



Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials

Alexa B Kimball, Gregor B E Jemec, Afsaneh Alavi, Ziad Reguiai, Alice B Gottlieb, Falk G Bechara, Carle Paul, Evangelos J Giamarellos Bourboulis, Axel P Villani, Andreas Schwinn, Franziska Rueff, Larisha Pillay Ramaya, Adam Reich, Ines Lobo, Rodney Sinclair, Thierry Passeron, Antonio Martorell, Pedro Mendes-Bastos, Georgios Kokolakis, Pierre-Andre Becherel, Magdalena B Wozniak, Angela Llobet Martinez, Xiaoling Wei, Lorenz Uhlmann, Anna Passera, Deborah Keefe, Ruvie Martin, Clarice Field, Li Chen, Marc Vandemeulebroecke, Shoba Ravichandran, Elisa Muscianisi

Summary

Background Few therapeutic options are available for patients with moderate-to-severe hidradenitis suppurativa. We aimed to assess the efficacy of secukinumab in patients with moderate-to-severe hidradenitis suppurativa in two randomised trials.

Methods SUNSHINE and SUNRISE were identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials done in 219 primary sites in 40 countries. Patients aged 18 years old or older with the capacity to provide written informed consent and with moderate-to-severe hidradenitis suppurativa (defined as a total of ≥ 5 inflammatory lesions affecting ≥ 2 distinct anatomical areas) for at least 1 year were eligible for inclusion. Included patients also agreed to daily use of topical over-the-counter antiseptics on the areas affected by hidradenitis suppurativa lesions while on study treatment. Patients were excluded if they had 20 or more fistulae at baseline, had ongoing active conditions requiring treatment with prohibited medication (eg, systemic biological immunomodulating treatment, live vaccines, or other investigational treatments), or met other exclusion criteria. In both trials, patients were randomly assigned (1:1:1) by means of interactive response technology to receive subcutaneous secukinumab 300 mg every 2 weeks, subcutaneous secukinumab 300 mg every 4 weeks, or subcutaneous placebo all via a 2 mL prefilled syringe in a double-dummy method as per treatment assignment. The primary endpoint was the proportion of patients with a hidradenitis suppurativa clinical response, defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline, at week 16, assessed in the overall population. Hidradenitis suppurativa clinical response was calculated based on the number of abscesses, inflammatory nodules, draining fistulae, total fistulae, and other lesions in the hidradenitis suppurativa affected areas. Safety was assessed by evaluating the presence of adverse events and serious adverse events according to common terminology criteria for adverse events, which were coded using Medical Dictionary for Regulatory Activities terminology. Both the SUNSHINE, NCT03713619, and SUNRISE, NCT03713632, trials are registered with ClinicalTrials.gov.

Findings Between Jan 31, 2019, and June 7, 2021, 676 patients were screened for inclusion in the SUNSHINE trial, of whom 541 (80%; 304 [56%] women and 237 [44%] men; mean age 36.1 years [SD 11.7]) were included in the analysis (181 [33%] in the secukinumab every 2 weeks group, 180 [33%] in the secukinumab every 4 weeks group, and 180 [33%] in the placebo group). Between the same recruitment dates, 687 patients were screened for inclusion in the SUNRISE trial, of whom 543 (79%; 306 [56%] women and 237 [44%] men; mean age 36.3 [11.4] years) were included in the analysis (180 [33%] in the secukinumab every 2 weeks group, 180 [33%] in the secukinumab every 4 weeks group, and 183 [34%] in the placebo group). In the SUNSHINE trial, significantly more patients in the secukinumab every 2 weeks group had a hidradenitis suppurativa clinical response (rounded average number of patients with response in 100 imputations, 81.5 [45%] of 181 patients) compared with the placebo group (60.7 [34%] of 180 patients; odds ratio 1.8 [95% CI 1.1–2.7]; $p=0.0070$). However, there was no significant difference between the number of patients in the secukinumab every 4 weeks group (75.2 [42%] of 180 patients) and the placebo group (1.5 [1.0–2.3]; $p=0.042$). Compared with the placebo group (57.1 [31%] of 183 patients), significantly more patients in the secukinumab every 2 weeks group (76.2 [42%] of 180 patients; 1.6 [1.1–2.6]; $p=0.015$) and the secukinumab every 4 weeks group (83.1 [46%] of 180 patients; 1.9 [1.2–3.0]; $p=0.0022$) had a hidradenitis suppurativa clinical response in the SUNRISE trial. Patient responses were sustained up to the end of the trials at week 52. The most common adverse event by preferred term up to week 16 was headache in both the SUNSHINE (17 [9%] patients in the secukinumab every 2 weeks group, 20 [11%] in the secukinumab every 4 weeks group, and 14 [8%] in the placebo group) and SUNRISE (21 [12%] patients in the secukinumab every 2 weeks group, 17 [9%] in the secukinumab

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Harvard Medical School and Clinical Laboratory for Epidemiology and Applied Research in Skin, Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, MA, USA

(Prof A B Kimball MD); Department of Dermatology, Zealand University Hospital, Roskilde, Denmark

(Prof G B E Jemec DMSc); Department of Dermatology, Mayo Clinic, Rochester, MN, USA (Prof A Alavi MD);

Dermatology Department, Polyclinique Courlancy-Bezannes, Reims, France

(Z Reguiai MD); Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

(Prof A B Gottlieb MD); Department of Dermatology, Venereology and Allergology, Ruhr-University Bochum, Bochum, Germany

(Prof F G Bechara MD); Department of Dermatology, INSERM Infinity, Toulouse University, Toulouse, France

(Prof C Paul MD); 4th Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Athens, Greece (Prof E J Giamarellos Bourboulis MD);

Department of Dermatology, Edouard Herriot Hospital, Hospices Civils de Lyon, Claude Bernard Lyon I

University, Lyon, France (A P Villani MD); Beldio Research, Memmingen, Germany (A Schwinn MD); Department of Dermatology and Allergy, University Hospital Ludwig Maximilian University of Munich, Munich, Germany (F Rueff MD); Department of Dermatology, Global Clinical Trials, Pretoria, South Africa (L Pillay Ramaya MD); Department of Dermatology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszów, Poland (Prof A Reich MD); Centro Hospitalar do Porto, Hospital de Santo Antonio Porto, Porto, Portugal (I Lobo MD); Sinclair Dermatology, Melbourne, VIC, Australia (Prof R Sinclair MD); Department of Dermatology, Centre Hospitalier Universitaire de Nice, C3M, INSERM U1065, Côte d'Azur University, Nice, France (Prof T Passeron MD); Department of Dermatology, Hospital de Manises, Valencia, Spain (A Martorell PhD); Dermatology Centre, Hospital Companhia União Fabril Descobertas, Lisbon, Portugal (P Mendes-Bastos MD); Psoriasis Research and Treatment Center, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany (G Kokolakis MD); Department of Dermatology, Venereology and Allergology, Antony Private Hospital, Antony, France (P-A Becherel MD); Novartis Ireland, Dublin, Ireland (M B Wozniak PhD, C Field PhD); Novartis Pharma, Basel, Switzerland (A L Martinez MSc, L Uhlmann PhD, A Passera MSc, M Vandemeulebroecke PhD); Novartis Pharma Shanghai, Shanghai, China (X Wei MSc); Novartis Pharmaceuticals, East Hanover, NJ, USA (D Keefe MD, R Martin PhD, L Chen PhD, S Ravichandran MD, E Muscianisi MD)

Correspondence to: Prof Alexa B Kimball, Harvard Medical School and Clinical Laboratory for Epidemiology and Applied Research in Skin, Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, MA 02215, USA clears@bidmc.harvard.edu

every 4 weeks group, and 15 [8%] in the placebo group) trials. No study-related deaths were reported up to week 16. The safety profile of secukinumab in both trials was consistent with that previously reported, with no new or unexpected safety findings detected.

Interpretation When given every 2 weeks, secukinumab was clinically effective at rapidly improving signs and symptoms of hidradenitis suppurativa with a favourable safety profile and with sustained response up to 52 weeks of treatment.

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Introduction

Hidradenitis suppurativa is a chronic, disabling, recurrent, inflammatory skin disease characterised by superficial and deep dermal nodules, abscesses, draining fistulae, and disfiguring scarring. Hidradenitis suppurativa typically presents in the apocrine gland-bearing skin folds and follicles of the axillary, inguinal, gluteal, and perineal regions.^{1,2}

Despite a prevalence of around 1% in Europe and North America,³ hidradenitis suppurativa is under-recognised and undertreated, resulting in substantial delays in diagnosis and intervention.^{4–6} Moreover, hidradenitis suppurativa is profoundly debilitating; the pain, malodorous fistulae discharge, and scarring substantially affect quality of life, physical functioning,

and psychological health (eg, including increased depression and social isolation).^{7–9}

The pathogenesis of hidradenitis suppurativa begins at the pilosebaceous unit and is propelled by dysbiosis, proinflammatory signalling, and genetic predisposition.¹⁰ Secretion of proinflammatory cytokines, including TNF α , interleukin (IL)-1 β , and IL-17, leads to an aggressive pattern of immune cell infiltration into the skin and disrupted wound healing patterns.¹⁰

Therapeutic approaches include topical drugs; systemic therapies, such as antibiotics, hormonal therapies, and corticosteroids; and surgical interventions, often used in combination.^{11,12} To date, adalimumab (TNF α inhibitor) is the only biologic therapy approved for the treatment of moderate-to-severe hidradenitis suppurativa.^{13–15}

Research in context

Evidence before this study

Hidradenitis suppurativa is a chronic inflammatory skin disease of young people characterised by pain, disability, and the potential for progression to scarring. Few therapeutic options exist for the treatment of moderate-to-severe hidradenitis suppurativa. To date, adalimumab, a TNF α inhibitor, is the only biologic therapy approved for treating adolescents and adults with moderate-to-severe hidradenitis suppurativa. Secukinumab, a fully human monoclonal antibody that selectively neutralises interleukin (IL)-17A, has been reported to improve clinical signs and symptoms of hidradenitis suppurativa in open-label studies and case reports, but it has yet to be investigated in a large-scale phase 3 clinical trial.

