NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication(s)

Ankylosing spondylitis

Protocol Number

CAIN457FDE03

Protocol Title

A randomized, double-blind, placebo-controlled multicenter study of Secukinumab (AIN457) to examine the clinical efficacy and the NSAID-sparing effect of Secukinumab over 16 weeks in patients with ankylosing spondylitis (ASTRUM)

Clinical Trial Phase

Phase 4

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: May 2016 (Actual)
Primary Completion Date: September 2019 (Actual)
Study Completion Date: September 2019 (Actual)

Study Design/Methodology

This was a phase IV, 20-week, randomized, double-blind, 3-arm, placebo-controlled, parallel-group, multicenter study to examine the clinical response of secukinumab treatment in patients with ankylosing spondylitis as measured by the Assessment of SpondyloArthritis international Society (ASAS) 20 response and the nonsteroidal anti-inflammatory drug (NSAID)-sparing effect. This study evaluated to which extent nonsteroidal anti-inflammatory drug (NSAID) treatment can be reduced between Week 4 and Week 12 in patients randomized to secukinumab 150 mg or placebo following an initial run-in phase of 4 weeks on stable NSAID therapy. Two NSAID tapering approaches were evaluated in this study:

1) an early tapering approach in which NSAID were tapered at the start of secukinumab treatment,
2) a delayed tapering approach in which NSAID were tapered following 4 weeks of secukinumab treatment.

Patients were randomized 1:1:1 to one of the following treatment groups:

- Secukinumab - delayed NSAID tapering: Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).
- Secukinumab – early NSAID tapering: Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).
- Placebo: Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.

Centers

Germany(40)

Objectives:

The primary objective of the study was to demonstrate that the efficacy of secukinumab 150 mg subcutaneous (s.c.) injection (with NSAID tapering) is superior to placebo based on the proportion of patients achieving an **ASAS20 response** at Week 12. To show superiority, both secukinumab treatment arms were pooled and compared against placebo.

The secondary objectives were:

1. To demonstrate that the change from baseline in **ASAS-NSAID score** at Week 12 was superior for secukinumab 150 mg s.c. as compared to placebo. To show superiority, both secukinumab treatment arms were pooled and compared against placebo.
2. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 12 was superior to placebo based on the change from baseline in the **total BASDAI**. To show superiority, both secukinumab treatment arms were pooled and compared against placebo.
3. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 0 with NSAID tapering allowed from week 4; "delayed tapering") at Week 12 was superior to placebo based on the proportion of patients achieving an **ASAS20 response**.
4. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") at Week 12 was superior to placebo based on the proportion of patients achieving an **ASAS20 response**.
5. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") at Week 16 was superior to placebo based on the proportion of patients achieving an **ASAS20 response**.
6. To demonstrate that the change from baseline in **ASAS-NSAID score** at Week 12 was superior for secukinumab 150 mg s.c. (secukinumab from Week 0 with NSAID tapering allowed from Week 4; "delayed tapering") as compared to placebo.
7. To demonstrate that the change from baseline in **ASAS-NSAID score** at Week 12 was superior for secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") as compared to placebo.

8. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 0 with NSAID tapering allowed from Week 4; "delayed tapering") at Week 12 was superior to placebo based on the change from baseline in the **total BASDAI**.
9. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") at Week 12 was superior to placebo based on the change from baseline in the **total BASDAI**.
10. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") at Week 16 was superior to placebo based on the change from baseline in the **total BASDAI**.
11. To demonstrate that the efficacy of secukinumab 150 mg s.c. at Week 12 was superior to placebo based on the change from baseline in health-related Quality of Life as measured by the **SF-36 Physical Component Summary (PCS)**.
12. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 0 with NSAID tapering allowed from Week 4; "delayed tapering") at Week 12 was superior to placebo based on the change from baseline in health-related Quality of Life as measured by the **SF-36 PCS**.
13. To demonstrate that the efficacy of secukinumab 150 mg s.c. (secukinumab from Week 4 with NSAID tapering allowed from Week 4; "early tapering") at Week 12 was superior to placebo based on the change from baseline in health-related Quality of Life as measured by the **SF-36 PCS**.
14. To compare between both secukinumab regimens concerning the change from baseline in **ASAS-NSAID score** after 12 weeks of secukinumab exposure (ASAS-NSAID index at Week 12 for "delayed tapering" vs. Week 16 for "early tapering").

