 53.8 µg/mL, confirming sufficient assay

sensitivity for measuring immunogenicity during treatment with secukinumab. (30) Other than one patient with PsA, all TE-ADA were non-neutralizing and none of the TE-ADA were associated with any immunogenicity-related adverse events (Table 1).

Effect of TE-ADA on serum levels of secukinumab

In all three PsA studies and the four AS studies, the TE-ADA were associated with normal secukinumab pharmacokinetics.

The individual trough concentrations in ADA-negative and ADA-positive patients during 52 weeks of secukinumab treatment are shown in Figure 3. They demonstrate that TE-ADA have no effect on serum levels of secukinumab. In both indications, the trough serum secukinumab concentrations of TE-ADA-positive patients show steady-state PK behavior and are within the range of the serum concentrations observed in ADA-negative patients.

Drug tolerance and serum levels of secukinumab

Figure 4B shows that in patients with AS, Week 16 concentrations were higher than at the later time points due to the loading regimens during the first month. As also shown in Figure 4 and across both indications, steady-state behavior is apparent at Weeks 24 and 52 i.e. mean concentrations remained stable at these two time points. Mean and median concentrations are approximately 2-fold higher with the 300 mg than with the 150 mg dose level. Only a few patients receiving the 75 mg and 150 mg doses had serum secukinumab levels higher than the drug tolerance threshold at Weeks 24 and 52, whereas this occurred more frequently at the 300 mg dose level. For individual drug concentrations higher than the drug tolerance level of the ADA assay (symbols above the dashed line), weak ADA responses may have been missed (false negatives).

ADA effects on efficacy and safety

As shown in Table 1, there were no observed effects of TE-ADA on the efficacy of secukinumab, and none of the TE-ADA were associated with immunogenicity-related AEs.

DISCUSSION

In this study, secukinumab treatment was associated with a low incidence of immunogenicity in PsA and AS patients, as shown by TE-ADA detection in only 0.35% of PsA patients and 0.69% of AS patients over 52 weeks in a database of more than 2,500 patients from clinical studies. These results are consistent with the low incidence of immunogenicity (0.40%) seen with secukinumab through Week 52 in clinical studies of patients with moderate to severe plaque psoriasis (20).

Drug tolerance is an important aspect in immunogenicity analysis and represents the ability of the analysis to detect ADA without interference from the drug under investigation,(31) in this case, secukinumab. Levels of secukinumab below the drug tolerance threshold at the time of immunogenicity measurement confirm sufficient assay sensitivity for measuring immunogenicity during treatment with secukinumab. In line with this concept, the secukinumab concentration in most (96%) of the samples was below the drug tolerance limit of the assay, a result that is similar to that observed in patients with moderate to severe plaque psoriasis treated with secukinumab (20).

The presence of ADA has been identified as an important contributor to reduced treatment efficacy and increased risk of AEs in patients receiving biologic therapy.(32) Therefore, low incidence of immunogenicity could be an important clinical consideration when selecting a therapy for patients with chronic immune mediated inflammatory diseases. Indeed, available evidence based on a systematic literature review, suggests that the immunogenicity of different biologics and biosimilars used to treat

PsA and AS varies widely.(32) As yet we cannot explain the low immunogenicity levels on the basis of target biology, as has been proposed for tocilizumab on the basis of IL-6R activity upon B cell activation and immunoglobulin production;(33, 34) nevertheless, there is an emerging literature concerning the role of IL-17A in B cell activation and regulation, and this remains a theoretical possibility requiring future studies.(35)

The low incidence of immunogenicity of secukinumab observed in these clinical studies is consistent with secukinumab being a fully human monoclonal antibody.(36, 37) However, there are other possible mechanisms associated with immunogenicity, even with human antibodies. These include potential epitopes formed within the highly diverse amino acid composition of the complementarity-determining regions (CDRs) of immunoglobulin G (IgG) molecules, the loss of tolerance to self-sequences, and product-specific attributes, such as dosing frequency, dose amount, administration route, and formulation factors such as impurities, host cell proteins, and the tendency to aggregate. (38) The low immunogenicity incidence for secukinumab found in the PsA and AS analysis is consistent with results from two different *in vitro* immunogenicity assays (Major Histocompatibility Complex-associated Peptide Proteomics (MAPPs) and T-cell activation assays) in which secukinumab was consistently associated with relatively low numbers of potential T-cell epitopes and low T-cell response rates.(38) Additionally, it aligns well with a recent *in vitro* immunogenicity study in which low numbers of pre-existing T-cells were observed for secukinumab. (39) Further research is required to confirm the association between these *in vitro* findings and the incidence of clinical immunogenicity.

