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McInnes, I. B. et al. (2015) 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*, 386(9999), pp. 1137-1146

This is the accepted version.

<http://eprints.gla.ac.uk/110960/>

Deposited on: 31 March 2016

Article

Secukinumab, a human anti-interleukin-17A monoclonal antibody, in psoriatic arthritis: a randomized, double-blind, placebo-controlled, phase 3 trial (FUTURE 2)

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Word count of main article = 2999 [journal word-count limit = 3000 words]

Word count of 'Research in Context' Panel = 291 [journal limit = 300 words]

Abstract word count = 266 words [journal word-count limit = 300 words]

Figures and tables = 6 [2 figures and 4 tables] [no specified journal limit]

References = 29 [journal limit = 30]

Summary

Background Interleukin-17A (IL-17A) is a proinflammatory cytokine implicated in the pathogenesis of psoriatic arthritis (PsA). We assessed the efficacy and safety of subcutaneous treatment with secukinumab, a human anti-IL-17A monoclonal antibody, in patients with PsA.

Methods In this phase 3, double-blind, placebo-controlled study conducted at 76 centers worldwide, adults with active PsA were randomized (1:1:1:1) via computer-generated blocks to receive subcutaneous placebo or secukinumab 300mg, 150mg, or 75mg weekly from baseline, and then every 4 weeks from week 4. The primary endpoint was the proportion of patients achieving a $\geq 20\%$ improvement in American College of Rheumatology response criteria (ACR20) at week 24. This study is registered with ClinicalTrials.gov (NCT01752634).

Findings Between April and November 2013, 397 patients were randomly assigned to receive secukinumab 300mg (n=100), 150mg (n=100), 75mg (n=99), or placebo (n=98). A significantly higher proportion of patients achieved an ACR20 response at week 24 with secukinumab 300mg (54/100 [54.0%]; odds ratio versus placebo [OR] 6.81, 95% confidence interval [CI] 3.42–13.56; $p < 0.0001$), 150mg (51/100 [51.0%]; OR 6.52, 95% CI 3.25–13.08; $p < 0.0001$), and 75mg (29/99 [29.3%]; OR 2.32, 95% CI 1.14–4.73; $p = 0.0399$), versus placebo (15/98 [15.3%]). Through week 16 the most common adverse events were upper respiratory tract infections (4.0%, 8.0%, 10.1% and 7.1% with secukinumab 300mg, 150mg, and 75mg, and placebo, respectively) and nasopharyngitis (6.0%, 4.0%, 6.1% and 8.2%, respectively). Serious adverse event rates through week 16 were 5.0%, 1.0% and 4% with secukinumab 300mg, 150mg and 75mg, respectively, compared with 2.0% with placebo. No deaths were reported.

Interpretation Subcutaneous treatment with secukinumab 300mg and 150mg improved the signs and symptoms of PsA, suggesting this agent as a potential future treatment option.

Funding Novartis Pharma AG.

Keywords Secukinumab; psoriatic arthritis; FUTURE 2; spondyloarthritis; biologic

Introduction

Psoriatic arthritis (PsA), a chronic inflammatory disease that can affect peripheral and axial joints, entheses, and the skin, is associated with impaired physical function and poor quality of life.^{1,2} Pathogenesis-based interventions, particularly therapies targeting tumor necrosis factor (TNF), have improved outcomes in PsA patients.³⁻⁷ Recently, the interleukin (IL)-12/23 inhibitor ustekinumab and the phosphodiesterase-4 inhibitor apremilast have also demonstrated efficacy.⁸⁻¹⁰ Despite this progress, not all patients respond to or tolerate therapy, and significant unmet clinical needs remain.

IL-17A and its requisite receptor are expressed in synovial tissues and as such the IL-17 pathway is proposed to contribute to PsA pathogenesis.¹¹⁻¹⁵ IL-17A can mediate a variety of effector biologic functions that can result in joint and enthesial inflammation, damage, and tissue remodeling.¹⁶

Secukinumab, a human, monoclonal antibody that inhibits the effector function of IL-17A, has been shown to be superior to placebo and etanercept in improving psoriasis signs and symptoms.¹⁷ In the recent phase 3 FUTURE 1 study conducted in 606 PsA patients, intravenous (iv) loading with secukinumab followed by subcutaneous (sc) maintenance dosing significantly improved key clinical domains of disease versus placebo, including signs and symptoms, radiographic disease progression, physical functioning, and quality of life.¹⁸

We report the primary results from FUTURE 2 (NCT01752634), an ongoing phase 3 trial assessing the efficacy and safety of subcutaneous loading and maintenance dosing of secukinumab in PsA.

Methods

Study design

This randomized, double-blind, placebo-controlled phase 3 trial was conducted at 76 centers across Asia, Australia, Europe, and North America. All centers received approval from

independent ethics committees or institutional review boards. The study was carried out in accordance with the principles of the Declaration of Helsinki. Changes to the protocol after commencement of the study are summarized in the supplementary appendix. The study protocol is available from the sponsor.

Patients

Patients were aged ≥ 18 years, fulfilled the CIASsification criteria for Psoriatic ARthritis (CASPAR) and had active disease, defined as ≥ 3 tender joints and ≥ 3 swollen joints, despite previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, and/or anti-TNF agents. Concomitant oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and methotrexate (≤ 25 mg/week) were permitted provided the dose was stable for ≥ 2 and ≥ 4 weeks prior to randomization, respectively. Patients who had previously used up to 3 anti-TNF agents could enroll if they had experienced an inadequate response or stopped treatment due to safety or tolerability reasons (anti-TNF-IR). Anti-TNF therapy required a washout period of 4–10 weeks prior to randomization, depending upon the agent's half-life. Key exclusion criteria included previous use of any biologic other than anti-TNF agents; active inflammatory diseases other than PsA; active infection in the 2 weeks prior to randomization, or a history of ongoing, chronic, or recurrent infections; history of malignancy (excluding basal cell carcinoma or actinic keratosis, in-situ cervical cancer or non-invasive malignant colon polyps); pregnancy.

Patients provided written informed consent prior to study-related procedures being undertaken.

