NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication(s)

Active ankylosing spondylitis

Protocol Number

CAIN457F2314

Protocol Title

A randomized, double-blind, placebo-controlled phase III study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long-term safety, tolerability and efficacy up to 3 years in subjects with active ankylosing spondylitis

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: January 2014 (Actual)
Primary Completion Date: February 2015 (Actual)
Study Completion Date: December 2017 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

Multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group design.

A screening period (SCR) running up to 10 weeks before randomization was used to assess eligibility. At baseline (BSL), 226 subjects whose eligibility was confirmed were randomized to one of three treatment groups (1:1:1) and were planned to be treated for 156 weeks:

Group 1: secukinumab iv (10 mg/kg) at BSL, Weeks 2 and 4, followed by secukinumab 150 mg sc (1.0 mL) plus placebo sc (1.0 mL) every four weeks starting at Week 8 through Week 152

Group 2: secukinumab iv (10 mg/kg) at BSL, Weeks 2 and 4, followed by secukinumab 300 mg sc (2 x 1.0 mL) every four weeks starting at Week 8 through Week 152

Group 3: placebo iv at BSL, Weeks 2 and 4, followed by placebo sc at Weeks 8 and 12; At Week 16, subjects who were randomized to placebo at baseline were re-randomized by the Interactive Response Technology (IRT) to receive secukinumab 150 mg plus placebo or secukinumab 300 mg (1:1) every four weeks through Week 152

Centers

54 centers in 10 countries: United States(11), Spain(5), Russia(5), Greece(5), Germany(14), Mexico(3), Belgium(2), Czech Republic(2), Portugal(4), United Kingdom(3)

Objectives:

Primary Objective

The primary objective was to demonstrate that at least one dose of secukinumab (150 mg sc or 300 mg sc) at Week 16 is superior to placebo in subjects with active AS (despite current or previous NSAID, DMARD and/or anti-TNFα therapy) based on the proportion of subjects achieving an ASAS20 (Assessment of Spondyloarthritis International Society criteria) response.

Secondary objectives

1. To demonstrate the efficacy of at least one dose of secukinumab (150 mg or 300 mg) at Week 16 is superior to placebo in subjects with active AS based on the proportion of subjects achieving an ASAS40 response.
2. To demonstrate the efficacy of at least one dose of secukinumab (150 mg or 300 mg) at Week 16 is superior to placebo in subjects with active AS based on the change from baseline of hsCRP.
3. To demonstrate the efficacy of at least one dose of secukinumab (150 mg or 300 mg) at Week 16 is superior to placebo in subjects with active AS based on the proportion of subjects meeting the ASAS 5/6 response criteria.
4. To demonstrate the efficacy of at least one dose of secukinumab (150 mg or 300 mg) at Week 16 is superior to placebo in subjects with active AS based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
5. To demonstrate the efficacy of at least one dose of secukinumab (150 mg or 300 mg) at Week 16 is superior to placebo in subjects with active AS based on the change from baseline in the proportion of subjects achieving ASAS partial remission.
6. To assess prefilled syringe (PFS) usability utilizing the Self-Injection assessment checklist and Possible Hazard assessment check list and to assess subject satisfaction with prefilled syringes utilizing the Self-Injection Assessment Questionnaire (SIAQ).
7. The overall safety and tolerability of secukinumab liquid-in-vial (LiV) and PFS formulations compared to placebo as assessed by vital signs, clinical laboratory values and AEs monitoring.

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

Investigational treatment:

- Secukinumab LiV for iv infusion provided in glass vials, each containing 125 mg/5 mL secukinumab
- Secukinumab 150 mg provided in 1.0 mL PFS for sc injection

Statistical Methods

The primary and key secondary analyses were performed after all subjects had completed the visit associated with the primary endpoint (Week 16) in order to support regulatory filing. As these analyses were performed on all subjects and no changes have been made to the corresponding pre-specified analyses methods, no adjustment to the type I error rate was necessary for this Week 156 analysis.

Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomized subjects who were assigned to study treatment (Full Analysis Set). Baseline characteristics were analyzed for all randomized subjects.

Safety analyses were performed for all randomized subjects who received at least one dose of study treatment (Safety Set).

A sequentially rejective testing strategy was used to evaluate the study hypotheses for the primary and secondary variables while retaining a family-wise type I error of 5%, adjusting for multiplicity of testing across the doses and endpoints.