Added value of this study

The SUNSHINE and SUNRISE trials are the largest development plan ever done in hidradenitis suppurativa and the first reporting efficacy and safety results up to 52 weeks of treatment. The trials were done in 40 countries and enrolled 1084 patients, representative of a real-world population of patients with moderate-to-severe hidradenitis suppurativa. The trials showed that secukinumab 300 mg every 2 weeks (secukinumab every 2 weeks group) was consistently efficacious compared with placebo in improving clinical and patient outcomes following 16 weeks of treatment, with a favourable safety profile and responses sustained up to 52 weeks. In both trials, the primary endpoint, hidradenitis suppurativa clinical

response, was met with the secukinumab every 2 weeks group. The secukinumab every 4 weeks group did not meet the primary endpoint in the SUNSHINE trial, but it was met in the SUNRISE trial. Hidradenitis suppurativa clinical response values observed in both secukinumab groups at week 16 were sustained up to week 52. There were no new or unexpected safety concerns detected across both trials for the duration of the study.

Implications of all the available evidence

The SUNSHINE and SUNRISE trials are the first phase 3 trials in hidradenitis suppurativa to assess the effects of selective IL-17A inhibition. Additionally, they are only the second medication tested in large phase 3 trials since the last therapy was approved more than 5 years ago. The outcomes of these trials validate the role of IL-17A in the pathogenesis of the disease and show that secukinumab has the potential to change clinical practice in hidradenitis suppurativa, offering patients a new, effective, sustainable, and safe treatment option. Additional analyses and subgroup evaluations are required to deepen the understanding of the effect of secukinumab in treating a population with moderate-to-severe hidradenitis suppurativa. Although secukinumab is an effective treatment, hidradenitis suppurativa remains a difficult to treat disease and adjunctive therapies might be required to improve patient outcomes. Future trials should investigate targeting different or multiple targets to enable a greater understanding of disease pathogenesis and improve treatment outcomes.

Translational studies have shown a central role for IL-17A in hidradenitis suppurativa,^{16–18} and case reports and open-label studies, published since 2018, have reported clinical improvement following treatment with secukinumab, a fully human monoclonal antibody that selectively neutralises IL-17A.^{19–21}

We aimed to assess the short-term and long-term efficacy and safety results of secukinumab in patients with moderate-to-severe hidradenitis suppurativa.

Methods

Study design and participants

The SUNSHINE and SUNRISE trials were identical, multicentre, randomised, placebo-controlled, double-blind, phase 3 trials done in 219 primary sites in 40 countries (appendix 1 pp 3–25).

Eligible patients were 18 years old or older and had moderate-to-severe hidradenitis suppurativa (defined as a total of five or more inflammatory lesions affecting at least two distinct anatomical areas) for at least 1 year. Included patients also agreed to daily use of topical over-the-counter antiseptics on the areas affected by hidradenitis suppurativa lesions while on study treatment. Patients were excluded if they had 20 or more fistulae at baseline, had ongoing active conditions requiring treatment with prohibited medications (eg, systemic biological immunomodulating treatment, live vaccines, or other investigational treatments), or met other exclusion criteria (appendix 1 pp 26–28). Patients previously treated with TNF α inhibitors or on a stable dose of selected antibiotics (antibiotic stratum; tetracycline up to 500 mg twice daily, minocycline up to 100 mg twice daily, or doxycycline up to 100 mg twice daily) were eligible for inclusion. Furthermore, the use of rescue medications (eg, antibiotics for increases in abscess and inflammatory nodule count or single lesion interventions, including intralesional steroid administration or incision and drainage) was permitted if patients had a worsening of their disease severity.

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre. The study was done according to The International Conference on Harmonisation Guidelines for Good Clinical Practice that have their origin in the Declaration of Helsinki. Written informed consent was obtained from each patient during the screening visit and before any study-specific procedure was done.

Randomisation and masking

A patient randomisation list was produced centrally by the interactive response technology provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. The randomisation numbers were linked to the different treatment groups, which in turn were linked to medication numbers. In both the SUNSHINE and SUNRISE trials, patients were

randomly assigned (1:1:1) to receive secukinumab 300 mg every 2 weeks (secukinumab every 2 weeks group), secukinumab 300 mg every 4 weeks (secukinumab every 4 weeks group) or placebo (placebo group) in a double-dummy fashion as per treatment assignment (appendix 2 p 54). Random assignment of patients in the placebo group to receive secukinumab at week 16 was done in a 1:1 ratio at baseline and did not account for potential discontinuations during treatment period one. A separate medication list was produced by, or under the responsibility of, Novartis Clinical Drug Supply (Basel, Switzerland) using a validated system that automated the random assignment of medication numbers to packs containing secukinumab. Randomisation was stratified by region (Europe, Asia-Pacific, Middle East and Africa, Latin America, the Caribbean and Canada, USA, and Japan), concomitant antibiotic use (yes vs no), and bodyweight (weight <90 vs \geq 90 kg). Randomisation codes and treatment allocations were masked to investigators, patients, study personnel, and study teams (with the exception of select study team members who were unmasked for the primary endpoint analysis) until study completion. Treatment allocation was concealed by the use of study treatments that had identical packaging, labelling, appearance, and schedule of administration.

Procedures

The entire study period consisted of a placebo-controlled treatment period from study initiation (week 0) to week 16 (treatment period one), a long-term treatment period to week 52 (treatment period two), and a follow-up period to week 60 (follow-up period; appendix 2 pp 25–32). Treatment period one began with an introductory phase during which patients in both secukinumab groups received 300 mg secukinumab subcutaneously via a 2 mL prefilled syringe on weeks 0, 1, 2, 3, and 4. Patients in the placebo group received subcutaneous placebo via a 2 mL prefilled syringe on weeks 0, 1, 2, 3, and 4. At week 16 (start of treatment period two), patients originally assigned to either secukinumab group continued with the same dose regimen, whereas patients assigned to placebo were randomly reassigned, based on baseline randomisation, to receive secukinumab 300 mg every 2 weeks (placebo–secukinumab every 2 weeks group) or secukinumab 300 mg every 4 weeks (placebo–secukinumab every 4 weeks group; appendix 1 p 54). This placebo-controlled design is currently considered appropriate to assess hidradenitis suppurativa clinical and patient reported outcomes (PROs) and is used in ongoing trials (eg, NCT04242446 and NCT04242498).

Efficacy assessments included hidradenitis suppurativa clinical response, abscess and inflammatory nodule count, flares, and skin pain. Hidradenitis suppurativa clinical response was calculated based on the number of abscesses, inflammatory nodules, and draining fistulae. Abscesses were defined as lesions that were often inflammatory, painful, and tender but had fluctuating

See Online for appendix 2

See Online for appendix 1

mass with a diameter of more than 10 mm, surrounded by an erythematous area and with the middle area containing purulent material. Inflammatory nodules were defined as lesions that were typically raised, deep-seated, three-dimensional, round, tender, erythematous, infiltrated, and possibly pyogenic granuloma lesions with a diameter of more than 10 mm. Draining fistulae were defined as sinus tracts that were raised, tender, and had fluctuating longitudinal tunnels of variable length and depth, with communications to skin surface, and draining purulent fluid. Flares were defined as a 25% or greater increase in abscess and inflammatory nodule count with a minimum increase of two abscesses and inflammatory nodules compared with baseline. Skin pain was assessed via the Patient's Global Assessment of Skin Pain numeric rating scale in the past 24 h at its worst. The numeric rating scale is a segmented numeric version of the visual analogue scale (VAS) in which a respondent selects a whole number (0–10) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine).

Outcomes

The primary objective of both trials was to assess the clinical efficacy of secukinumab compared with placebo at week 16. The **primary endpoint** was assessed using the hidradenitis suppurativa clinical response at week 16, defined as a **decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline**. The primary endpoint was assessed separately in both trials.

Secondary endpoints were mean percentage change from baseline in abscess and inflammatory nodule count at week 16; the proportion of patients with flares over 16 weeks; and the proportion of patients at week 16 with a 30% or more reduction and reduction of two units or more from baseline in Patient's Global Assessment of Skin Pain on a continuous numeric rating scale (NRS30) assessed in patients with a baseline numeric rating scale of three or more. NRS30 is the currently accepted criterion for pain evaluation by health authorities and was reported using pooled data from both trials as predefined in the study protocol (appendix 2 p 43). All other secondary endpoints were assessed at the individual trial level. PROs were assessed as predefined exploratory endpoints and included the Dermatology Life Quality Index (DLQI) and the EQ-5D VAS. For DLQI, the response rate over time was reported; a DLQI response was defined as a decrease of five points or more from baseline.