Randomization and masking

After a 4-week screening period, patients were randomized (1:1:1:1) to receive sc secukinumab 300mg, 150mg, or 75mg, or placebo, weekly from baseline to week 4, and every 4 weeks thereafter. At week 16, patients were classified as responders ($\geq 20\%$ improvement from baseline in tender and swollen joint counts) or non-responders. Placebo-

treated patients were re-randomized (1:1) to receive subcutaneous secukinumab 300mg or 150mg every 4 weeks from week 16 (non-responders) or 24 (responders).

Randomization was performed using an interactive voice/web response system that assigned patients to randomization numbers identifying assigned treatments and unique medication numbers for the packages of study treatment to be prepared. Randomization was stratified according to prior anti-TNF therapy use, with patients being anti-TNF-naïve (planned enrolment approximately 60%) or anti-TNF-IR. Medication numbers were accessible only to the unblinded pharmacist or other qualified personnel at each site. Doses were prepared from open-label secukinumab or placebo vials by the independent unblinded pharmacist or other qualified person and provided in identical syringes of reconstituted secukinumab/placebo solutions. Data analysts remained blinded until the week 24 analysis.

Procedures

Additional information on the assessments undertaken during the trial is provided in the supplementary appendix. Key efficacy, safety, tolerability, and biochemical assessments were conducted at screening, baseline, weeks 24 and 52, and timepoints in between. Secukinumab immunogenicity was assessed via a MesoScale Discovery bridging assay¹⁹ using blood samples collected at baseline, and at weeks 24 and 52.

Outcomes

The primary endpoint was the proportion of patients achieving an ACR20 response at week 24, defined as $\geq 20\%$ improvement from baseline in: the number of tender and swollen joints and at least three of the following five domains: patient's global assessment; physician's global assessment; pain; disability; and an acute-phase reactant.²⁰

Secondary endpoints at week 24 were: $\geq 75\%$ and $\geq 90\%$ improvement in Psoriasis Area-and-Severity Index (PASI75 and PASI90)²¹; change from baseline in 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP)²²; change from baseline in Medical Outcomes

Study 36-item Short-Form Health Survey v2 physical component summary score (SF36-PCS)²³; change from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) score²⁴; ACR50 response; resolution of dactylitis and enthesitis; and overall safety and tolerability. PASI75 and PASI90 responses were assessed in patients with $\geq 3\%$ body surface area (BSA) affected by psoriasis at baseline. Resolution of dactylitis and enthesitis was assessed in patients with these characteristics at baseline, with pooled data (all secukinumab groups combined) used for analysis.

Pre-specified exploratory endpoints included: ACR70 responses; presence of dactylitis and enthesitis in each treatment group (unpooled data); primary and secondary efficacy assessments at week 52; and subgroup analyses according to prior anti-TNF use. Analysis of secukinumab efficacy with and without concomitant methotrexate therapy was conducted post-hoc.

Safety analyses assessed adverse events (AEs), serious AEs (SAEs), and routine laboratory values. Biochemical investigations were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.²⁵

Statistical analyses

A sample size of 100 patients per group was estimated to provide approximately 92% power to detect a treatment difference of 26% for the primary endpoint of ACR20 response at week 24 by Fisher's exact test, and approximately 80% power for secondary endpoints. The expected treatment difference of 26% for the primary endpoint was based on an expected overall placebo response of 21% (weighted average of placebo data in anti-TNF-naïve [25%] and anti-TNF-IR [15%] patients from PSUMMIT I and II^{8,9}) and an expected overall secukinumab response of 47% (weighted average of expected response in anti-TNF-naïve [55%] and anti-TNF-IR [35%] patients). Averages were weighted based on planned enrolment of approximately 40% anti-TNF-IR patients.

The primary and secondary and relevant pre-specified exploratory endpoints were analyzed according to the pre-specified analysis plan using SAS software, Version 9.3.²⁶ Safety data are presented at week 16, when all patients remained in the originally randomized groups, and across the entire study period; efficacy was assessed at week 24 (primary analysis) and up to week 52. A sequential hierarchical testing method was used to maintain the family-wise type I error rate at 5% across the primary and ranked secondary endpoints. If the primary efficacy analysis was statistically significant, secondary analyses were completed in the following sequence: ACR20; PASI75; PASI90; DAS28-CRP; SF36-PCS; HAQ-DI; ACR50; dactylitis (pooled data across doses); and enthesitis (pooled data across doses) (see Supplementary Figure S1 for further details).

For week 24 analyses of binary variables, patients who switched from placebo to secukinumab at week 16 due to non-response were imputed as non-responders at week 24 (early escape penalty). Week 16 non-responders in secukinumab groups were also considered non-responders at week 24. Patients with missing data or who had prematurely discontinued were imputed as non-responders. Odds ratios (ORs), 95% confidence intervals (CIs) and p-values were computed for comparisons of secukinumab regimens versus placebo regimen from a logistic regression model with treatment and prior anti-TNF use as factors and baseline weight as a covariate. Baseline PASI score was a covariate in PASI75 and PASI90 analyses.

Analyses of continuous variables at week 24 used a mixed-effects model with treatment regimen, analysis visit, and prior anti-TNF use as factors, and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline score by analysis visit were interaction terms, and an unstructured covariance structure was assumed.

Inferential analyses (with imputation) and descriptive summaries (observed data) were performed on primary and secondary endpoints from week 28 onwards. In the inferential analysis of binary variables over this period, patients who withdrew from the study were considered non-responders from the time of withdrawal, without the penalty for early escape

that was applied in the primary analysis. Efficacy analyses from week 28 onwards include only patients originally randomized to secukinumab.

Safety endpoints were evaluated for all patients who received at least one dose of study drug and are summarized descriptively. A data monitoring committee reviewed unblinded safety data at regular intervals. Potential major adverse cardiac events were adjudicated by an independent expert committee.

This study is registered with ClinicalTrials.gov (NCT01752634).