The primary efficacy variable was the response to treatment according to the ASAS 20 criteria at Week 16, defined as an improvement of ≥20% and ≥1 unit on a scale of 0-10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 0-10 in the remaining domain. The statistical hypothesis for ASAS 20 being tested was that there was no difference in the proportion of subjects fulfilling the ASAS 20 criteria at Week 16 in any of the secukinumab regimens versus the placebo regimen. The primary analysis was conducted via logistic regression with treatment and TNF-α inhibitor status as factors and weight as a covariate. Odds ratios and 95% CI were presented comparing each secukinumab regimen to placebo. A sensitivity analysis to determine the robustness of the logistic regression model was performed using a non-parametric ANCOVA model with the same independent variables as the logistic regression model. The impact of missing data on the analysis results of ASAS 20 response was assessed as well by repeating the logistic regression model using multiple imputation and observed data analysis to handle missing data.

For the binary secondary efficacy variables, the proportion of subjects meeting the ASAS 40 (defined as an improvement of ≥40% and ≥2 units on a scale of 0-10 in at least three of the four main domains and no worsening at all in the remaining domain), the ASAS 5/6 improvement criteria (defined as an improvement of ≥20% in at least five domains) or the ASAS partial remission criteria (defined as a value not above 2 units in each of the 4 core ASAS domains on a scale of 0-10) were presented by treatment sequence up to Week 156 based on the observed and imputed data. The respective summaries were also provided by TNF-α IR status based on the observed data only.

For the continuous secondary efficacy variables, between-treatment differences in the change from baseline in hsCRP and total BASDAI were evaluated using a mixed-effect model repeated measures (MMRM) model based on the observed data with treatment group and analysis visit.

Treatment-emergent AEs (i.e. events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) were defined as events with an onset on or before last dose + 84 days. The crude incidence of treatment-emergent AEs was summarized by primary SOC and PT. In addition, exposure time-adjusted rates incidence rates including 95% confidence intervals were provided for the entire treatment period (up to the data cut-off date of 11-Dec-2017) to adjust for differences in exposure between treatment

groups. For laboratory parameters, vital signs and ECG parameters summary tables on number and percentage of subjects with newly occurring notable abnormalities were provided.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria: moderate to severe AS, prior radiographic evidence according to the Modified NY Criteria (1984), inadequate response to NSAIDs. -- Exclusion criteria: pregnancy or lactation, on-going infectious or malignant process on a chest X-ray or MRI, previous exposure to IL-17 or IL-17R targeting therapies, previous exposure to any biological immunomodulating agent excluding TNF antagonists, previous cell depleting therapy.

Participant Flow Table

Primary Assessment (up to Week 16)

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Started	74	76	76
FAS	74	76	76
Safety Set	74	76	75
Completed	74	75	73
Not Completed	0	1	3
Withdrawal by Subject	0	1	3

Week 16 - 156

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Started	74	75	73
Completed	55	62	63
Not Completed	19	13	10

Adverse Event	4	2	3
Withdrawal by Subject	7	3	5
No longer requires treatment	0	1	0
Lost to Follow-up	5	0	0
Lack of Efficacy	3	5	2
Pregnancy	0	1	0
Physician Decision	0	1	0

Baseline Characteristics

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.	Total
Number of Participants [units: participants]	74	76	76	226
Age Continuous (units: Years) Mean ± Standard Deviation				
	42.9±11.11	42.1±11.81	42.7±11.43	42.5±11.41
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	28	26	36	90
Male	46	50	40	136

Race/Ethnicity, Customized
(units:)
Count of Participants (Not Applicable)

White	54	52	58	164
Black or African American	2	2	1	5
Asian	1	2	0	3
American Indian or Alaska Native	4	6	5	15
Unknown	0	1	0	1
Other	13	13	12	38

Summary of Efficacy

Primary Outcome Result(s)

Assessment of Spondyloarthritis International Society criteria / ASAS 20 response

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
Assessment of Spondyloarthritis International Society criteria / ASAS 20 response (units: Participants) Count of Participants (Not Applicable)			

Week 16 : Responder	43	46	28
Week 16 : Non-Responder	31	30	48

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	0.0093
Method	Regression, Logistic
Odds Ratio (OR)	2.41
95 % Confidence Interval 2-Sided	1.24 to 4.69

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.
P Value	0.0037
Method	Regression, Logistic
Odds Ratio (OR)	2.68
95 % Confidence Interval 2-Sided	1.38 to 5.21

Secondary Outcome Result(s)

ASAS 40 response

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
ASAS 40 response (units: Participants) Count of Participants (Not Applicable)			
Week 16 : Responder	30	32	16
Week 16 : Non-Responder	44	44	60

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	0.0100
Method	Regression, Logistic
Odds Ratio (OR)	2.59
95 % Confidence Interval 2-Sided	1.26 to 5.35

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.