The results presented here add to the consistent evidence of low immunogenicity incidence with secukinumab (20, 32) and, therefore, provides useful information for clinicians considering therapeutic options for patients with PsA and AS.

CONCLUSION

Secukinumab treatment was associated with TE-ADA in only 0.35% of PsA patients and 0.69% of AS patients over 52 weeks in a database of more than 2500 patients from clinical studies. The formation of ADA was not linked with immunogenicity-related adverse events, loss of clinical response and/or deviations in the expected pharmacokinetics of secukinumab. These results are consistent with the low incidence of immunogenicity (0.4%) seen with secukinumab over 52 weeks in clinical studies of patients with moderate to severe plaque psoriasis. (20)

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GB, SS, RM, BP, JS, LP and AS designed the analysis; RM, GB, and SS performed that analysis; AD, DG, IBM collected the data. A first draft of the manuscript was developed by the first author with editorial assistance provided by Paul Coyle, Jackie Johnson, and Aine Abautret-Daly, (employees of Novartis). All authors reviewed and critically revised the manuscript for content and approved the final version of the manuscript for submission.

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FIGURE LEGENDS

Figure 1. ADA and neutralizing antibody assays.

A. ADA detection.

Schematic diagram of the anti-secukinumab antibody assay. Biotinylated secukinumab was immobilized on a streptavidin-coated plate, and unbound biotinylated secukinumab was washed away. Free antidrug antibodies were captured by binding to immobilized secukinumab. Antidrug antibodies, acting as a bridge, were bound to SULFO-tagged secukinumab, added subsequently, and detected by electrochemiluminescence.

B. Neutralizing antibody assay.

Schematic diagram of the neutralizing antibody assay. Subject serum samples, after acid dissociation and neutralization, were applied to immobilized secukinumab, followed by addition of excess human IL-17A. In the absence of neutralizing antidrug antibodies in patient samples, IL-17A became bound to immobilized secukinumab. Excess unbound IL-17A was removed. Bound IL-17A was recognized by addition of noncompeting mouse antihuman IL-17A antibodies. The detection signal of IL-17A binding was produced by binding of horseradish peroxidase (HRP)-linked rabbit anti-mouse IgG antibody to anti-IL-17A antibodies. Neutralizing antidrug antibodies were detected by their ability to inhibit IL-17A binding to secukinumab competitively, thereby disrupting anti-IL-17A antibody binding. Absence of signal produced by enzyme-linked secondary antibody binding indicated the presence of neutralizing antidrug antibodies. IgG: immunoglobulin G; IL: interleukin.

Figure 1A and **1**B are reproduced with permission from Reich et al. British Journal of Dermatology 2017;176:752-8 (20).

Figure 2: Summary of secukinumab immunogenicity across clinical studies of (A) PsA* and (B) AS#.

*Immunogenicity in patients with PsA (FUTURE 1–3 studies, N=1414). Four out of five patients were biologic naive. Two out of five patients received concomitant methotrexate.

#Immunogenicity in patients with AS (MEASURE 1–4 studies, N=1164). One out of eight patients received concomitant methotrexate. Two out of eight patients received concomitant sulfasalazine. All TE-ADA were non-neutralizing.

AS: ankylosing spondylitis; PsA: psoriatic arthritis; TE-ADA: treatment-emergent anti-drug antibodies.

Figure 3: Individual trough concentrations in TE-ADA-negative and TE-ADA-positive patients with (A) PsA and (B) AS.

Black solid lines, individual secukinumab serum concentrations in TE-ADA-negative patients; red solid lines, individual secukinumab serum concentrations in TE-ADA-positive patients. From left to right, at 75, 150 and 300 mg dose levels with q4w dosing intervals, trough levels at Weeks 16 (AS only), 24, and 52 are shown. Pooled trough levels from the three PsA clinical studies and the four AS clinical studies.