Test Product (s), Dose(s), and Mode(s) of Administration

Secukinumab 150 mg provided in a 1 mL pre-filled syringe for subcutaneous (s.c.) injection. Secukinumab 150 mg s.c. was administered once per week during the induction period and once every 4 weeks during the maintenance period.

Secukinumab placebo (Placebo) provided in a 1 mL pre-filled syringe for subcutaneous (s.c.) injection.

Statistical Methods

Hierarchical testing strategy

P-values and confidence intervals (CIs) were 2-sided, and the level of significance was set to 5% (2-sided, family-wise Type-1 error). The hierarchical testing strategy comprised the primary efficacy analysis (comparison of secukinumab-Pooled vs. placebo for proving superiority of secukinumab in terms of ASAS20 response at Week 12) and the hypotheses formulated in secondary study objectives 1 to 10 (relating to the various outcomes in ASAS-NSAID score and BASDAI total score), which were to be tested in descending order at the family-wise Type 1 error of 5% (i.e., 11 hypotheses overall). The secondary efficacy variable SF-36 PCS was not included in the hierarchical testing cascade.

Inferential treatment group comparisons of binary efficacy variables (ASAS20 response)

ASAS20 responder rates were analyzed using logistic regression with treatment, TNFα status (TNFα blocker-naïve / TNFα blocker-inadequate response [IR]), and hsCRP status (> central laboratory upper limit of normal / ≤ upper limit of normal) as factors. The 2 secukinumab groups were pooled using a linear contrast. Odds ratios (ORs) and 95%-CI were presented comparing the pooled secukinumab groups to placebo.

For the primary efficacy analysis, missing ASAS20 response data at Week 12 were imputed conservatively and set to "non-response (NR)".

The ASAS20 response comparisons of single secukinumab groups vs. placebo were performed in a similar fashion.

Treatment group comparisons of continuous efficacy variables

The changes from baseline in secondary endpoints with continuous data (i.e., ASAS-NSAID, BASDAI total score, SF-36 PCS) were analyzed using a longitudinal mixed effects ANCOVA model (mixed model for repeated measures; MMRM) with "treatment" and "visit" as factors, and "body weight", "parameter baseline value", "treatment*visit" and "baseline value*visit" interactions as covariates. An unstructured covariance structure was initially assumed for this model, and the "Kenward-Roger (KR) method" for computing the denominator degrees of freedom was initially used. For the ASAS-NSAID score, this initial model was later replaced by a compound symmetry covariance matrix (CS) and "BETWITHIN (BW) method" for computing the denominator degrees of freedom in order to achieve convergence of the model.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
- Diagnosis of active AS with prior documented radiologic evidence fulfilling the Modified New York criteria for AS
- Active AS assessed by total BASDAI ≥ 4 (0-10) at baseline
- Spinal pain as measured by BASDAI Question 2 ≥ 4 cm on a 0-10 cm numeric rating scale at baseline
- Total back pain as measured by VAS ≥ 40 mm (0-100 mm) at baseline
- Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks prior to randomization, with an inadequate response or failure to respond, or less if therapy had to be reduced due to intolerance, toxicity or contraindications
- Patients must report regular intake of NSAIDs of at least 50% of the highest recommended dose at Screening.
- Patients with prior TNFα inhibitor therapy must report regular intake of NSAIDs of at least 50% of the highest recommended dose at baseline after the appropriate washout
- Patients are required to be on a stable dose of NSAIDs for at least 2 weeks before randomization
- Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization
- Patients who have been on a TNFα inhibitor (not more than two) must have experienced an inadequate response to previous or current treatment given at an approved dose for at least 3 months prior to randomization or have been intolerant to at least one administration of an anti-TNFα agent.
- Patients taking MTX or sulfasalazine are allowed to continue their medication and must have taken it for at least 3 months and be on a stable dose for at least 4 weeks prior to randomization

Key Exclusion Criteria:
- Chest X-ray or MRI with evidence of ongoing infectious or malignant process.
- Previous exposure to Secukinumab or any other biologic drug directly targeting IL-17 or IL-17 receptor
- Patients previously treated with any biological immunomodulating agents, except those targeting TNFα
- Patients who have taken more than two anti-TNFα agents
- Pregnant or nursing (lactating) women.
- History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection.
- Patients who are intolerant to NSAIDs