Role of the funding source

The study was designed by representatives from the scientific steering committee and the funding source, Novartis Pharma AG. Data were collected according to Good Clinical Practice guidelines by the study investigators. Data and statistical analyses were performed by statisticians employed by the funding source. All authors had access to the study data and participated in the decision to publish. The corresponding author, with approval from coauthors, made the final decision to submit for publication.

Results

Between April 14 and November 25, 2013, 397 patients were randomly assigned to receive secukinumab 300mg (n=100), 150mg (n=100), 75mg (n=99), or placebo (n=98), 373 (94.0%) of whom completed week 24 (figure 1). No patients were excluded from efficacy and safety analyses.

Baseline demographics, disease characteristics, and prior/concomitant medication usage were similar across study groups, except for imbalances in baseline PASI score and the proportion of female patients, patients with psoriasis affecting $\geq 3\%$ BSA, and patients with

dactylitis or enthesitis (table 1). Most (65%) patients were anti-TNF-naïve and 47% were receiving concomitant methotrexate.

The primary endpoint was met with all secukinumab doses. ACR20 response rates at week 24 were significantly higher in the secukinumab 300mg (54/100 [54.0%]; $p < 0.0001$), 150mg (51/100 [51.0%]; $p < 0.0001$), and 75mg (29/99 [29.3%]; $p = 0.0399$) groups versus placebo (15/98 [15.3%]) (figure 2; table 2).

Assessing subsequent secondary endpoints in hierarchical order, PASI75 and PASI90 response rates, and mean changes from baseline in DAS28-CRP and SF36-PCS were all significantly higher with secukinumab 300mg and 150mg versus placebo at week 24.

Secukinumab 300mg significantly improved HAQ-DI (table 2) and ACR50 (figure 2).

Secukinumab 75mg did not significantly improve PASI75 response versus placebo; thus, subsequent endpoints in the hierarchy were not met with this dose. Improvements in dactylitis and enthesitis with secukinumab (pooled) versus placebo were not statistically significant using the hierarchical analysis since the testing strategy required all other endpoints on all doses to be significant in order to test, and this requirement was not met. The proportions of patients whose dactylitis and enthesitis resolved at week 24 in each individual treatment group are in supplementary table S1.

In pre-specified exploratory analyses, ACR70 response was achieved by 20/100 (20.0%), 21/100 (21.0%), and 6/99 (6.1%) patients in the secukinumab 300 mg, 150 mg, and 75 mg groups, respectively, compared with 1/98 (1.0%) patient in the placebo group. ACR and PASI response rates were higher with secukinumab than placebo in both anti-TNF-naïve and anti-TNF-IR patients, with the magnitude of response being higher in the anti-TNF-naïve population (pre-specified exploratory analysis; table 3). The interaction between treatment and anti-TNF-status was tested and was not statistically significant ($p = 0.24$); however, clinically meaningful differences were observed between the effect sizes for the 300mg and 150mg doses in anti-TNF-IR patients. In post-hoc analyses, improvements in

ACR response rates were observed with secukinumab versus placebo at week 24, with and without concomitant methotrexate use (supplementary table S2).

At week 52, 335/397 patients (84.4%) remained in the study. Clinical responses observed with secukinumab 300 mg and 150 mg across the PsA domains assessed at week 24 were maintained through 52 weeks of therapy in patients initially randomized to these treatments (supplementary table S3). Using a conservative estimate of efficacy with missing values imputed as non-response, ACR20/50/70 response rates at week 52 were 64.0/44.0/24.0%, 64.0/39.0/20.0%, and 50.5/30.3/16.2% in patients initially randomized to secukinumab 300mg, 150mg, and 75mg, respectively (figure 2; supplementary table S3). Corresponding response rates with observed data were 72.7/50.0/27.3%, 72.7/44.3/22.7%, and 66.7/40.0/21.3%, respectively.

No deaths were reported during the study. No reports of suicide or suicidal ideation were reported in secukinumab-treated patients. The incidence of AEs during the placebo-controlled period was similar across study groups, except for a slightly higher incidence of SAEs in the secukinumab 300mg and 75mg groups (table 4). Over the entire treatment period (mean exposure: secukinumab, 411.7 days; placebo, 130.6 days), the exposure-adjusted SAE rates were 6.4, 5.1, and 11.2 per 100 patient-years in patients who received at least one dose of secukinumab 300mg, 150mg, and 75mg, respectively, compared with 8.6 amongst placebo-treated patients (table 4). Reported SAEs are listed in supplementary table S4. Exposure-adjusted incidence rates of infections and infestations were 78.7, 86.7, and 63.7 per 100 patient-years in patients who received secukinumab 300mg, 150mg, and 75mg, respectively, compared with 108.0 amongst placebo-treated patients. Upper respiratory tract infections and nasopharyngitis were the most common infections, occurring at similar rates across secukinumab treatment groups. No active tuberculosis cases were reported.

Candida infections were reported in 11 patients, all on secukinumab: six oral candidiasis cases (reported in two, three, and one patient in the 300mg, 150mg, and 75mg groups,

respectively); four vulvovaginal candidiasis (one in the 300mg group and three in the 150mg group), one esophageal candidiasis (300mg group), and one *Candida* infection (300mg group). One patient experienced concurrent vulvovaginal and oral candidiasis (150mg group). These events were considered by the investigators to be mild or moderate, resolved spontaneously or with oral therapy, and did not lead to study withdrawal.

There were three cases of squamous cell carcinoma with secukinumab (two in the 75mg group and one in the 150mg group). Both cases in the 75mg group resulted in discontinuation of study treatment. A myocardial infarction was recorded in a patient with a history of sinus tachycardia and ongoing hypertension and hyperlipidemia who received secukinumab 75mg. The patient continued in the study. Crohn's disease was not reported as an AE in any patient. One patient receiving secukinumab 300mg experienced hemorrhagic diarrhea, which resolved. The patient continued in the study. There were two cases of ulcerative colitis (one in the 300mg group which resolved, and one in the 150mg group which did not resolve). Both patients continued in the study. Transient CTCAE grade 3 neutropenia occurred in one patient (300mg group). No patients withdrew from the study due to neutropenia. Treatment-emergent (positive during study but negative at baseline) anti-secukinumab antibodies were detected in one patient originally randomized to placebo who switched to secukinumab 150mg at week 24. There was no loss of efficacy or immunogenicity-related AEs reported in this patient.