Additional predefined exploratory endpoints evaluated the long-term efficacy of secukinumab up to 52 weeks (including hidradenitis suppurativa clinical response, abscess and inflammatory nodule count, flares, NRS30, DLQI response, and EQ-5D VAS). Predefined sensitivity analyses of week 52 data were assessed using a

mixed-effects logistic regression model or mixed model for repeated measures (appendix 1 p 32). The proportion of patients with at least a 50% reduction in the abscess and inflammatory nodule count compared with baseline (AN50) was also assessed as a predefined supportive analysis.

Safety and tolerability were assessed by evaluating the presence of adverse events and serious adverse events, clinical laboratory evaluations, vital signs, and immunogenicity throughout the trials up to week 52 according to common terminology criteria for adverse events, which were coded using medical dictionary for regulatory activities terminology.

Statistical analysis

A 5% two-sided α level was used to control for the type I error. Two secukinumab doses were tested versus placebo with respect to the primary and secondary endpoints. The α level was split unequally: 4% for the secukinumab every 2 weeks group versus the placebo group and 1% for the secukinumab every 4 weeks group versus the placebo group. One-sided p values were reported for hypothesis testing for all primary and secondary endpoints with a 2.5% level of significance, given that the aim of both trials was to show superiority of either secukinumab dose compared with placebo.

Sample size calculations were primarily driven by the primary endpoint of the trials. A total of 471 patients was originally planned to be randomly assigned to each of the trials. Both trials were independently powered to test the primary endpoint and the secondary endpoints. The secondary endpoint, NRS30, was analysed in the pooled populations of both trials, provided the primary null hypothesis could be rejected in both trials. To account for the disruptive effect of the COVID-19 pandemic, the number of randomly assigned patients was increased to approximately 541 in both trials. This was done to ensure the originally planned power in the statistical test procedure was maintained. More details on sample size calculations are provided in appendix 1 (pp 28–29).

The full analysis set, used for efficacy analyses, was comprised of all patients who were randomly assigned to study treatment (excluding misrandomised patients). Logistic regression was used to assess the primary endpoint, using Hurley stage, baseline abscess and inflammatory nodule count, geographical region, concomitant use of antibiotics, and baseline bodyweight (<90 vs ≥ 90 kg) as covariates, and reported as estimated odds ratios (ORs) and 95% CIs of secukinumab groups versus the placebo group. On the basis of a post-hoc analysis, patients who achieved a hidradenitis suppurativa clinical response at week 16 and week 52 were assessed to analyse the sustainability of response.

The percentage change from baseline in abscess and inflammatory nodule count at week 16 was based on an ANCOVA model using the same covariates as the primary endpoint. Flares over 16 weeks and NRS30 at

week 16 were analysed using logistic regression, using the same covariates as the primary endpoint (for analysis of NRS30 at week 16, the baseline abscess and inflammatory nodule count covariate was exchanged for baseline NRS). Estimated least squares means (LSM) differences were recorded for the percentage change from baseline in abscess and inflammatory nodule counts and ORs were recorded for flares and NRS30 for comparisons of the two secukinumab dose regimens with the placebo group.

A statistical testing hierarchy was used (appendix 1 pp 31–32). Multiple imputation was applied to address missing data, with consideration of the definition of intercurrent events and the respective analysis strategies based on the primary and secondary estimands (appendix 1 pp 31–32). For multiply imputed binary variables, the rounded average number of patients with response in 100 imputations was used. **Rescue therapy was considered as an intercurrent event in the estimand, and a composite strategy was applied. If an intercurrent**

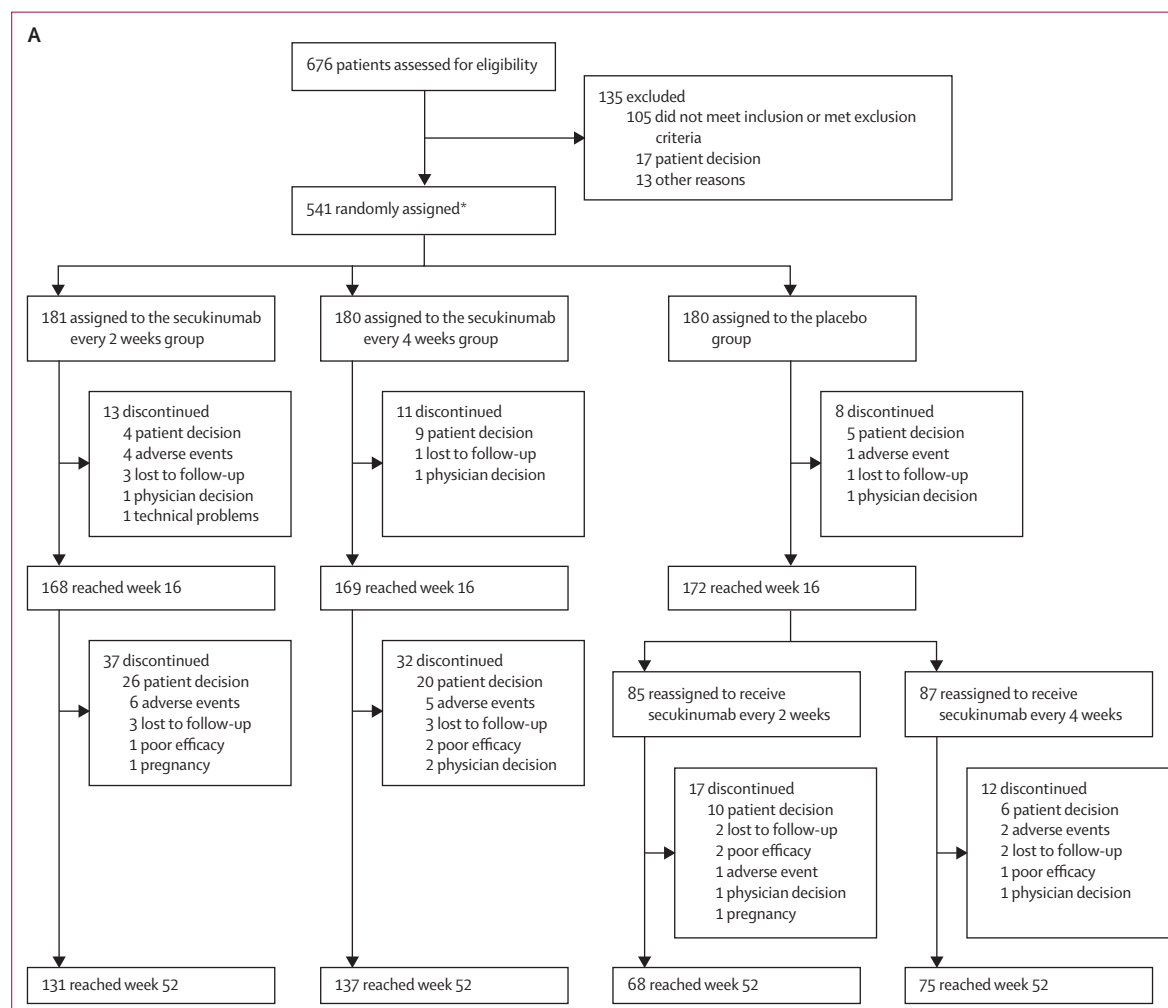
event occurred, the patient was considered a non-responder.

For exploratory endpoints, no formal statistical tests were done; analyses were based on observed data (following the intention-to-treat principle). For AN50 up to week 16, secondary estimand definitions and multiple imputation for missing data were used. Long-term AN50 responses (from week 18 to week 52) were reported as observed.

Adverse events were summarised by the number of patients reporting any treatment-emergent adverse events by primary system organ class, preferred term, and severity. Both the SUNSHINE, NCT03713619, and SUNRISE, NCT03713632, trials are registered with ClinicalTrials.gov.

Role of the funding source

The sponsor was responsible for the conduct of both the SUNSHINE and SUNRISE trials and data collection, data analysis, and interpretation.



(Figure 1 continues on next page)