Participant Flow Table

Overall Study

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering	Placebo	Total
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.	
Started	71	70	70	211
Completed	62	65	62	189
Not Completed	9	5	8	22
Adverse Event	5	4	0	9
Lack of Efficacy	1	1	3	5
Physician Decision	1	0	1	2
Subject/guardian decision	2	0	4	6

Baseline Characteristics

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering	Placebo	Total
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.	
Number of Participants [units: participants]	71	70	70	211
Age Continuous (units: Years) Mean ± Standard Deviation				
	46.2±13.36	44.1±11.02	45.4±12.55	45.2±12.32
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	30	28	31	89
Male	41	42	39	122
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)				
Caucasian	69	67	68	204
Black	1	0	0	1
Asian	0	2	1	3

Other	1	1	1	3

Primary Outcome Result(s)

Proportion of patients who achieved ASAS20 response in the pooled secukinumab group compared with the placebo group at Week 12

(Time Frame: Baseline, Week 12)

	Secukinumab - pooled	Placebo
Arm/Group Description	The 2 secukinumab arms (delayed NSAID tapering and early NSAID tapering) pooled.	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.
Number of Participants Analyzed [units: participants]	141	70
Proportion of patients who achieved ASAS20 response in the pooled secukinumab group compared with the placebo group at Week 12 (units: Participants) Count of Participants (Not Applicable)		
	72 (51.06%)	31 (44.29%)

Statistical Analysis

Groups	Placebo, Secukinumab - pooled
P Value	0.3512
Method	Regression, Logistic

Odds Ratio (OR)	1.32
95 % Confidence Interval 2-Sided	0.74 to 2.36

Secondary Outcome Result(s)

Proportion of patients who achieved ASAS20 response in each secukinumab group (delayed NSAID tapering and early NSAID tapering) compared with the placebo group

(Time Frame: Baseline, Week 12, Week 16)

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering	Placebo
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.
Number of Participants Analyzed [units: participants]	71	70	70
Proportion of patients who achieved ASAS20 response in each secukinumab group (delayed NSAID tapering and early NSAID tapering) compared with the placebo group (units: Participants) Count of Participants (Not Applicable)			
Week 12	37 (52.11%)	35 (50%)	31 (44.29%)
Week 16	40 (56.34%)	35 (50%)	29 (41.43%)

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo	Week 12
P Value	0.4010	
Method	Regression, Logistic	
Odds Ratio (OR)	1.33	
95 % Confidence Interval 2-Sided	0.68 to 2.60	

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo	Week 12
P Value	0.4382	
Method	Regression, Logistic	
Odds Ratio (OR)	1.30	
95 % Confidence Interval 2-Sided	0.67 to 2.55	

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo	Week 16
P Value	0.0934	

Method	Regression, Logistic
Odds Ratio (OR)	1.78
95 % Confidence Interval 2-Sided	0.91 to 3.50

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo	Week 16
P Value	0.2619	
Method	Regression, Logistic	
Odds Ratio (OR)	1.47	
95 % Confidence Interval 2-Sided	0.75 to 2.90	

Mean change from baseline in ASAS-NSAID score at Week 12

(Time Frame: Baseline, Week 12)

	Secukinumab - delayed NSAID tapering	**Secukinumab - early NSAID tapering**	**Placebo**	**Secukinumab - pooled**
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly	The 2 secukinumab arms (delayed NSAID tapering and early NSAID tapering) pooled.

	tapering allowed from Week 4 (delayed tapering).	intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.	
Number of Participants Analyzed [units: participants]	71	70	70	141
Mean change from baseline in ASAS-NSAID score at Week 12 (units: Score on scale) Mean ± Standard Deviation				
	-44.9 ± 47.32	-40.3 ± 71.48	-31.5 ± 36.54	-42.6 ± 60.53

Statistical Analysis

Groups	Placebo, Secukinumab - pooled
P Value	0.0997
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS (least square) Mean	-10.29
Standard Error of the mean	6.25
95 % Confidence Interval 2-Sided	-22.55 to 1.96

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo

P Value	0.0888
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	-12.30
Standard Error of the mean	7.23
95 % Confidence Interval 2-Sided	-26.47 to 1.87

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo
P Value	0.2484
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	-8.29
Standard Error of the mean	7.18
95 % Confidence Interval 2-Sided	-22.36 to 5.79