Discussion

In this phase 3 trial, sc administration of the anti-IL-17A monoclonal antibody secukinumab significantly improved the signs and symptoms of PsA versus placebo. ACR20 response rates at week 24 were superior to placebo with all secukinumab groups. Additional efficacy outcomes at week 24 also showed significant benefits with secukinumab 300mg and 150mg versus placebo, but responses with secukinumab 75mg were lower and not significantly different from placebo in the hierarchical analysis. These results confirm and significantly

extend the findings of earlier studies with secukinumab in PsA.¹⁸ Consistent with the psoriasis phase 3 program,¹⁷ improvements in psoriasis symptoms in FUTURE 2 were greater with secukinumab 300mg than with 150mg.

While anti-TNF agents improve outcomes in PsA,³⁻⁷ many patients still experience inadequate disease control and/or are intolerant of these agents. Loss of response over time is also clinically problematic. Although responses were generally higher in the anti-TNF-naïve population, the clinical benefits of secukinumab were observed in both anti-TNF-naïve and anti-TNF-IR patients. Secukinumab may offer an additional treatment option for both populations.

The safety profile of secukinumab was consistent with earlier reports of secukinumab in PsA^{8,18} and psoriasis.¹⁷ The types and incidence of AEs with secukinumab were comparable with placebo at week 16, with no apparent relationship to dose. The rate of discontinuation due to AEs with secukinumab was low. There were no deaths in the study. *Candida* infections were more frequent on secukinumab than placebo. IL-17 is important to mucocutaneous defense against *Candida*²⁷ and continued vigilance regarding such infections will be required when assessing inhibitors of this pathway. Immunogenicity with secukinumab was low and was not associated with a loss of efficacy or immunogenicity-related AEs.

This study has several limitations. The pre-defined hierarchical testing procedure adequately protected the type I error rate and demonstrated the effectiveness of both the 300mg and 150mg secukinumab doses for the primary endpoint and multiple ranked secondary endpoints. The limitation of this procedure is that it is sensitive to the ordering of the endpoints and, as such, clinically relevant results fail to meet statistical significance if a preceding ranked endpoint was non-significant. Furthermore, it may not be practical or desirable to extend the statistical hierarchy to include every relevant endpoint in a multi-faceted disease such as PsA. This study did not include assessment of radiographic disease progression, but inhibition of radiographic progression has been demonstrated previously

with secukinumab.¹⁸ This trial was not designed to identify a difference between doses, or to examine differences in response according to prior anti-TNF use or concomitant methotrexate use. Finally, axial disease was not assessed in FUTURE 2.

In summary, treatment with secukinumab 300mg or 150mg sc provided significant and sustained improvements in key clinical domains of PsA, with a safety profile consistent with that seen in other studies with secukinumab. These data provide further evidence that IL-17A is an important cytokine in the pathogenesis of PsA, and suggest that secukinumab, by providing an alternative mechanism of action to current therapies, may be a useful future therapeutic option.

Panel: Research in context

Evidence before this study

We searched the PubMed database using the terms “psoriatic arthritis (PsA)”, “biologic”, and “interleukin-17 (IL-17)” for English language articles published up to April 2015 with no limitation or restriction for year of publication or article type. Increasing clinical and laboratory evidence has linked IL-17 to the pathogenesis of immune-mediated inflammatory diseases, such as psoriasis and PsA.^{12–15} Several studies, including large phase 3 studies with secukinumab, have demonstrated that inhibiting IL-17 improves signs and symptoms in patients with moderate to severe psoriasis,^{17,28,29} and secukinumab is approved for this indication. Recent clinical data have provided evidence for IL-17 inhibition being of therapeutic benefit in PsA. A trend towards improvement in clinical response, markers of inflammation, and quality of life measures was reported in a phase 2, proof-of-concept study evaluating intravenous administration of secukinumab in patients with PsA, although the study did not meet its primary endpoint of superior ACR20 response rates versus placebo at week 6.⁸ More recently, a phase 2 study has shown that inhibiting the IL-17 receptor improves PsA signs and symptoms.³⁰

Added value of this study

FUTURE 2 is the first large phase 3 study to demonstrate that inhibiting IL-17 with an sc dosing regimen provides significant improvements in important clinical domains of PsA, including joint and skin symptoms, physical function, and quality of life. Moreover, 52-week data from this study suggest that efficacy with secukinumab is sustained over extended periods of time. The safety profile of secukinumab in this study was similar to that reported in patients with moderate to severe psoriasis.

Implications of all the available evidence

Our findings build and expand upon previous reports of IL-17 having an important role in the pathogenesis of PsA and suggest that secukinumab may be a suitable alternative biological treatment in this disease setting.

Contributors

All authors were involved in the design of the study. Data collection was undertaken by the Study Investigators, including the following authors: IBM, BK. Analysis of the data was undertaken by the funding source, with all authors contributing to the interpretation of the data and preparation of the manuscript.

FUTURE 2 study investigators

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Kaszuba; Malgorzata Szymanska; Marina Stanislav; Olga Nesmeyanova; Natalia Vezikova; Olga Ershova; Nadezda Izmozherova; Eugeny Zotkin; Marianna Petrova; Alexander Kastanayan; Svetlana Yakupova; Alina Agafina; Pajjit Asavatanabodee; Parawee Suwannalai; Jerome Kerrane; Hasan Tahir; Bruce Kirkham; Iain McInnes; Christopher Edwards; Hector Chinoy; Helena Marzo-Ortega; Arvind Kaul; Thomas Sheeran; Gavin Clunie; Joy Schechtman; Norman Gaylis; Jeffrey Kaine; Jeffrey Lawson; Hisham El-Kadi; Kathleen Flint; Alan Kivitz; Melvin Churchhill; David Sikes; Mitchell Lowenstein; Elias Halpert; Mary Abdulky; William Palmer; Christine Coddling; Clarence Legerton III; Atul Singhal; Prashanth Sunkureddi; William Gough; Seth Forman; Jane Box; Mohamed Khan; Elizabeth Barranco.