Figure 4: Drug tolerance and comparison of mean and median trough secukinumab serum concentrations at Weeks 16 (AS only), 24 and 52 for (A) PsA (B) AS.

Dashed line from Y-axis represents the drug tolerance threshold of 53.8 µg/mL.

For each box-and-whisker plot, the whisker represents the range, the box represents the 25th to 75th percentile, the solid and dashed lines within the box represent the mean and median trough serum concentrations, respectively. Symbols above the whisker represent outliers.

Table 1: Overview of patients with TE-ADAs[#]

AS: ankylosing spondylitis; IG: immunogenicity; N-Ab: neutralizing antibodies; PsA: psoriatic arthritis; Wk: week.

[#]Only positive ADA results at the respective study week are shown.

[~]IG-related AEs refers to preferred terms in the SMQ hypersensitivity

[≠]Impact on efficacy: PsA – failure to achieve > 20% reduction in both tender and swollen joint counts for at least 2 consecutive visits prior to the first detection of ADA; AS – failure to achieve ASAS20 while on treatment after previously achieving ASAS20 for at least 2 consecutive visits at any time prior to first detection of ADA. Assessment for impact on efficacy has been done only up to week 52.

[∞]Normal PK: Concentrations at various time points in individual ADA-positive patients that fit into the observed range for all patients without ADA

*Insufficient sample volume to determine titer.

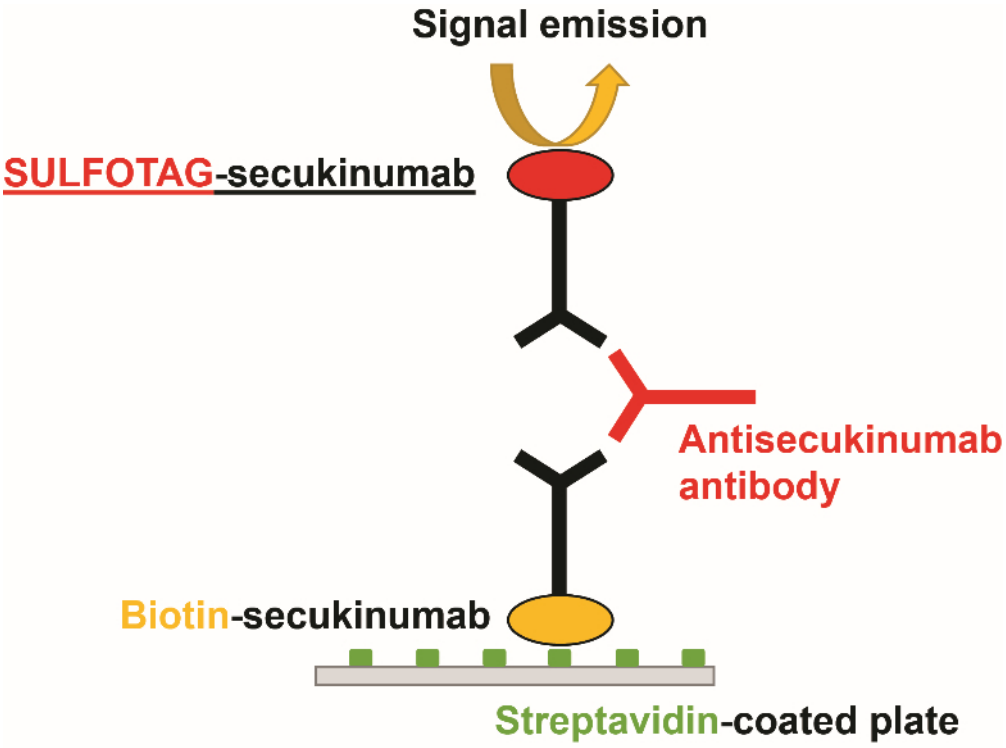

Figure 1A. ADA detection

90x67mm (220 x 220 DPI)