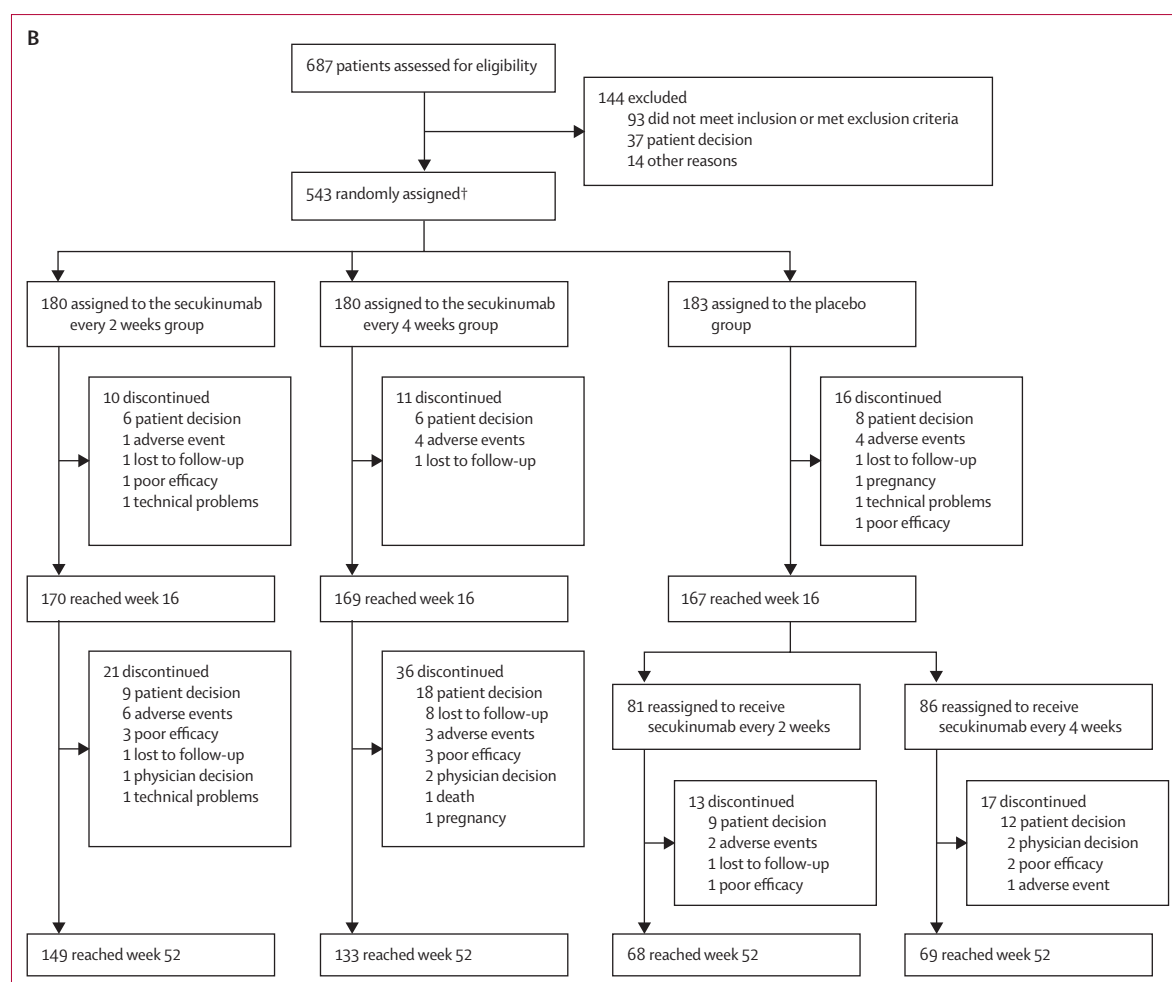


Figure 1: Trial profiles

The SUNSHINE (A) and SUNRISE (B) trial profiles. *In SUNSHINE, three patients were randomised but excluded from the analysis (two serious Good Clinical Practice violations; one misrandomised). †SUNRISE, one patient was randomised but excluded from the analysis (one misrandomised).

Results

Between Jan 31, 2019, and June 7, 2021, 676 patients were screened for inclusion in the SUNSHINE trial, of whom 541 (80%; 304 [56%] women, 237 [44%] men; mean age 36.1 years [SD 11.7]) were included in the analysis (181 [33%] in the secukinumab every 2 weeks group, 180 [33%] in the secukinumab every 4 weeks group; and 180 [33%] in the placebo group; figure 1); 687 patients were screened for inclusion in the SUNRISE trial, of whom 543 (79%; 306 [56%] women, 237 [44%] men; mean age 36.3 [11.4] years) were included in the analysis (180 [33%] in the secukinumab every 2 weeks group, 180 [33%] in the secukinumab every 4 weeks group; and 183 [34%] in the placebo group; figure 1).

255 (24%) of 1084 patients had previously received biologic therapy (table 1). In the SUNRISE trial, more patients had severe disease (Hurley stage III) in the secukinumab every 2 weeks group than the other two treatment groups (table 1).

For both trials, the primary endpoint was met in the secukinumab every 2 weeks group. In the SUNSHINE trial, 81.5 (45%) of 181 patients in the secukinumab every 2 weeks group compared with 60.7 (34%) of 180 patients in the placebo group had a hidradenitis suppurativa clinical response (OR 1.8 [95% CI 1.1–2.7]; $p=0.0070$; figure 2A). In the SUNRISE trial, 76.2 (42%) of 180 patients in the secukinumab every 2 weeks group compared with 57.1 (31%) of 183 patients in the placebo group had a hidradenitis suppurativa clinical response (1.6 [1.1–2.6]; $p=0.015$; figure 2B). The onset of efficacy in the secukinumab every 2 weeks group was rapid in both trials (figure 2). Compared with placebo, a clinically meaningful difference in hidradenitis suppurativa clinical response was seen as early as week 4 in the SUNSHINE trial and week 2 in the SUNRISE trial.

The primary endpoint was not met in the secukinumab every 4 weeks group in the SUNSHINE trial (75.2 [42%] of 180 patients in the secukinumab every 4 weeks group vs 60.7 [34%] of

	SUNSHINE (n=541)			SUNRISE (n=543)		
	Secukinumab every 2 weeks group (n=181)	Secukinumab every 4 weeks group (n=180)	Placebo group (n=180)	Secukinumab every 2 weeks group (n=180)	Secukinumab every 4 weeks group (n=180)	Placebo group (n=183)
Age, years	37.1 (12.5)	35.7 (11.7)	35.5 (10.8)	37.3 (11.5)	35.5 (11.4)	36.2 (11.3)
Age group, years						
<30	58 (32%)	69 (38%)	51 (28%)	52 (29%)	60 (33%)	57 (31%)
30 to <40	56 (31%)	45 (25%)	70 (39%)	48 (27%)	61 (34%)	65 (36%)
40 to <65	64 (35%)	63 (35%)	58 (32%)	77 (43%)	57 (32%)	59 (32%)
≥65	3 (2%)	3 (2%)	1 (1%)	3 (2%)	2 (1%)	2 (1%)
Sex						
Female	102 (56%)	100 (56%)	102 (57%)	98 (54%)	103 (57%)	105 (57%)
Male	79 (44%)	80 (44%)	78 (43%)	82 (46%)	77 (43%)	78 (43%)
Race, n (%)						
White	145 (80%)	146 (81%)	139 (77%)	133 (74%)	139 (77%)	143 (78%)
Black or African American	15 (8%)	10 (6%)	12 (7%)	18 (10%)	19 (11%)	12 (7%)
Asian	19 (11%)	23 (13%)	24 (13%)	16 (9%)	16 (9%)	19 (10%)
Other or not reported	2 (1%)	1 (1%)	5 (3%)	13 (7%)	6 (3%)	9 (5%)
Body mass, kg						
<90	82 (45%)	80 (44%)	83 (46%)	86 (48%)	89 (49%)	92 (50%)
≥90	99 (55%)	100 (56%)	97 (54%)	94 (52%)	91 (51%)	91 (50%)
BMI, kg/m ²	32.6 (7.9; n=181)	32.8 (7.9; n=179)	32.0 (7.1; n=180)	31.9 (7.8)	32.0 (7.5)	31.4 (7.4)
Smoking status						
Current smokers	95 (53%)	96 (53%)	101 (56%)	97 (54%)	90 (50%)	106 (58%)
Former smokers	26 (14%)	28 (16%)	30 (17%)	32 (18%)	25 (14%)	24 (13%)
Hurley stage						
I	7 (4%)	10 (6%)	8 (4%)	6 (3%)	6 (3%)	3 (2%)
II	104 (58%)	107 (59%)	121 (67%)	92 (51%)	106 (59%)	110 (60%)
III	70 (39%)	63 (35%)	51 (28%)	82 (46%)	68 (38%)	70 (38%)
Time since hidradenitis suppurativa diagnosis, years	7.4 (8.0)	6.6 (6.7)	7.5 (7.0)	7.1 (7.0; n=180)	8.2 (8.4; n=180)	7.0 (6.7; n=182)
Abscess and inflammatory nodule count	12.9 (9.6)	12.6 (8.4)	12.8 (8.2)	13.9 (9.9)	13.3 (8.8)	12.8 (8.5)
Inflammatory nodule count	10.1 (7.8)	9.9 (7.6)	10.1 (7.0)	10.0 (7.7)	10.4 (7.6)	9.6 (6.8)
Abscess count	2.9 (4.3)	2.7 (4.0)	2.7 (3.8)	3.9 (5.4)	2.9 (4.1)	3.2 (5.0)
Draining fistulae count	2.9 (3.4)	2.5 (3.5)	2.4 (3.2)	3.0 (3.6)	2.5 (3.5)	2.6 (3.2)
Numeric rating scale pain	5.2 (2.5; n=163)	4.9 (2.5; n=163)	5.0 (2.6; n=162)	5.4 (2.4; n=166)	5.3 (2.5; n=163)	5.3 (2.5; n=166)
Previous surgery for hidradenitis suppurativa	71 (39%)	73 (41%)	72 (40%)	78 (43%)	70 (39%)	78 (43%)
Previous exposure to systemic biologics	44 (24%)	39 (22%)	46 (26%)	36 (20%)	42 (23%)	48 (26%)
Previous exposure to systemic antibiotics	146 (81%)	149 (83%)	150 (83%)	151 (84%)	152 (84%)	151 (83%)
Concomitant antibiotic therapy	26 (14%)	25 (14%)	18 (10%)	18 (10%)	21 (12%)	19 (10%)

Data are n (%) or mean (SD). Due to rounding, some percentages do not summate to 100%.

Table 1: Baseline demographic and disease characteristics in the SUNSHINE and SUNRISE trials

180 patients in the placebo group; OR 1.5 [95% CI 1.0–2.3]; $p=0.042$; figure 2A). However, the primary endpoint was met in the **SUNRISE trial (83.1 [46%] of 180 patients in the secukinumab every 4 weeks group vs 57.1 [31%] of 183 patients in the placebo group; 1.9 [1.2–3.0]; $p=0.0022$; figure 2B).** Similar to the secukinumab every 2 weeks group, the onset of efficacy in the secukinumab every 4 weeks group was rapid in both trials. Of note, the weekly loading dose was identical in both secukinumab groups until week 4. Individual hidradenitis suppurativa clinical response components are shown in appendix 1 (p 54).