Acknowledgments

The authors would like to thank: the patients who participated in the study, the study investigators, and John Gallagher, a medical consultant for Novartis Pharma AG. The initial manuscript draft was written by Chris Strutynskyj-Stannard, with assistance from Joanne Swainston and Jessica Breen, medical writers from Seren Communications, an Ashfield Company, part of UDG Healthcare plc, the funding for which was provided by Novartis Pharma AG.

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Figures and tables

Figure 1: Patient disposition and flow through the trial from screening to week 52

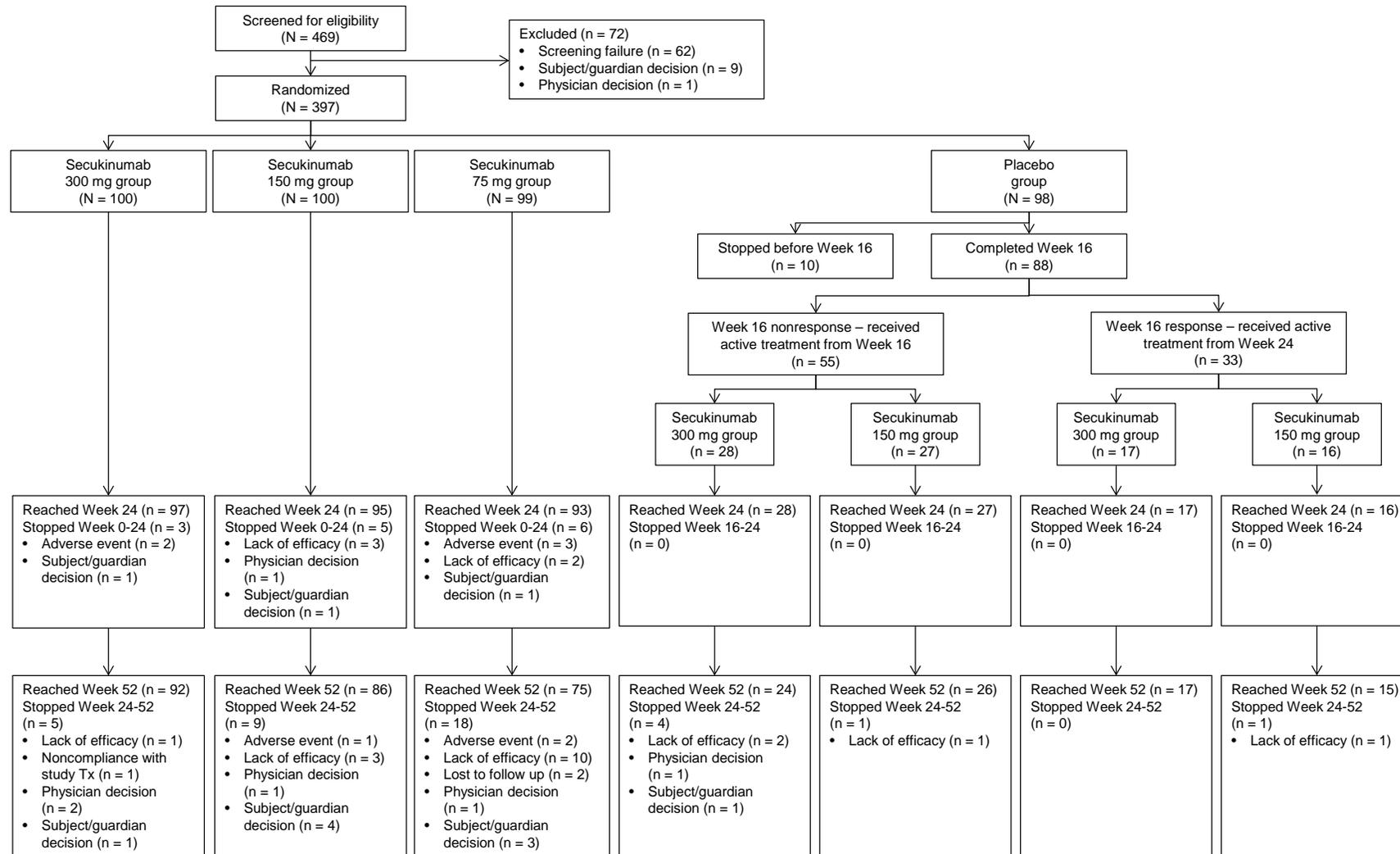
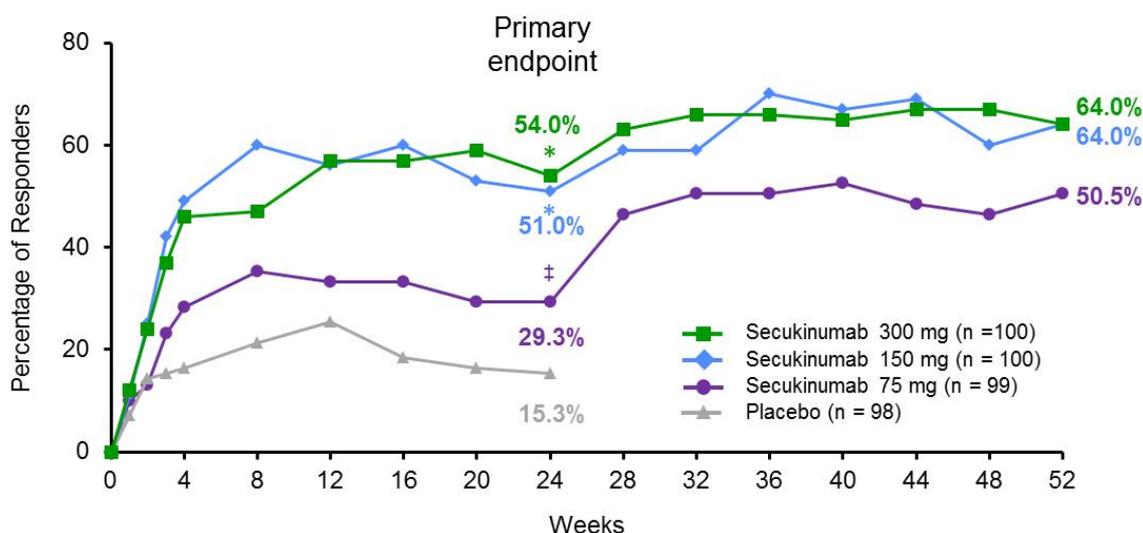


Figure 2: ACR20 and ACR50 response rates over time from baseline to week 52

Missing data were imputed as non-response through week 52.