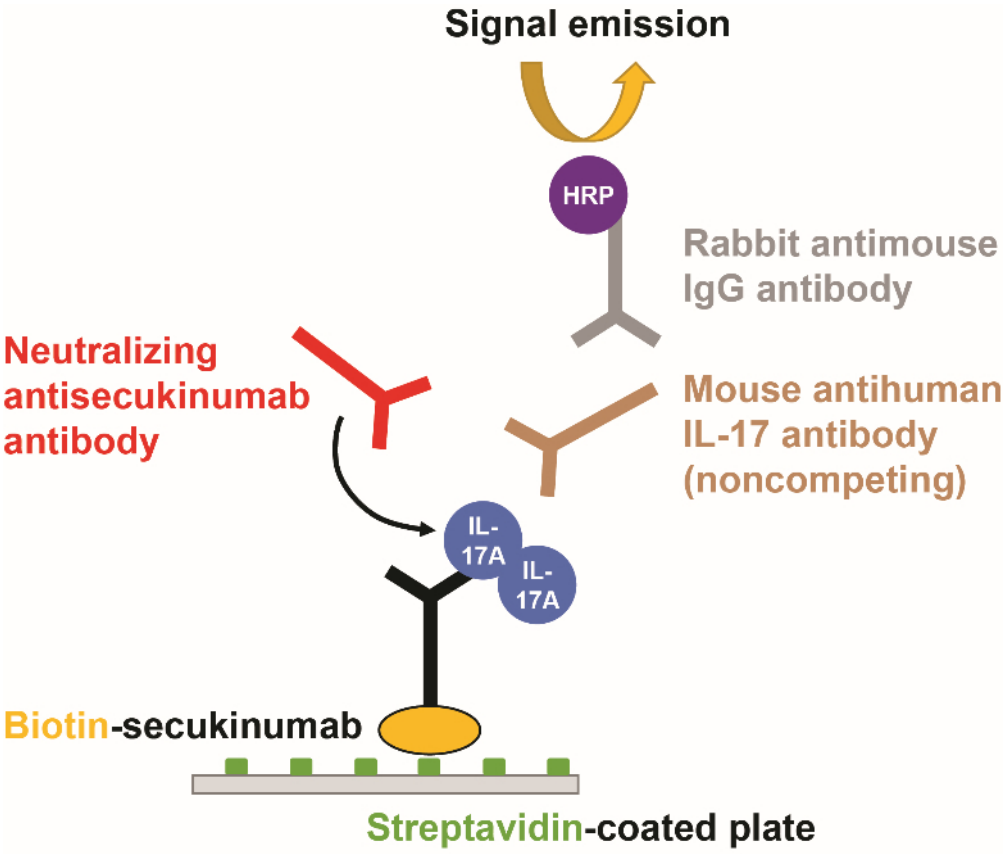

Figure 1B. Neutralizing antibody assay

90x76mm (220 x 220 DPI)