The secukinumab every 2 weeks regimen was superior to placebo with respect to the percentage change from baseline in abscess and inflammatory nodule count at week 16 in both the SUNSHINE trial (–46.8% [SE 3.3] in the secukinumab every 2 weeks group vs –24.3% [4.3] in the placebo group; LSM –23.1 [95% CI –33.9 to –12.2]; $p<0.0001$) and the SUNRISE trial (–39.3% [4.4] in the secukinumab every 2 weeks group vs –22.4% [4.8] in the placebo group; LSM –16.3 [–28.8 to –3.9]; $p=0.0051$; figure 3A, B).

On the basis of hierarchical testing, the secukinumab every 4 weeks regimen did not significantly improve the

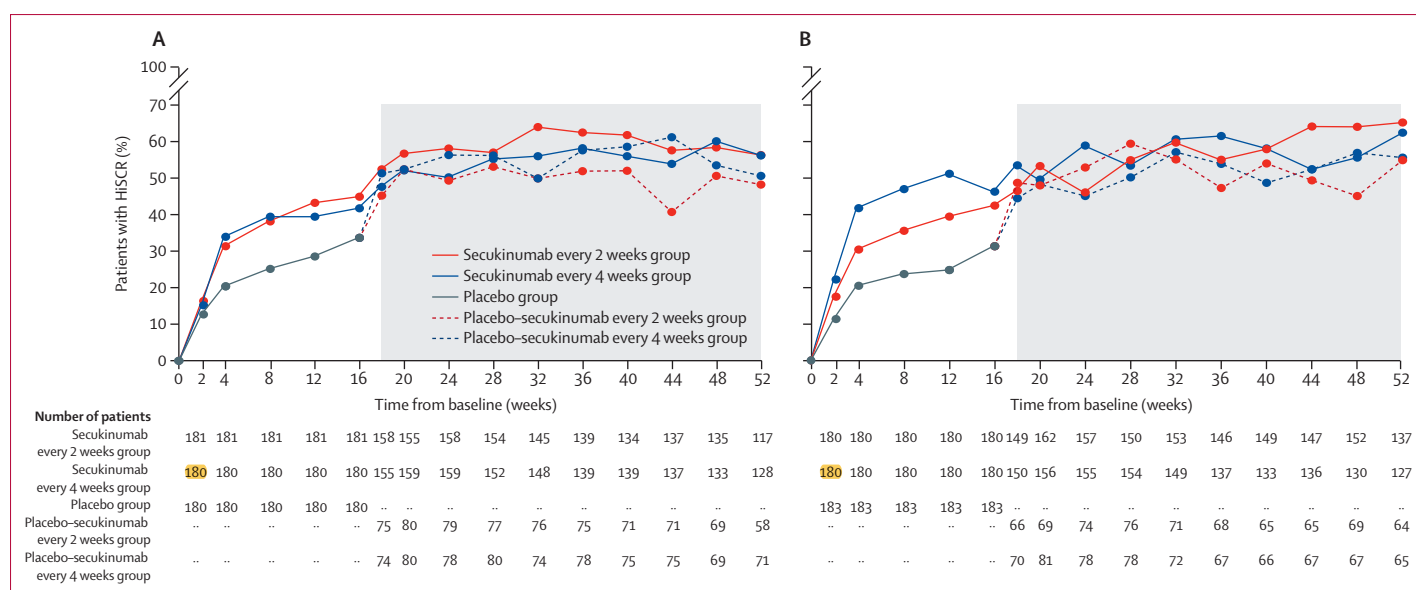


Figure 2: The effects of secukinumab and placebo on HiSCR

The effects of secukinumab every 2 weeks, secukinumab every 4 weeks, and placebo on HiSCR from baseline to week 52 in the SUNSHINE (A) and SUNRISE (B) trials. Data for baseline to week 16 are based on the primary estimand and multiple imputation from the week 16 database lock. Data for week 18 to 52 are based on observed data from the week 52 database lock. Dashed lines represent patients switching from placebo at week 16. Grey box represents observed data. HiSCR=hidradenitis suppurativa clinical response.

abscess and inflammatory nodule count at week 16 compared with placebo in the SUNSHINE trial (-42.4% [4.0] in the secukinumab every 4 weeks group vs -24.3% [4.3] in the placebo group; LSM -18.5 [-29.3 to -7.6]; $p=0.0004$; figure 3A). However, there was a significant difference between the groups in the SUNRISE trial (-45.5% [4.1] in the secukinumab every 4 weeks group vs -22.4% [4.8]; LSM -22.9 [-35.2 to -10.6] in the placebo group; $p=0.0001$; figure 3B). In both trials, clear differentiation from placebo was observed in both dosing regimens from week 2 onwards.

Significantly fewer patients had flares in the secukinumab every 2 weeks group than in the placebo group in the SUNSHINE trial (27.8 [15%] of 181 patients in the secukinumab every 2 weeks group vs 52.2 [29%] of 180 patients in the placebo group; OR 0.4 [95% CI 0.3 – 0.7]; $p=0.0010$; figure 3C) during the first 16 weeks. There was no significant difference between the two groups in the SUNRISE trial (36.1 [20%] of 180 patients in the secukinumab every 2 weeks group vs 49.5 [27%] of 183 patients in the placebo group; 0.7 [0.4 – 1.1]; $p=0.073$; figure 3D) during the first 16 weeks. Although numerically fewer, there was no statistically significant difference in the proportion of patients with flares between the secukinumab every 4 weeks group (41.7 [23%] of 180 patients) and the placebo group (52.2 [29%] of 180 patients; 0.7 [0.4 – 1.2]; $p=0.093$; figure 3C) during the first 16 weeks in the SUNSHINE trial, whereas, in the SUNRISE trial, a significant difference was reported (28.0 [16%] of 180 patients in the secukinumab every 4 weeks group vs 49.5 [27%] of 183 patients in the placebo group; 0.5 [0.3 – 0.8]; $p=0.0049$; figure 3D).

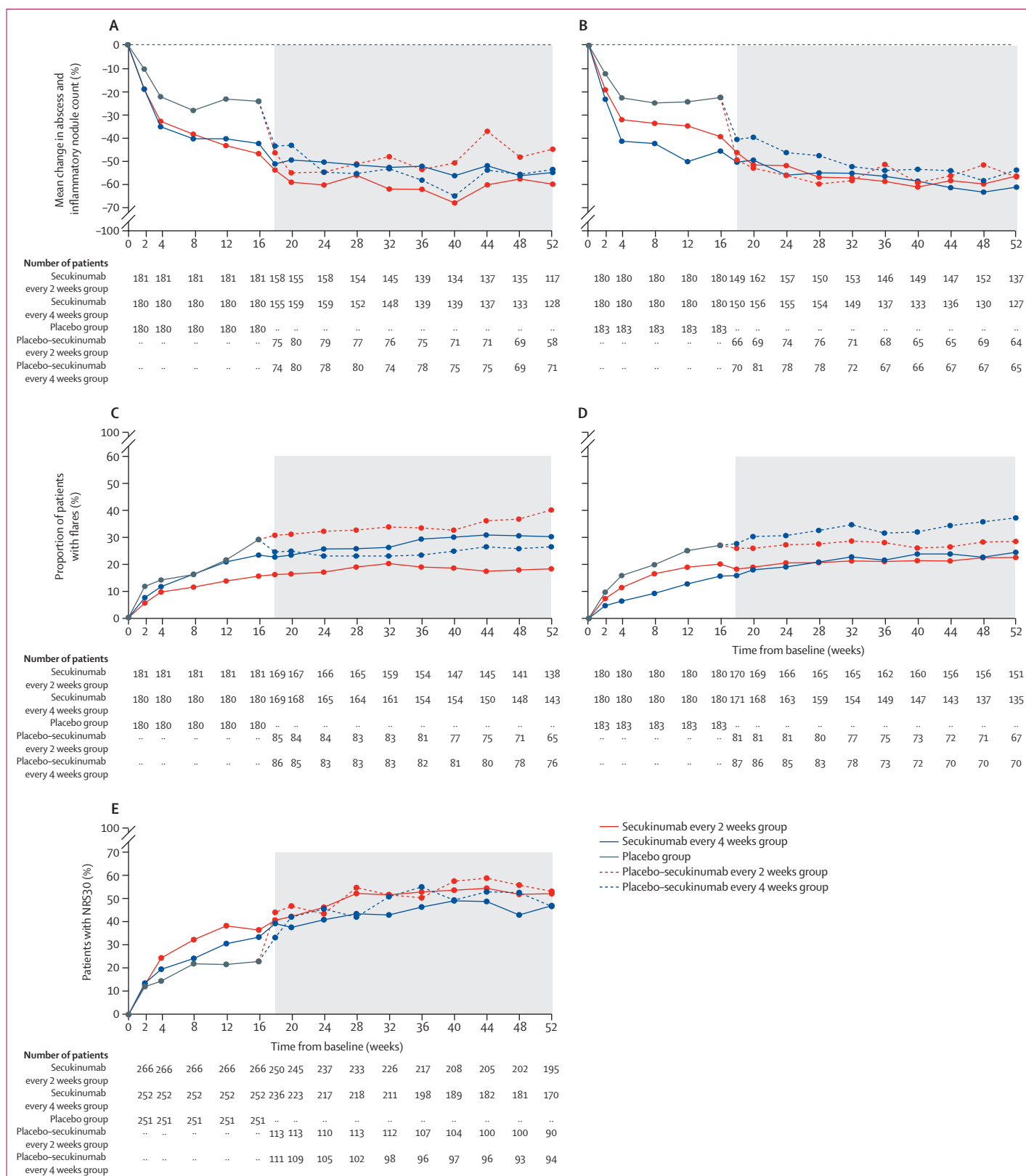
For the pooled analysis of skin pain at week 16, NRS30 response was significantly higher in the secukinumab every 2 weeks group (97.2 [37%] of 266 patients) than in the placebo group (57.8 [23%] of 251 patients; OR 2.1 [95% CI 1.4 – 3.2]; $p=0.0003$; figure 3E). Although the proportion of patients achieving NRS30 at week 16 was higher in the secukinumab every 4 weeks group (84.4 [33%] of 252 patients) than in the placebo group (57.8 [23%] of 251 patients), the difference was not statistically significant on the basis of hierarchical testing (1.8 [1.2 – 2.7]; $p=0.0044$; figure 3E).