*p<0.0001; §p<0.01; ‡p<0.05 vs. placebo. P-values at week 24 were analyzed as part of the statistical hierarchy and are adjusted for multiplicity of testing. Response rates over time are presented for patients as per the treatment group at randomization.

ACR20



ACR50

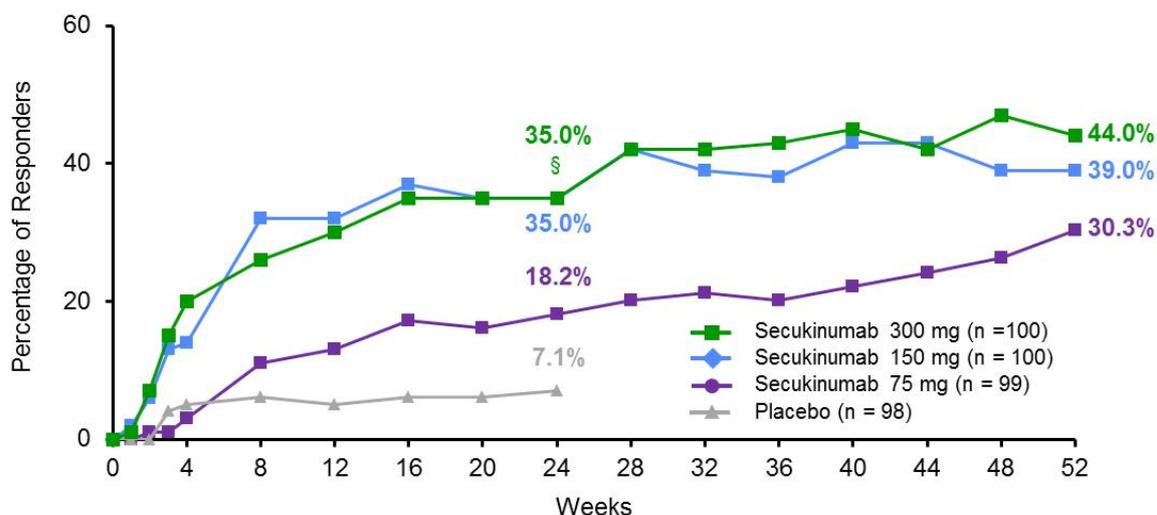


Table 1: Baseline characteristics of patients assigned to each treatment group

Demographic variable	Secukinumab 300 mg (n=100)	Secukinumab 150 mg (n=100)	Secukinumab 75 mg (n=99)	Placebo (n=98)
Age in years, mean (SD)	46.9 (12.6)	46.5 (11.7)	48.6 (11.4)	49.9 (12.5)
Female, n (%)	49 (49.0)	45 (45.0)	52 (52.5)	59 (60.2)
Race, n (%)				
White	96 (96.0)	90 (90.0)	90 (90.9)	94 (95.9)
Black	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (2.0)	6 (6.0)	5 (5.1)	1 (1.0)
Unknown	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Other	1 (1.0)	4 (4.0)	3 (3.0)	3 (3.1)
Weight in kg, mean (SD)	85.4 (18.4)	91.2 (19.8)	85.6 (20.6)	86.2 (19.8)
Number of prior anti-TNF therapies for PsA, n (%)				
0	67 (67.0)	63 (63.0)	65 (65.7)	63 (64.3)
1	16 (16.0)	26 (26.0)	21 (21.2)	16 (16.3)
2 or 3	17 (17.0)	11 (11.0)	13 (13.1)	19 (19.4)
Methotrexate use at randomization, n (%)	44 (44.0)	44 (44.0)	47 (47.5)	50 (51.0)
Systemic glucocorticoid use at randomization, n (%)	18 (18.0)	23 (23.0)	19 (19.2)	21 (21.4)
Patients with specific disease characteristics, n (%) unless stated				
Psoriasis BSA \geq 3%	41 (41.0)	58 (58.0)	50 (50.5)	43 (43.9)
PASI \leq 10	21 (51.2)	25 (43.1)	28 (56.0)	23 (53.5)
PASI score >10	20 (48.8)	33 (56.9)	22 (44.0)	20 (46.5)
Dactylitis	46 (46.0)	32 (32.0)	33 (33.3)	27 (27.6)
Dactylitis count, mean (SD)	3.6 (3.5)	4.5 (5.1)	3.0 (3.6)	2.7 (2.2)
Enthesitis	56 (56.0)	64 (64.0)	68 (68.7)	65 (66.3)
Enthesitis count, mean (SD)	2.8 (1.7)	3.2 (1.6)	3.2 (1.7)	3.1 (1.7)

Baseline disease and quality of life scores, mean (SD)

TJC (78 joints)	20.2 (13.3)	24.1 (19.4)	22.2 (16.3)	23.4 (19.0)
SJC (76 joints)	11.2 (7.8)	11.9 (10.1)	10.8 (9.2)	12.1 (10.7)
DAS28-CRP	4.8 (1.0)	4.9 (1.1)	4.7 (1.0)	4.7 (1.0)
PASI	11.9 (8.4)	16.2 (14.3)	12.1 (10.2)	11.6 (8.3)
Physician's global assessment (VAS)	55.0 (14.7)	56.7 (16.6)	59.0 (17.9)	55.0 (16.0)
HAQ-DI	1.3 (0.6)	1.2 (0.6)	1.2 (0.6)	1.2 (0.7)
Pain (VAS)	57.7 (19.0)	58.9 (19.8)	56.7 (21.1)	55.4 (22.1)
Patient's global assessment (VAS)	60.7 (18.9)	62.0 (19.5)	59.0 (19.1)	57.6 (19.8)
SF36-PCS	36.9 (8.0)	36.2 (8.1)	36.2 (8.1)	37.4 (8.8)

Mean (SD) reported for those patients with these symptoms at baseline.