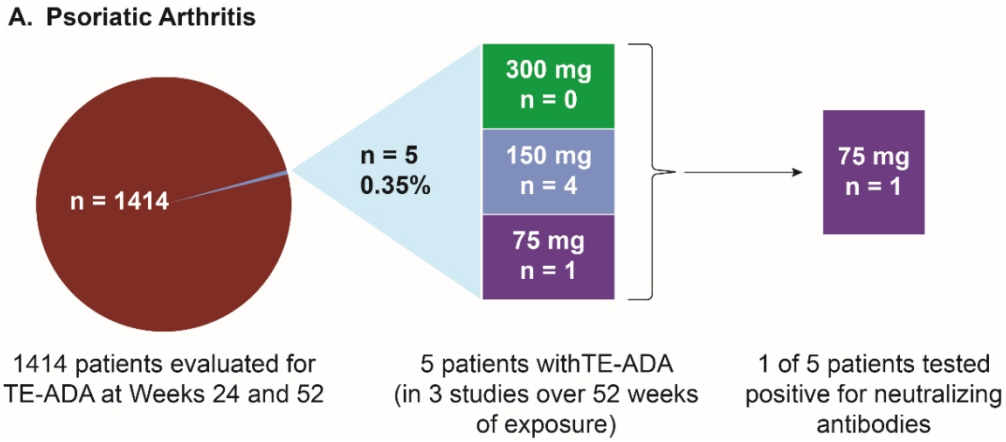

Figure 2A. Summary of secukinumab immunogenicity across clinical studies of PsA

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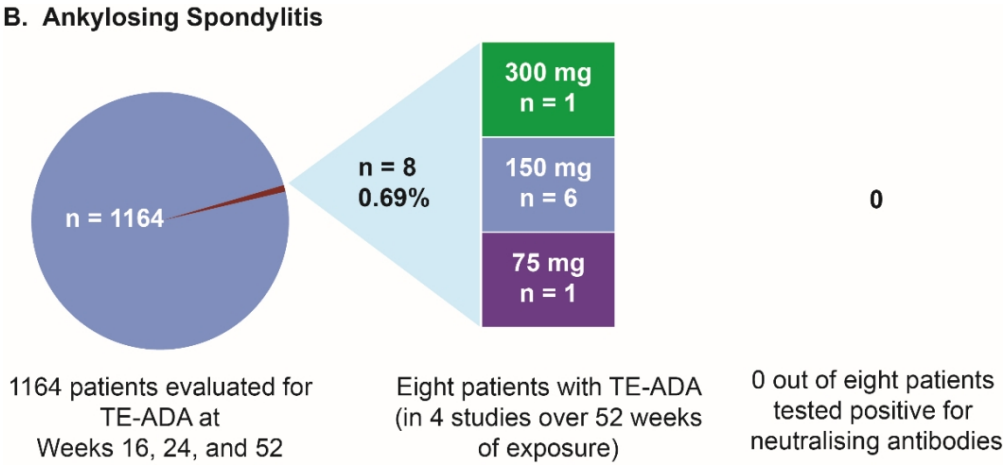

Figure 2B. Summary of secukinumab immunogenicity across clinical studies of AS

138x63mm (220 x 220 DPI)

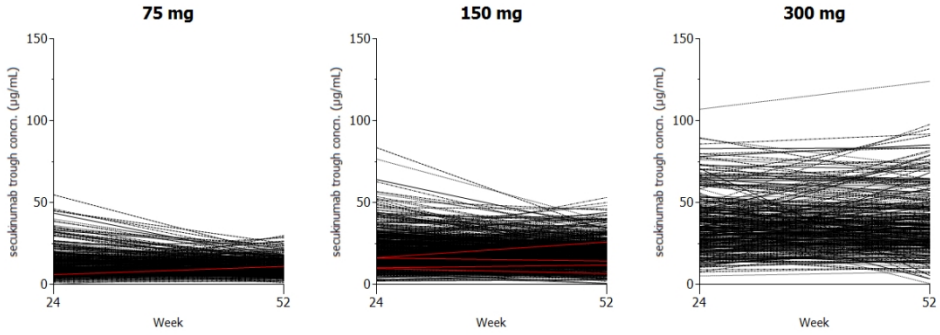

Figure 3A. Individual trough concentrations in TE-ADA-negative and TE-ADA-positive patients with PsA

222x232mm (144 x 144 DPI)

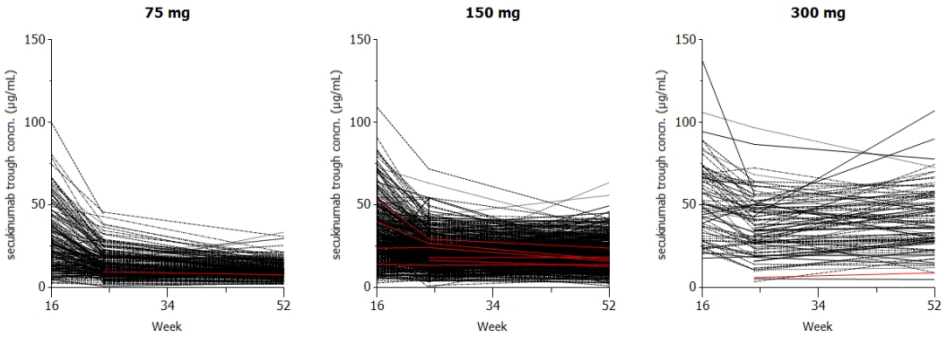

Figure 3B. Individual trough concentrations in TE-ADA-negative and TE-ADA-positive patients with AS

222x232mm (144 x 144 DPI)