In both trials, the clinical efficacy observed at week 16 was sustained to week 52 (figures 2, 3). Hidradenitis suppurativa clinical response values observed at week 16 following either dose regimen of secukinumab were improved over time to week 52 in both the SUNSHINE (figure 2A) and SUNRISE (figure 2B) trials.

Of note, in a post-hoc analysis, many patients with a hidradenitis suppurativa clinical response at week 16 maintained the response at week 52 in both the SUNSHINE (44 [76%] of 58 patients in the secukinumab every 2 weeks group; 42 [81%] of 52 patients in the secukinumab every 4 weeks group) and the SUNRISE trials

Figure 3: The effects of secukinumab and placebo on secondary endpoints

The effects of secukinumab every 2 weeks, secukinumab every 4 weeks, and placebo on percentage change in abscess and inflammatory nodule count from baseline up to week 52 in the SUNSHINE (A) and SUNRISE (B) trials; the proportion of patients with flares in the SUNSHINE (C) and SUNRISE (D) trials over 52 weeks; and a pooled assessment of skin pain, assessed by NRS30, using data from the SUNSHINE and SUNRISE trials up to 52 weeks (E). NRS30=30% or more reduction in Patient's Global Assessment of Skin Pain.



(51 [84%] of 61 patients in the secukinumab every 2 weeks group; 50 [77%] of 65 patients in the secukinumab every 4 weeks group). Rapid increases in the number of patients with a hidradenitis suppurativa clinical response, which lasted until week 52, were reported when patients originally randomly assigned to the placebo group were reassigned to receive secukinumab in both the SUNSHINE (28 [48%] of 58 patients in the placebo–secukinumab every 2 weeks group; 36 [51%] of 71 patients in the placebo–secukinumab every 4 weeks group) and SUNRISE trials (35 [55%] of 64 patients in the placebo–secukinumab every 2 weeks group; 36 [55%] of 65 patients in the placebo–secukinumab every 4 weeks group; figures 2A, B).

The percentage change in abscess and inflammatory nodule count, proportion of patients with flares reported, and number of patients with NRS30 improved in both secukinumab groups of both trials up to week 52. Rapid improvements in all outcomes were observed in both trials when patients from the placebo groups were reassigned to one of the secukinumab groups, which were maintained to week 52 (figure 3).

Predefined sensitivity analyses of week 52 data using a mixed-effects logistic regression model or mixed model for repeated measures gave similar results to long-term analyses reported using observed data (appendix 1 pp 33, 59–60). **The pooled SUNSHINE and SUNRISE efficacy data are reported in appendix 1 (pp 33, 61).**

Secukinumab improved patients' health-related quality of life (HRQoL) up to 52 weeks in both the SUNSHINE and SUNRISE trials, as assessed by the DLQI response rate (decrease of five points or more from baseline). In the SUNSHINE trial, both the secukinumab every 2 weeks (64 [48%] of 134 patients) and secukinumab every 4 weeks (62 [48%] of 128 patients) groups had higher DLQI responder rates than the placebo group (37 [29%] of 128 patients) at week 16. Likewise, in the SUNRISE trial a higher proportion of patients in the secukinumab every 2 weeks (54 [38%] of 144 patients) and secukinumab every 4 weeks groups (67 [47%] of 142 patients) had higher DLQI responder rates than in the placebo group (46 [32%] of 145 patients). The differences in both trials were sustained up to week 52 (appendix 1 p 56). In addition, improvements in DLQI response rates were observed once patients originally assigned to the placebo group were reassigned to receive secukinumab (appendix 1 p 56).

Both the secukinumab every 2 weeks and secukinumab every 4 weeks regimens resulted in a larger increase in the EQ-5D VAS score from baseline to week 16 compared with placebo in both the SUNSHINE and SUNRISE trials (appendix 1 p 56). In both trials and in both secukinumab regimens, improvements were sustained up to week 52. In addition, improvements in the EQ-5D VAS score were observed up to week 52 in patients originally assigned to the placebo group after reassignment to receive secukinumab (appendix 1 p 56).

In both trials, treatment with both secukinumab regimens was well tolerated; analysis of safety data from

the placebo-controlled period showed similar results across the secukinumab every 2 weeks, secukinumab every 4 weeks, and placebo groups (table 2). The most frequently reported adverse events by preferred term in both trials were headache, nasopharyngitis, and worsening of hidradenitis up to week 16 (table 2; appendix 1 p 41).

No new treatment-emergent adverse events were identified up to week 52 (appendix 1 pp 39, 42, 46, 49). In the SUNSHINE trial, at least one adverse event was reported in 154 (85%) of 181 patients in the secukinumab every 2 weeks group and 154 (86%) of 180 patients in the secukinumab every 4 weeks group. Similarly, in SUNRISE, at least one adverse event was reported in 147 (82%) of 180 patients in the secukinumab every 2 weeks group and 153 (85%) of 180 patients in the secukinumab every 4 weeks group (appendix 1 p 39).

Up to week 52, two deaths were reported in the SUNRISE trial. One patient in the secukinumab every 4 weeks group had pre-existing aortic valve stenosis and had a fatal myocardial infarction on day 219 (21 days after last treatment administration). One patient in the placebo–secukinumab every 4 weeks group who entered the study with a history of stable Crohn's disease had a severe upper gastrointestinal haemorrhage due to duodenal ulcers on day 219 (49 days after last dose of secukinumab) during concomitant treatment with ibuprofen; the patient died on day 249 (79 days after last dose of secukinumab) due to this event. Both events were not considered to be related to study treatment due to pre-existing conditions and use of concomitant medications.

Serious adverse events were infrequent and generally occurred at similar rates between treatment groups in both trials at week 16 and week 52 (table 2; appendix 1 pp 41–42). In the placebo-controlled period, the most frequently reported serious adverse event (two or more events in any group) by preferred term in both trials was worsening of hidradenitis (table 2; appendix 1 p 41). In the SUNSHINE trial, the frequency of patients with fungal infectious disorders (high-level group term) was higher in the secukinumab every 2 weeks group (28 [15%] of 181 patients) than in the secukinumab every 4 weeks group (15 [8%] of 180 patients). In both trials, most fungal infectious disorders were localised, transient, mild or moderate, resolved upon treatment, and did not lead to study treatment discontinuation. *Tinea* and *Candida* infections (appendix 1 pp 34, 51–52) were the most common fungal infections reported. One case of oesophageal candidiasis was reported in one patient in the secukinumab every 4 weeks group of the SUNSHINE trial (appendix 1 pp 34, 51–52). The case was reported as mild and was treated with fluconazole; the case did not lead to study discontinuation and was not suspected to be related to the study medication. The rate of study discontinuation due to adverse events was balanced across both trials and treatment groups. Three cases of new-onset inflammatory

	SUNSHINE (n=541)			SUNRISE (n=543)		
	Secukinumab every 2 weeks group (n=181)	Secukinumab every 4 weeks group (n=180)	Placebo group (n=180)	Secukinumab every 2 weeks group (n=180)	Secukinumab every 4 weeks group (n=180)	Placebo group (n=183)
Patients with any adverse event	122 (67%)	118 (66%)	120 (67%)	113 (63%)	114 (63%)	116 (63%)
Most common adverse events by preferred term						
Headache	17 (9%)	20 (11%)	14 (8%)	21 (12%)	17 (9%)	15 (8%)
Nasopharyngitis	20 (11%)	16 (9%)	13 (7%)	13 (7%)	9 (5%)	16 (9%)
Hidradenitis	11 (6%)	5 (3%)	24 (13%)	10 (6%)	11 (6%)	14 (8%)
Most common serious adverse events by preferred term (two or more events in any group)						
Hidradenitis	1 (1%)	0	2 (1%)	1 (1%)	0	0
Patients with serious or other significant events, n (%)						
Death	0	0	0	0	0	0
Non-fatal serious adverse events	3 (2%)	3 (2%)	6 (3%)	6 (3%)	6 (3%)	5 (3%)
Discontinued study treatment due to any adverse events	5 (3%)	1 (1%)	1 (1%)	1 (1%)	4 (2%)	4 (2%)
Adverse events of special interest						
Infections and infestations by system organ class	59 (33%)	51 (28%)	53 (29%)	52 (29%)	59 (33%)	62 (34%)
Upper respiratory tract infection (HLT)	33 (18%)	26 (14%)	22 (12%)	27 (15%)	21 (12%)	29 (16%)
Fungal infectious disorders (HLGT)*	12 (7%)	1 (1%)	7 (4%)	7 (4%)	13 (7%)	3 (2%)
Candida infections (HLT)†	2 (1%)	1 (1%)	4 (2%)	5 (3%)	5 (3%)	2 (1%)
Hypersensitivity (standardised MedDRA queries, narrow)	12 (7%)	9 (5%)	9 (5%)	7 (4%)	5 (3%)	7 (4%)
Malignant or unspecified tumours (standardised MedDRA queries)	0	0	1 (1%)	0	2 (1%)	1 (1%)
Major adverse cardiovascular events (Novartis MedDRA query)	0	0	0	0	0	0
Inflammatory bowel disease‡	0	0	0	1 (1%)	1 (1%)	0