Mean PASI score is from those patients with $\geq 3\%$ BSA psoriasis

BSA = body surface area; DAS28-CRP = disease activity score 28 based on C-reactive protein; HAQ-DI = health assessment questionnaire disability index; PASI = psoriasis area and severity index; PsA = psoriatic arthritis; SD = standard deviation; SF36-PCS = short form 36 physical component summary; SJC = swollen joint count; TJC = tender joint count; TNF = tumor necrosis factor; VAS = visual analog scale.

Table 2: Efficacy of secukinumab versus placebo at week 24 across pre-specified primary and secondary endpoints

Efficacy endpoint	Secukinumab 300 mg (n=100)			Secukinumab 150 mg (n=100)			Secukinumab 75 mg (n=99)			Placebo (n=98)
	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	Value ^a
ACR20 response	54 (54.0%)	OR 6.81 (3.42–13.56)	<0.0001	51 (51.0%)	OR 6.52 (3.25–13.08)	<0.0001	29 (29.3%)	OR 2.32 (1.14–4.73)	0.0399	15 (15.3%)
PASI75 response	26/41 (63.4%)	OR 9.48 (3.33–27.0)	<0.0001	28/58 (48.3%)	OR 5.70 (2.12–15.34)	0.0017	14/50 (28.0%)	OR 2.07 (0.74–5.81)	0.1650	7/43 (16.3%)
PASI90 response	20/41 (48.8%)	OR 10.74 (3.13–36.84)	0.0005	19/58 (32.8%)	OR 6.36 (1.89–21.47)	0.0057	6/50 (12.0%)	OR 1.38 (0.36–5.36)	0.6421	4/43 (9.3%)
DAS28-CRP, LS mean change from baseline	-1.61 (0.11)	Δ -0.65 ^b (-1.02, -0.29)	0.0013	-1.58 (0.11)	Δ -0.62 (-0.98, -0.26)	0.0057	-1.12 (0.11)	Δ -0.16 (-0.53, 0.20)	0.6421	-0.96 (0.15)
SF36-PCS, LS mean change from baseline	7.25 (0.74)	Δ 5.30 ^b (2.91–7.69)	0.0013	6.39 (0.73)	Δ 4.44 (2.05–6.83)	0.0057	4.38 (0.75)	Δ 2.42 (0.02–4.83)	0.6421	1.95 (0.97)
HAQ-DI, LS mean change from baseline	-0.56 (0.05)	Δ -0.25 ^b (-0.40, -0.10)	0.0040	-0.48 (0.05)	Δ -0.17 (-0.32, -0.02)	0.0555	-0.32 (0.05)	Δ -0.01 (-0.16, 0.15)	0.9195	-0.31 (0.06)

ACR50 response	35 (35.0%)	OR 7.15 (2.97– 17.22)	0.0040	35 (35.0%)	OR 7.54 (3.11–18.25)	0.0555	18 (18.2%)	OR 2.91 (1.15–7.36)	0.9195	7 (7.1%)
Resolution of dactylitis [†]	52/111 (46.8%) [pooled data; p=0.9195]									4/27
	OR (95% CI) for presence of dactylitis vs placebo: 0.23 (0.07–0.72)									(14.8%)
Resolution of enthesitis [†]	76/188 (40.4%) [pooled data; p=0.9195]									14/65
	OR (95% CI) for presence of enthesitis vs placebo: 0.29 (0.13–0.65)									(21.5%)

^aData are n (%), n/N (%), or least-square mean (standard error).

Δ, Difference in LS mean change vs. placebo (95% CI).

OR and 95% CI are from a logistic regression model with treatment and randomization stratum (anti-TNF-naive or anti-TNF-IR) as factors and baseline weight as a covariate; OR >1 favors secukinumab.

LS mean and 95% CI are from a mixed model repeated measures with treatment regimen, analysis visit and randomization stratum (anti-TNF status -naive or -IR) as factors, weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure.

All cited p-values are versus placebo and are adjusted for multiplicity.

PASI responses were assessed in patients with ≥3% BSA affected by psoriasis at baseline.

Resolution of dactylitis and enthesitis was assessed only in those patients with these symptoms at baseline. Improvements in dactylitis and enthesitis with secukinumab (pooled) versus placebo were not statistically significant using the hierarchical analysis since the testing strategy required all other endpoints on all doses to be significant in order to test, and this requirement was not met.

ACR = American College of Rheumatology; BSA = body surface area; CI, confidence interval; DAS28-CRP = disease activity score 28 based on C-reactive protein; HAQ-DI = health assessment questionnaire disability index; LS, least-square; OR, odds ratio; PASI = psoriasis area and severity index; SE, standard error; SF36-PCS = short form 36 physical component summary.

Table 3: Efficacy of secukinumab at week 24 in anti-TNF-naïve and anti-TNF-IR patients