Mean change from baseline in ASAS-NSAID score in each secukinumab group after 12 weeks of exposure (at Week 12 in the secukinumab-delayed NSAID tapering group and at Week 16 in the secukinumab-early NSAID tapering group)

(Time Frame: Baseline, Week 12 (delayed NSAID tapering), Week 16 (early NSAID tapering))

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).
Number of Participants Analyzed [units: participants]	71	70
Mean change from baseline in ASAS-NSAID score in each secukinumab group after 12 weeks of exposure (at Week 12 in the secukinumab-delayed NSAID tapering group and at Week 16 in the secukinumab-early NSAID tapering group) (units: Score on scale) Mean ± Standard Deviation		
Week 12 (delayed NSAID tapering), Week 16 (early NSAID tapering)	-44.9 ± 47.32	-42.5 ± 68.62

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Secukinumab - early NSAID tapering	delayed tapering (W12) vs early tapering (W16)

P Value	0.7735
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	-2.06
95 % Confidence Interval 2-Sided	-16.11 to 11.98

Mean change from baseline in the BASDAI total score

(Time Frame: Baseline, Week 12, Week 16)

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering	Placebo	Secukinumab - pooled
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering).	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.	The 2 secukinumab arms (delayed NSAID tapering and early NSAID tapering) pooled.
Number of Participants Analyzed [units: participants]	71	70	70	141

Mean change from baseline in the BASDAI total score (units: Score on scale) Mean ± Standard Deviation				
Week 12	-2.1 ± 2.16	-2.0 ± 2.10	-1.8 ± 2.00	-2.1 ± 2.12
Week 16	-2.3 ± 1.90	-2.0 ± 1.96	-1.7 ± 1.96	-2.2 ± 1.93

Statistical Analysis

Groups	Placebo, Secukinumab - pooled	Week 12
P Value	0.1926	
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other LS Mean	-0.39	
Standard Error of the mean	0.30	
95 % Confidence Interval 2-Sided	-0.99 to 0.20	

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo	Week 12
P Value	0.1914	
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other LS Mean	-0.46	

Standard Error of the mean	0.35
95 % Confidence Interval 2-Sided	-1.14 to 0.23

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo	Week 12
P Value	0.3397	
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other LS Mean	-0.33	
Standard Error of the mean	0.34	
95 % Confidence Interval 2-Sided	-1.01 to 0.35	

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo	Week 16
P Value	0.0384	
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other LS Mean	-0.68	
Standard Error of the mean	0.33	

95 % Confidence Interval 2-Sided	-1.33 to -0.04

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo	Week 16
P Value	0.2116	
Method	Other Mixed Model for Repeated Measures (MMRM)	
Other LS Mean	-0.41	
Standard Error of the mean	0.33	
95 % Confidence Interval 2-Sided	-1.05 to 0.23	

Mean change from baseline in health-related Quality of Life as measured by the Short Form-36 Health Survey (SF-36) Physical Component Summary (PCS) Score

(Time Frame: Baseline, Week 12)

	Secukinumab - delayed NSAID tapering	Secukinumab - early NSAID tapering	Placebo	Secukinumab - pooled
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of	The 2 secukinumab arms (delayed NSAID tapering and early NSAID tapering) pooled.

	allowed from Week 4 (delayed tapering).	injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering).	secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4.	
Number of Participants Analyzed [units: participants]	71	70	70	141
Mean change from baseline in health-related Quality of Life as measured by the Short Form-36 Health Survey (SF-36) Physical Component Summary (PCS) Score (units: Score on scale) Mean ± Standard Deviation				
	4.8 ± 7.03	6.1 ± 6.92	4.8 ± 7.43	5.5 ± 6.98

Statistical Analysis

Groups	Placebo, Secukinumab - pooled
P Value	0.5384
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	0.63
Standard Error of the mean	1.02
95 % Confidence Interval 2-Sided	-1.38 to 2.63

Statistical Analysis

Groups	Secukinumab - delayed NSAID tapering, Placebo
P Value	0.9251
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	-0.11
Standard Error of the mean	1.18
95 % Confidence Interval 2-Sided	-2.43 to 2.21