Data are n (%). HLGT=high-level group term. HLT=high-level term. MedDRA=medical dictionary for regulatory activities. *Fungal infectious disorders include the following preferred terms: vulvovaginal mycotic infection, oral candidiasis, fungal skin infection, tongue fungal infection, *Tinea* infection, tinea pedis, body tinea, genital infection fungal, vulvovaginal candidiasis, *Candida* infection, ear infection fungal, tinea versicolour, skin candida, tinea cruris, and balanitis candida. †*Candida* infections includes the following preferred terms: vulvovaginal candidiasis, candida infection, skin candida, oral candidiasis, and balanitis candida. ‡One case of inflammatory bowel disease and one case of ulcerative colitis were reported.

Table 2: Deaths, other serious or clinically significant adverse events, or related discontinuations to week 16 in the SUNSHINE and SUNRISE trials

bowel disease were reported across both trials (none in SUNSHINE and three in SUNRISE; appendix 1 pp 39–40–41).

Discussion

In the SUNSHINE and SUNRISE phase 3 trials, secukinumab treatment given in 2-week intervals improved signs and symptoms of disease and HRQoL outcomes in patients with hidradenitis suppurativa compared with placebo at week 16, with a rapid onset of response. Beyond placebo-controlled primary efficacy analyses at week 16, sustained clinical responses continued to improve over 52 weeks of treatment. In both trials, the secukinumab every 2 weeks group was significantly superior versus placebo for the primary outcome and all secondary outcomes assessed (abscess and inflammatory nodule count, flares, and NRS30), except for the flares endpoint in the SUNRISE trial.

Treating hidradenitis suppurativa often requires higher doses of established medications compared with psoriasis,^{14,22} and existing biologic medications for

hidradenitis suppurativa have been reported to have lower drug survival²³ and exposure^{24,25} compared with other chronic inflammatory conditions.

The secukinumab every 4 weeks group performed inconsistently across the two trials. For example, in the SUNRISE trial, the secukinumab every 4 weeks group unexpectedly had a more robust response in the placebo-controlled period compared with the secukinumab every 2 weeks group. Of note, this better performance was evident during the first 4 weeks of the trial (ie, induction phase), during which time all patients in both secukinumab groups received the same subcutaneous 300 mg injections at baseline and weeks 1, 2, 3, and 4. The baseline demographics confirmed that the patients in the secukinumab every 4 weeks group in SUNRISE had less severe disease than those in the every 2 weeks group, which would be expected to be more responsive to treatment, consistent with what was observed. In SUNSHINE, the secukinumab every 4 weeks group did not reach a statistical difference versus placebo. Research and subgroup analyses are required and might improve

our understanding of the effect of patient characteristics on treatment response and further refine the dosing recommendations for different populations.

Hidradenitis suppurativa is well recognised as a difficult to treat chronic disease and week 16 endpoints are considered early in the treatment course.^{1,26} Week 52 exploratory analyses of the SUNSHINE and SUNRISE trials showed that the efficacy shown by both secukinumab dose regimens at week 16 was sustained to week 52, with a trend for incremental improvements observed after 16 weeks. Moreover, more than 75% of all patients with a hidradenitis suppurativa clinical response at week 16 maintained this response at week 52, highlighting the sustained disease control achieved by secukinumab. Secukinumab also controlled pain, as assessed by NRS30, which is considered to be the most common and disabling symptom of hidradenitis suppurativa and is associated with the largest effect on HRQoL.^{27–29} Other HRQoL outcomes, such as DLQI, met minimally clinically relevant differences and validated that the clinical improvements observed were accompanied by improvements in physical function and patient experience. The secukinumab every 2 weeks group had a significantly higher response compared with placebo in both trials, despite the population randomly assigned to the secukinumab every 2 weeks group in the SUNRISE trial having more severe disease. Of note, NRS30 response rates continued to increase from weeks 16 to 52 in both secukinumab dose regimens and improved rapidly in patients originally assigned to the placebo group after they were reassigned to receive secukinumab. Patients reassigned from placebo to receive secukinumab had similar NRS30 responses at week 52 to those who had received continuous secukinumab treatment from baseline. Exploratory analyses of PROs also showed meaningful improvements in HRQoL, which were sustained to week 52.

The long-term safety of secukinumab is well established in several approved indications.³⁰ The safety profile in the SUNSHINE and SUNRISE trials is consistent with that already reported, with no new or unexpected safety concerns detected. There is a known association with an elevated risk of inflammatory bowel disease in patients with hidradenitis suppurativa,³¹ and patients should be monitored carefully for the occurrence of this disease. Three cases of new-onset inflammatory bowel disease were identified in more than 1000 patients enrolled with up to 52 weeks of exposure to secukinumab. Hidradenitis suppurativa is also associated with increased risk of fungal infections;³² despite this, the rate of fungal infections (including candidiasis) remained low to week 52. Two deaths were reported in SUNRISE; neither were suspected to be related to study treatment. Discontinuations due to adverse events were low and balanced between the treatment groups with few serious adverse events observed. Overall, up to 52 weeks the safety profile of both secukinumab dose regimens were

similar, except for fungal infectious disorders, which, as expected,³³ were higher in the secukinumab every 2 weeks group.

A limitation of these trials is a modest imbalance with respect to disease severity between the treatment groups at baseline. However, patients randomly assigned to the secukinumab every 2 weeks group in the SUNRISE trial had a clinically superior response compared with the placebo group. Data beyond the primary endpoint analysis are presented as observed and did not include a control group. In both trials, placebo response rates were high, which is consistent with reports from other studies.¹⁴ Of note, although permitted, only a minority of patients entered the study on stable doses of permitted antibiotics, which are currently considered standard of care, are often used as concomitant treatment, and might affect the generalisability of the findings. Other limitations include a low number of Black patients included in the trials (a population which appears to have a higher risk of disease); the short controlled period of evaluation, which makes later efficacy data harder to interpret; an inability to detect rare safety events because of the study size; and the absence of an active comparator.

High placebo rates for clinical efficacy endpoints are a well known observation in hidradenitis suppurativa clinical trials, and the high rates appear to be linked to natural disease fluctuation, concomitant medications (eg, antibiotics), or scoring systems used in clinical trials. In both the SUNSHINE and SUNRISE trials, provisions were made for patients in the placebo groups with worsening hidradenitis suppurativa symptoms, which included allowing rescue treatments and the continuation of stable doses of antibiotic therapy. These confounding factors might have contributed to the high placebo response observed in these trials. Hidradenitis suppurativa clinical response was the first thoroughly validated clinical endpoint in hidradenitis suppurativa and was designed and tested for its ability to capture important inflection points of clinical improvement and PROs.³⁴ The high placebo response rates seen in hidradenitis suppurativa trials might be mitigated with the use of assessments that measure higher levels of efficacy (eg, hidradenitis suppurativa clinical response 75 or 90), in which placebo response rates decrease substantially. High placebo response rates have also been observed in clinical trials in other dermatological diseases.³⁵ Due to the high variability in clinical response, use of non-controlled clinical trials should be discouraged because they can lead to misleading results; some therapies that showed promise in open-label studies have subsequently been terminated when larger randomised trials have been done (eg, NCT04988308).^{36,37}

Since the SUNSHINE and SUNRISE trials were designed (2018) and initiated (2019), guidelines have been published updating and elucidating treatment patterns and standards of care. Antibiotics remain an

important part of these recommended approaches. Although they were not mandated, patients were allowed to enter the SUNSHINE and SUNRISE trials on a stable dose of permitted antibiotics. As a result of the progress in the knowledge and understanding of hidradenitis suppurativa, placebo-controlled study designs are likely to be replaced with active comparator trials in the future. A limitation of study designs including active comparators is that enrolment typically excludes patients previously exposed to the active comparator. Because many patients with severe hidradenitis suppurativa have previously received TNF α inhibitors, this exclusion can also lead to data that is not generalisable.

Lastly, we note that the SUNSHINE and SUNRISE clinical trials contribute to the understanding of the pathophysiology of hidradenitis suppurativa. Both TNF α inhibition and IL-17 inhibition are now validated therapeutic targets, but do not account for the entire pathogenic pathways involved. To date, IL-23 inhibition, which is very effective in psoriasis, has had no effect in hidradenitis suppurativa in randomised trials (NCT03926169 and NCT03628924). Future work is required to better understand the pathophysiology behind hidradenitis suppurativa, refine therapeutic targets, and develop integrated treatment approaches for this complex disease.

In the SUNSHINE and SUNRISE trials, secukinumab showed clinically meaningful efficacy in improving the signs and symptoms of hidradenitis suppurativa versus placebo at week 16, which was sustained until week 52. The clinical efficacy at week 16 was superior to placebo in both the SUNSHINE and SUNRISE trials for secukinumab administered every 2 weeks and was superior to placebo only in the SUNRISE trial for secukinumab dosed every 4 weeks. Both trials and dosing regimens confirmed the known favourable safety profile of secukinumab in patients with moderate-to-severe hidradenitis suppurativa.