Efficacy endpoint ^a	Secukinumab 300 mg			Secukinumab 150 mg			Secukinumab 150 mg			Placebo
	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	Value ^a	Effect size vs. placebo (95% CI)	p-value vs. placebo	
Anti-TNF-naïve patients										
ACR20 response	39/67 (58.2)	OR 7.77 (3.36–17.98)	0.0040	40/63 (63.5)	OR 9.99 (4.22–23.66)	<0.0001	24/65 (36.9)	OR 3.17 (1.36–7.40)	0.0075	10/63 (15.9)
ACR50 response	26/67 (38.8)	OR 9.72 (3.14–30.09)	<0.0001	28/63 (44.4)	OR 12.54 (4.03–39.05)	<0.0001	16/65 (24.6)	OR 4.90 (1.53–15.64)	0.0074	4/63 (6.3)
ACR70 response	15/67 (22.4)	OR 9.72 (3.14–30.09)	0.0003	17/63 (27.0)		<0.0001	4/65 (6.2)		0.3654	1/63 (1.6)
PASI75 response ^b	19/30 (63.3)	OR 7.96 (2.42–	0.0006	20/36 (55.6)	OR 6.33 (1.99–20.15)	0.0018	10/33 (30.3)	OR 1.94 (0.59–6.34)	0.2729	6/31 (19.4)
PASI90 response ^b	16/30 (53.3)	OR 13.11 (3.09–55.59)	0.0005	14/36 (38.9)	OR 8.09 (1.92–34.09)	0.0044	4/33 (12.1)	OR 1.40 (0.28–7.02)	0.6825	3/31 (9.7)
Anti-TNF-IR patients										
ACR20 response	15/33 (45.5)	OR 4.97 (1.05–18.26)	0.0077	11/37 (29.7)	OR 2.55 (0.78–8.32)	0.1216	5/34 (14.7)	OR 1.03 (0.27–3.95)	0.9639	5/35 (14.3)
ACR50 response	9/33 (27.3)	OR 4.37 (3.14–30.09)	0.0431	7/37 (18.9)	OR 2.39 (0.56–10.15)	0.2374	2/34 (5.9)	OR 0.69 (0.11–4.42)	0.6941	3/35 (8.6)

ACR70 response	5/33 (15.2)		0.0228	4/37 (10.8)		0.1151	2/34 (5.9)		0.2391	0/35 (0.0)
PASI75 response ^b	7/11 (63.6)	OR 19.29 (1.77– 210.18)	0.0152	8/22 (36.4)	OR 6.17 (0.66– 57.30)	0.1094	4/17 (23.5)	OR 3.46 (0.33– 36.06)	0.2986	1/12 (8.3)
PASI90 response ^b	4/11 (36.4)	OR 6.43 (0.58– 70.74)	0.1282	5/22 (22.7)	OR 3.50 (0.35– 34.91)	0.2859	2/17 (11.8)	OR 1.37 (0.11– 17.30)	0.8098	1/12 (8.3)

Data are n (%), n/N (%).

^aMissing data were imputed as non-response. *P*-values not adjusted for multiplicity of testing.

^bPASI responses were assessed in patients with ≥3% BSA affected by psoriasis at baseline.

ACR = American College of Rheumatology; BSA = body surface area; PASI = psoriasis area and severity index; TNF = tumor necrosis factor.

Table 4: Safety and tolerability profile of secukinumab through week 16 (placebo-controlled period) and across the entire treatment period*

Variable	Through week 16 (placebo-controlled period)				Entire treatment period*			
	Secukinumab 300 mg (n=100)	Secukinumab 150 mg (n=100)	Secukinumab 75 mg (n=99)	Placebo (n=98)	Any secukinumab 300 mg (n=145)	Any secukinumab 150 mg (n=143)	Secukinumab 75 mg (n=99)	Placebo (n=98)
	Number of patients with event (%)				Number of patients with event (number of events per 100 patient-years)			
Any AE	56 (56.0)	57 (57.0)	48 (48.5)	57 (58.2)	113 (189.1)	117 (209.0)	77 (175.3)	61 (323.5)
Serious AE	5 (5.0)	1 (1.0)	4 (4.0)	2 (2.0)	10 (6.4)	8 (5.1)	12 (11.2)	3 (8.6)
Death	0	0	0	0	0	0	0	0
Discontinuation of study treatment due to any AE	2 (2.0)	0	2 (2.0)	3 (3.1)	3 (2.1)	4 (2.8)	4 (4.0)	4 (4.1)
Infection or infestation	29 (29.0)	30 (30.0)	23 (23.2)	30 (30.6)	78 (78.7)	82 (86.7)	48 (63.7)	30 (108.0)
Common AEs [†]								
Upper respiratory tract infection	4 (4.0)	8 (8.0)	10 (10.1)	7 (7.1)	26 (17.9)	25 (17.6)	21 (21.8)	7 (20.7)
Nasopharyngitis	6 (6.0)	4 (4.0)	6 (6.1)	8 (8.2)	20 (13.5)	18 (12.3)	11 (10.5)	8 (24.2)
Diarrhea	2 (2.0)	2 (2.0)	3 (3.0)	3 (3.1)	10 (6.3)	8 (5.1)	8 (7.4)	3 (8.8)
Headache	7 (7.0)	4 (4.0)	2 (2.0)	4 (4.1)	9 (5.9)	10 (6.5)	5 (4.6)	5 (14.9)
Nausea	3 (3.0)	4 (4.0)	4 (4.0)	4 (4.1)	7 (4.5)	8 (5.2)	6 (5.6)	4 (11.9)
Sinusitis	1 (1.0)	2 (2.0)	0	1 (1.0)	10 (6.5)	6 (3.8)	5 (4.6)	1 (2.9)
Psoriatic arthropathy	0	3 (3.0)	1 (1.0)	2 (2.0)	5 (3.1)	10 (6.5)	6 (5.5)	2 (5.8)
Urinary tract infection	2 (2.0)	4 (4.0)	1 (1.0)	4 (4.1)	6 (3.8)	6 (3.9)	4 (3.6)	4 (11.8)
Hematuria	2 (2.0)	3 (3.0)	1 (1.0)	1 (1.0)	2 (1.3)	4 (2.5)	3 (2.7)	1 (2.9)
Vomiting	2 (2.0)	2 (2.0)	2 (2.0)	1 (1.0)	3 (1.9)	4 (2.5)	4 (3.6)	2 (5.8)

*The entire treatment period was defined as the period from baseline up to the week 52 visit of the last patient enrolled in the study.

‡Exposure-adjusted incidence rates were not calculated for discontinuations due to AEs. Percentages are shown in parentheses.

¶The most common AEs are expressed according to the preferred term in the *Medical Dictionary for Regulatory Activities*, and occurred in $\geq 2.0\%$ of patients in the pooled secukinumab group through week 16 or at an incidence rate of ≥ 5.0 per 100 patient-years in the pooled secukinumab group during the entire treatment period.

AE = adverse event; SD = standard deviation.