Statistical Analysis

Groups	Secukinumab - early NSAID tapering, Placebo
P Value	0.2432
Method	Other Mixed Model for Repeated Measures (MMRM)
Other LS Mean	1.36
Standard Error of the mean	1.16
95 % Confidence Interval 2-Sided	-0.93 to 3.66

Safety Results

All-Cause Mortality

	Secukinumab - delayed NSAID tapering - Treatment Period 1 N = 71	Secukinumab - early NSAID tapering - Treatment Period 1 N = 70	Placebo - Treatment Period 1 N = 70	Secukinumab - delayed NSAID tapering - Treatment Period 2 N = 71	Secukinumab - early NSAID tapering - Treatment Period 2 N = 70	Placebo - Treatment Period 2 N = 70
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.

	drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	controlled period of the study.			
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post-treatment (median duration of 24 weeks).
Additional Description	Any signs or symptoms that occurs from first study drug treatment until 30 days after the last study drug treatment. Adverse events were analyzed by treatment period, i.e., Treatment Period 1 from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16) and Treatment Period 2 (from the day of injection at visit Week 16 onwards until study end).
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment

	Secukinumab - delayed NSAID tapering - Treatment Period 1 N = 71	**Secukinumab - early NSAID tapering - Treatment Period 1 N = 70**	**Placebo - Treatment Period 1 N = 70**	**Secukinumab - delayed NSAID tapering - Treatment Period 2 N = 71**	**Secukinumab - early NSAID tapering - Treatment Period 2 N = 70**	**Placebo - Treatment Period 2 N = 70**
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4)	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4)	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of

	followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.
Total participants affected	4 (5.63%)	3 (4.29%)	1 (1.43%)	1 (1.41%)	0 (0.00%)	1 (1.43%)
Eye disorders						
Iridocyclitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Gastrointestinal disorders						

Abdominal hernia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Crohn's disease	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inguinal hernia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal ulcer	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
Erysipelas	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders						
Nephrolithiasis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders						
Vaginal cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Psoriasis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post-treatment (median duration of 24 weeks).
Additional Description	Any signs or symptoms that occurs from first study drug treatment until 30 days after the last study drug treatment. Adverse events were analyzed by treatment period, i.e., Treatment Period 1 from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16) and Treatment Period 2 (from the day of injection at visit Week 16 onwards until study end).

Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	1%

	Secukinumab - delayed NSAID tapering - Treatment Period 1 N = 71	**Secukinumab - early NSAID tapering - Treatment Period 1 N = 70**	**Placebo - Treatment Period 1 N = 70**	**Secukinumab - delayed NSAID tapering - Treatment Period 2 N = 71**	**Secukinumab - early NSAID tapering - Treatment Period 2 N = 70**	**Placebo - Treatment Period 2 N = 70**
Arm/Group Description	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 1: from first study drug administration at baseline through Week 16	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 1: from first study drug administration at baseline through Week 16 (concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds	Induction with secukinumab 150 mg s.c. once per week (Week 0, 1, 2, 3 and 4) followed by maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 8, 12, 16 and 20), with intermittent placebo injections at Week 5, 6, 7, 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (delayed tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	Placebo at weeks 0, 1, 2, 3 to maintain the blind; followed by induction with secukinumab 150 mg s.c. once per week (Week 4, 5, 6, 7, 8) and maintenance with secukinumab 150 mg s.c. every 4 weeks (Week 12, 16 and 20), with intermittent placebo injections at Week 17, 18 and 19 to maintain the blind. NSAID tapering allowed from Week 4 (early tapering). Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.	Placebo s.c. at Week 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12. After the Week 16 assessments of the secondary endpoint had been performed, these patients received weekly doses of secukinumab 150 mg s.c. (Week 16, 17, 18, 19 and 20). NSAID tapering allowed from Week 4. Treatment Period 2: from the day of injection at visit Week 16 onwards until study end.

	injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	(concretely: until the day before the injection of study drug scheduled at visit Week 16). This corresponds to the placebo-controlled period of the study.	to the placebo-controlled period of the study.			
Total participants affected	53 (74.65%)	56 (80.00%)	55 (78.57%)	25 (35.21%)	23 (32.86%)	22 (31.43%)
Blood and lymphatic system disorders						
Anaemia	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Iron deficiency anaemia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymph node pain	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphopenia	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Monoclonal B-cell lymphocytosis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Monocytosis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutrophilia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders						
Bradycardia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coronary artery disease	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Palpitations	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tachycardia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders						
Ear pain	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Tinnitus	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vertigo	1 (1.41%)	0 (0.00%)	3 (4.29%)	1 (1.41%)	0 (0.00%)	1 (1.43%)
Endocrine disorders						
Hyperprolactinaemia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypothyroidism	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders						
Diplopia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Dry eye	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye irritation	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Iritis	0 (0.00%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Macular degeneration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Presbyopia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Uveitis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Visual impairment	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders						
Abdominal pain	3 (4.23%)	3 (4.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain lower	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Abdominal pain upper	3 (4.23%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphthous ulcer	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea	3 (4.23%)	3 (4.29%)	3 (4.29%)	1 (1.41%)	1 (1.43%)	3 (4.29%)
Diarrhoea haemorrhagic	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Dry mouth	0 (0.00%)	2 (2.86%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Dyspepsia	0 (0.00%)	3 (4.29%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Dysphagia	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Enteritis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Frequent bowel movements	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastritis	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gingival discomfort	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematochezia	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hiatus hernia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inguinal hernia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Nausea	2 (2.82%)	2 (2.86%)	5 (7.14%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Stomatitis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toothache	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions						
Discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Fatigue	0 (0.00%)	1 (1.43%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Feeling hot	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Impaired healing	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza like illness	1 (1.41%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Injection site pruritus	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injection site urticaria	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Oedema peripheral	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral swelling	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Polyp	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thirst	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders						
Cholelithiasis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic steatosis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Immune system disorders						
Allergy to arthropod bite	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seasonal allergy	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations						
Bacterial vaginosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Bronchitis	5 (7.04%)	2 (2.86%)	3 (4.29%)	2 (2.82%)	1 (1.43%)	1 (1.43%)
Candida infection	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (2.82%)	0 (0.00%)	0 (0.00%)
Cystitis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Epstein-Barr virus infection	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erysipelas	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Folliculitis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Fungal infection	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fungal skin infection	1 (1.41%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Furuncle	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Gastroenteritis	2 (2.82%)	4 (5.71%)	3 (4.29%)	1 (1.41%)	0 (0.00%)	1 (1.43%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Gastrointestinal infection	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal viral infection	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes simplex	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Infected bite	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza	1 (1.41%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Laryngitis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lyme disease	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Nasopharyngitis	6 (8.45%)	13 (18.57%)	14 (20.00%)	7 (9.86%)	5 (7.14%)	3 (4.29%)
Oesophageal candidiasis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Onychomycosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Oral herpes	2 (2.82%)	2 (2.86%)	0 (0.00%)	1 (1.41%)	1 (1.43%)	0 (0.00%)
Otitis externa	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Otitis media	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Pharyngitis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Pneumonia	0 (0.00%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulpitis dental	1 (1.41%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory tract infection	2 (2.82%)	4 (5.71%)	3 (4.29%)	1 (1.41%)	1 (1.43%)	3 (4.29%)
Respiratory tract infection viral	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Rhinitis	4 (5.63%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sinusitis	0 (0.00%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Subcutaneous abscess	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Trichomoniasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	1 (1.41%)	3 (4.29%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	2 (2.86%)
Urinary tract infection	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Uterine infection	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications						
Animal bite	0 (0.00%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bone contusion	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Contusion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Fall	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Hand fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Joint dislocation	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Ligament rupture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Ligament sprain	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Limb injury	0 (0.00%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Muscle strain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Overdose	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post-traumatic neck syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	1 (1.43%)
Reactive gastropathy	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Road traffic accident	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	1 (1.43%)	0 (0.00%)

Spinal column injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Wound	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations						
Alanine aminotransferase increased	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aspartate aminotransferase increased	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood glucose increased	2 (2.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood pressure decreased	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood pressure increased	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase increased	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic enzyme increased	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Laboratory test abnormal	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Liver function test increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Red blood cell sedimentation rate increased	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Transaminases increased	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight decreased	2 (2.82%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