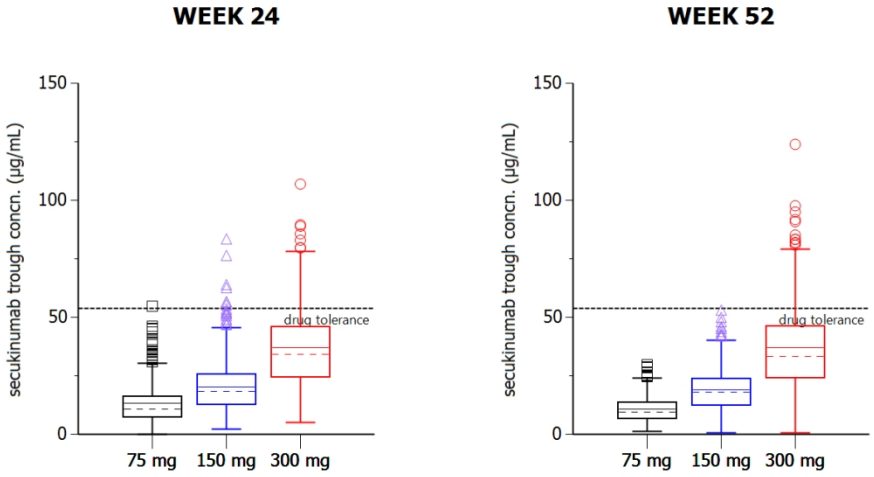

Figure 4A. Drug tolerance and comparison of mean and median trough secukinumab serum concentrations at Weeks 16 (AS only), 24 and 52 for PsA

238x264mm (144 x 144 DPI)

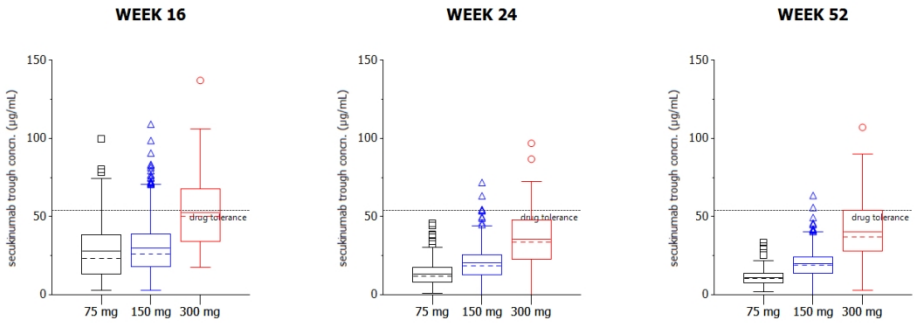

Figure 4B. Drug tolerance and comparison of mean and median trough secukinumab serum concentrations at Weeks 16 (AS only), 24 and 52 for AS

238x264mm (144 x 144 DPI)

PsA studies						
Study	SEC dose	Prior biologics	ADA (titer) /N-Ab	AE possibly IG related˜	Impact on efficacy≠	PK behavior ∞
FUTURE 1 (N=603)	Placebo - 75 mg	None	Wk 24 (no titer*)/Yes	No	None	Normal
FUTURE 2 (N=397)	Placebo - 150 mg	None	Wk 52 (2.99)/No	No	None	Normal
FUTURE 3 (N=414)	150 mg	Infliximab	Wk 52 (2.14)/No	No	None	Normal
	150 mg	None	Wk 24 (1.00)/No	No	None	Normal
	150 mg	None	Wk 52 (2.59)/No	No	None	Normal
AS studies						
MEASURE-1 (N=371)	10mg/kg -150 mg	None	Wk 52 (2.39)/No	No	None	Normal
	Placebo -150 mg	None	Wk 52 (10.61)/No	No	None	Normal
MEASURE-2 (N=220)	Placebo - 75 mg	None	Wk 52 (39.39)/No	No	None	Normal
MEASURE-3 (N=226)	Placebo - 300 mg	None	Wk 52 (1.02)/No	No	None	Normal
MEASURE-4 (N=346)	10mg/kg -150 mg	None	Wk 16 (6.35)/No Wk 52/(2.96)/No	No	None None	Normal
	150 mg No Load	None	Wk 16 (2.70)/No	No	None	Normal
	150 mg	None	Wk 24/(2.80)/No	No	None	Normal
	Placebo – 150 mg	None	Wk 52/(2.89)/No	No	None	Normal