Contributors

MBW and XW designed the trial and developed the protocol. ABK, GBEJ, AA, ZR, and AG provided scientific advice. MBW, ALM, DK, CF, EM, and SR were responsible for clinical operations and trial conduct. XW, LU, AP, RM, LC, and MV developed the statistical analysis plan and did the statistical analyses. ABK, AA, ZR, ABG, FGB, CP, EJGB, APV, AS, FR, LPR, AR, IL, RS, TP, AM, PM-B, GK, and P-AB were the principal investigators and recruited patients. ABK, GBEJ, AA, ZR, ABG, FGB, CP, EJGB, APV, AS, FR, LPR, AR, IL, RS, TP, AM, PM-B, MBW, ALM, XW, LU, AP, DK, RM, CF, LC, MV, SR, and EM contributed to the interpretation of the study results, drafted and critically reviewed the manuscript, and approved the final version for submission. All authors had full access to the study data, verified the data accuracy reported in the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

ABK reports grants from AbbVie, Anaptys Bio, Aristeia, Bristol Myers Squibb, ChemoCentryx, Eli Lilly, Incyte, Janssen, Moonlake, Novartis, Pfizer, UCB, and Sonoma Bio and fellowship funding from AbbVie and Janssen paid to her institution; royalties from BIDMC; consulting fees from AbbVie, Alumis, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Eli Lilly, FIDE, Novartis, Moonlake, Janssen, Pfizer, Priovant, Sonoma Bio, Sanofi, Target RWE, UCB, and Ventyx; stock in Ventyx; serving on advisory boards for Target RWE; serving as an advisory council member to the National

Institute of Health Director; and serves on the board of directors of Almirall. GBEJ reports grants from AbbVie, Boehringer-Ingelheim, CSL Behring, Regeneron, InflaRx, Novartis, LEO Foundation, and UCB, paid to their institution, and honoraria for advisory board meetings from Coloplast, Union Therapeutics, Toosonix, Boehringer-Ingelheim, Kymera, Sanofi, Viela Bio, ChemoCentryx, LEO Pharma, Afyx, Incyte, InflaRx, Janssen Cilag, Novartis, and UCB. AA reports consulting fees from AbbVie, Boehringer-Ingelheim, InflaRx, and UCB, paid to their institution, and consulting fees from Novartis, AbbVie, and Boehringer-Ingelheim. ZR reports consulting fees and honoraria from AbbVie, Amgen, Janssen-Cilag, Novartis, UCB, Sanofi; consulting fees from Celltrion; personal fees for attending meetings or for travel from AbbVie, Janssen-Cilag, Novartis, UCB, and Sanofi; and payment for expert testimony from AbbVie, Amgen, Celltrion, Janssen-Cilag, Novartis, and UCB. ABG reports research and educational grants from AnaptysBio, Janssen, Novartis, Ortho Dermatologics, Sun Pharma, BMS, and UCB Pharma, paid to their institution; consulting fees from Amgen, AnaptysBio, Avotres Therapeutics, Boehringer-Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB Pharma, and DiCE Therapeutics; honoraria as an advisory board member, or non-promotional speaker from Amgen, AnaptysBio, Avotres Therapeutics, Boehringer-Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, and UCB Pharma; is a president of International Dermatology Outcome Measures; and holds stock options in XBiotech, for work on a rheumatoid arthritis project. FGB reports consulting fees from AbbVie, Novartis, and UCB; honoraria and support for attending meetings or travel from AbbVie, Janssen Cilag, Novartis, and UCB; and served on a Data Safety Monitoring Board or Advisory Board for AbbVie, Boehringer-Ingelheim, Janssen Cilag, Novartis, UCB, Incyte, and Moonlake. CP reports consulting fees from Almirall, AbbVie, Amgen, BMS, Boehringer-Ingelheim, Celgene, GSK, Janssen, LEO Pharma, Eli Lilly, Merck, Novartis, Pfizer, Sanofi, and UCB and served on a Data Safety Monitoring Board or Advisory Board for IQVIA. EJGB reports grants from Horizon 2020 ImmunoSep and RISKinCOVID, Horizon Health EPIC-CROWN-2, Sobi, bioMérieux, MSD, Abbott, Novartis, UCB, and AbbVie, paid to their institution, and consulting fees from Sobi, Pfizer, Abbott, ThermoFisher, and Menarini. APV reports consulting fees from Janssen-Cilag; payment or honoraria from AbbVie, Almirall, BMS, Janssen-Cilag, Leo Pharma, Eli Lilly, MSD, Novartis, and UCB; and support for attending meetings or travel from Janssen-Cilag and UCB. AS reports consulting fees from Regeneron, Novartis, and AbbVie, paid to their institution; payment or honoraria from AbbVie, Novartis, Regeneron, Sanofi; support for attending meetings or travel from AbbVie, Janssen-Cilag, Novartis, and Sanofi; and fees for participation on a Data Safety Monitoring Board or Advisory Board from AbbVie, Novartis, and Sanofi. FR reports grants from ALK-Abelló, Allergopharma, Blueprint Medicines, Mylan, Novartis, and ThermoFisher; served on a Data Safety Monitoring Board or Advisory Board for ALK-Abelló, Boehringer-Ingelheim, Blueprint Medicines, Leo Pharma, and UCB; and is an active member of the German Association of Allergy and Clinical Immunology. AR and his institution received grants from AbbVie, Alvotech, Amgen, AnaptysBio, Argenx, Biothera, Bristol Myers Squibb, Celgene, Celltrion, Dermira, Galderma, InflaRx, Janssen, Kiniksa, Kymab, Leo Pharma, Novartis, Pfizer, Trevi Therapeutics, and UCB; payment or honoraria from Chema Rzeszow, Eli Lilly, Leo Pharma, Novartis, Sandoz, and Takeda; and served on a Data Safety Monitoring Board or Advisory Board for AbbVie, Galderma, Sandoz, and Sanofi Aventis. IL reports payment or honoraria from Novartis and support for attending meetings or travel from Sanofi. TP reports grants from Almirall, Incyte, and Pfizer, paid to their institution, and consulting fees from AbbVie, Almirall, Bristol Myers Squibb, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, and UCB. AM reports consulting fees from AbbVie, Boehringer-Ingelheim, Janssen, Eli Lilly, Novartis, Novo Nordisk, Sandoz, and UCB; payment for expert testimony or honoraria from AbbVie, Boehringer-Ingelheim, Janssen, Eli Lilly, Novartis, Novo Nordisk, Sandoz, and UCB; and support for attending meetings or travel from AbbVie, Novartis, Janssen, and UCB. PM-B reports consulting fees from AbbVie, Almirall, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, and Sanofi; payment or honoraria from AbbVie, Almirall, Janssen, LEO Pharma, Eli Lilly, Novartis, Organon, Pfizer, Sanofi, and Viartis; support for attending meetings or travel from AbbVie, Almirall, Janssen, LEO Pharma, Eli Lilly, Novartis, and Sanofi; and served on a Data Safety Monitoring Board

or Advisory Board for AbbVie, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, and Sanofi. GK reports consulting fees from Bayer; payment or honoraria from AbbVie, Abbott, Actelion Pharmaceuticals, Amgen, Basilea Pharmaceutica, Biogen IDEC, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Hexal, Janssen-Cilag, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Parexel, Pfizer, and UCB; support for attending meetings or travel from AbbVie, Abbott, Amgen, Basilea Pharmaceutica, Celgene, Janssen-Cilag, LEO Pharma, MSD, Novartis, Pfizer, Sanofi, and UCB; and served on a Data Safety Monitoring Board or Advisory Board for AbbVie, Abbott, Amgen, Basilea, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Janssen-Cilag, LEO Pharma, Eli Lilly, Novartis, and UCB. P-AB reports consulting fees from Novartis, AbbVie, Pfizer, and UCB pharma; payment or honoraria from Novartis and AbbVie; support for attending meetings or travel from Novartis; and served on a Data Safety Monitoring Board or Advisory Board for Novartis. MBW, ALM, XW, LU, AP, DK, RM, CF, LC, MV, SR, and EM are employees of Novartis and hold company stock. RS is Director and Founder of Samson Medical, has participated in pharmaceutical advisory boards for Eli Lilly and Company, Pfizer, and Leo Pharmaceutical, has participated in speaker bureaus for AbbVie, Novartis, and Pfizer, and has acted as a principal investigator in clinical trials for AbbVie, Aerotech, Akesobio, Amgen, Arcutis, Arena, Ascend AstraZeneca, Bayer, Biotherapeutics Boehringer-Ingelheim, Bristol-Myer Squibb, Celgene, Coherus BioSciences, Connect, Demira, Eli Lilly, Galderma, GlaxoSmithKline, F Hoffman–La Roche, Janssen, MedImmune, Merck, Merck Sharpe & Dohme, Novartis, Oncobiologics, Pfizer, Principia, Regeneron, Roche, Reistone Biopharma, Samson Clinical, Sanofi-Genzyme, Sun Pharma UCB, Valeant, and Zai Labs. RS is President of the Australasian Hair and Wool Research Society, and Vice President of the International Society of Dermatology and The International Academy of Dermatology. LPR declares no competing interests.

Data sharing

Novartis is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible trials. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trials in line with applicable laws and regulations.

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