White blood cell count decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
White blood cell count increased	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders						
Decreased appetite	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetes mellitus	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypercholesterolaemia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pseudohyperkalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Pseudohypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders						
Ankylosing spondylitis	3 (4.23%)	1 (1.43%)	6 (8.57%)	2 (2.82%)	0 (0.00%)	1 (1.43%)
Arthralgia	2 (2.82%)	2 (2.86%)	2 (2.86%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Arthritis	1 (1.41%)	1 (1.43%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Back pain	4 (5.63%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bursitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Joint swelling	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Muscle tightness	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myalgia	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteoarthritis	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity	1 (1.41%)	2 (2.86%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)

Rheumatic fever	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sacroiliitis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal osteoarthritis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal pain	0 (0.00%)	1 (1.43%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spondylitis	0 (0.00%)	1 (1.43%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spondyloarthropathy	1 (1.41%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spondylolisthesis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Synovial cyst	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tendon disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Tendon pain	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tendonitis	0 (0.00%)	1 (1.43%)	1 (1.43%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Tenosynovitis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders						
Ageusia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Autonomic nervous system imbalance	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Cervicobrachial syndrome	1 (1.41%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Disturbance in attention	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Dizziness	0 (0.00%)	2 (2.86%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Dysaesthesia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysgeusia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	12 (16.90%)	10 (14.29%)	6 (8.57%)	4 (5.63%)	3 (4.29%)	1 (1.43%)
Intercostal neuralgia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Migraine	1 (1.41%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nerve compression	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Paraesthesia	2 (2.82%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paresis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Presyncope	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sciatica	1 (1.41%)	1 (1.43%)	1 (1.43%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Tension headache	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders						
Apathy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Depression	1 (1.41%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Insomnia	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervousness	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Restlessness	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sleep disorder	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders						
Dysuria	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematuria	1 (1.41%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Proteinuria	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal failure	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders						
Dysmenorrhoea	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Menorrhagia	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Uterine pain	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vaginal haemorrhage	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Vulvovaginal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders						
Asthma	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic obstructive pulmonary disease	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cough	2 (2.82%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	3 (4.29%)	0 (0.00%)
Dyspnoea exertional	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal congestion	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	0 (0.00%)	2 (2.86%)	1 (1.43%)	0 (0.00%)	3 (4.29%)	0 (0.00%)
Rhinorrhoea	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders						
Angioedema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Dermatitis	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyshidrotic eczema	1 (1.41%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Eczema	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Eczema asteatotic	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erythema	1 (1.41%)	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Guttate psoriasis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperhidrosis	0 (0.00%)	2 (2.86%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Night sweats	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Palmoplantar pustulosis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Photosensitivity reaction	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus	1 (1.41%)	1 (1.43%)	3 (4.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psoriasis	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)

Rash	2 (2.82%)	1 (1.43%)	3 (4.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash maculo-papular	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Seborrhoea	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin exfoliation	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin fissures	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin irritation	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Solar dermatitis	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)
Xeroderma	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (1.41%)	0 (0.00%)	0 (0.00%)
Vascular disorders						
Circulatory collapse	0 (0.00%)	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematoma	1 (1.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertension	4 (5.63%)	3 (4.29%)	4 (5.71%)	0 (0.00%)	0 (0.00%)	1 (1.43%)
Hypotension	0 (0.00%)	1 (1.43%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Conclusion:

The descriptive efficacy outcomes in the placebo-controlled phase of the study were consistently in favor of the 2 secukinumab regimens compared with the placebo group by rapidly reducing the signs and symptoms of active ankylosing spondylitis (AS) in a study population consisting of both TNFα blocker-naïve and TNFα blocker-inadequate response patients. The observed treatment effects of secukinumab were in line with the results from previous clinical studies in patients with active AS across all clinical outcomes, including physical function and health-related quality of life measures. However, due to an unexpectedly high placebo response in the placebo group, the actual treatment contrasts were consistently smaller than anticipated and the prespecified, hierarchical statistical tests thus failed to demonstrate superiority of secukinumab in a confirmatory manner. The reasons for the exceptional placebo response observed in this study remain unclear. The safety analysis results were consistent with the established safety profile of secukinumab 150 mg and did not show new safety signals or other unexpected safety findings. In spite of the lack of statistically significant differences to placebo, the results of the present study are consistent with previous secukinumab studies in AS, showing that secukinumab is an effective, safe, and well-tolerated treatment option for patients with AS that allows a relevant NSAID reduction independently of early or delayed tapering without compromising its beneficial treatment effects.

Date of Clinical Trial Report

26-Aug-2020