P Value	0.0051
Method	Regression, Logistic
Odds Ratio (OR)	2.81
95 % Confidence Interval 2-Sided	1.36 to 5.78

Serum hsCRP

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
Serum hsCRP (units: mg/L) Mean ± Standard Deviation			
Baseline	15.79 ± 21.075	11.08 ± 13.285	13.91 ± 19.999
Week 16	7.68 ± 13.277	4.34 ± 5.433	15.34 ± 21.694
Change from Baseline to Week 16	-8.06 ± 21.132	-6.75 ± 13.778	0.57 ± 11.629

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	<0.0001

Method	Mixed Models Analysis	
Other Relative treatment effect	0.51	Relative treatment effect = exponential of the difference in LSM on the log e scale or the geometric LSM ratio on the original scale. For values less than 1, AIN457 has a greater reduction than Placebo.
95 % Confidence Interval 2-Sided	0.38 to 0.68	

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.	
P Value	<0.0001	
Method	Mixed Models Analysis	
Other Relative treatment effect	0.44	Relative treatment effect = exponential of the difference in LSM on the log e scale or the geometric LSM ratio on the original scale. For values less than 1, AIN457 has a greater reduction than Placebo.
95 % Confidence Interval 2-Sided	0.33 to 0.60	

ASAS 5/6 response

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
ASAS 5/6 response (units: Participants) Count of Participants (Not Applicable)			
Week 16 : Responder	31	30	11
Week 16 : Non-Responder	43	46	65

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	0.0002
Method	Regression, Logistic
Odds Ratio (OR)	4.46
95 % Confidence Interval 2-Sided	2.01 to 9.92

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.
P Value	0.0004

Method	Regression, Logistic
Odds Ratio (OR)	4.21
95 % Confidence Interval 2-Sided	1.89 to 9.38

Bath Ankylosing Spondylitis Disease Activity Index / BASDAI

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
Bath Ankylosing Spondylitis Disease Activity Index / BASDAI (units: Points) Mean ± Standard Deviation			
Baseline	6.958 ± 1.3913	6.963 ± 1.3766	6.907 ± 1.2600
Week 16	4.451 ± 2.5623	4.178 ± 2.7038	5.369 ± 2.2574
Change from Baseline to Week 16	-2.548 ± 2.4559	-2.796 ± 2.6374	-1.590 ± 2.0084

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	0.0347
Method	Mixed Models Analysis

Mean Difference (Final Values)	-0.83
Standard Error of the mean	0.390
95 % Confidence Interval 2-Sided	-1.60 to -0.06

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.
P Value	0.0018
Method	Mixed Models Analysis
Mean Difference (Final Values)	-1.23
Standard Error of the mean	0.390
95 % Confidence Interval 2-Sided	-2.00 to -0.46

Pre-filled syringe usability

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	**Secukinumab 10 mg/kg i.v. / 300 mg s.c.**	**Placebo i.v. and s.c.**
Number of Participants Analyzed [units: participants]	74	76	75
Pre-filled syringe usability (units:) Count of Participants (Not Applicable)			

Self-administration Week 8 : Successful Self-administration	72	73	71
Self-administration Week 8 : Unsuccessful Self-administration	0	0	1
Self-administration Week 8 : Missing	2	3	3
Self-administration Week 12 : Successful Self-administration	74	75	72
Self-administration Week 12 : Unsuccessful Self-administration	0	0	0
Self-administration Week 12 : Missing	0	1	3

Pre-filled syringe possible hazard

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	75
Pre-filled syringe possible hazard (units:) Count of Participants (Not Applicable)			
Week 8:Was needle stick in a critical area? : Yes	0	0	0
Week 8:Was needle stick in a critical area? : No	73	73	72
Week 8:Was needle stick in a critical area? : Missing	1	3	3

Week 8: Was needle stick in a non-critical area? : Yes	2	5	3
Week 8: Was needle stick in a non-critical area? : No	71	68	69
Week 8: Was needle stick in a non-critical area? : Missing	1	3	3
Week 8: Was any part of the device swallowed? : Yes	0	0	0
Week 8: Was any part of the device swallowed? : No	73	73	72
Week 8: Was any part of the device swallowed? : Missing	1	3	3
Week 8: Was allergic reaction to device noticed? : Yes	0	0	0
Week 8: Was allergic reaction to device noticed? : No	73	73	72
Week 8: Was allergic reaction to device noticed? : Missing	1	3	3
Week 8: Was pain increased due to bent needle? : Yes	0	0	0
Week 8: Was pain increased due to bent needle? : No	73	73	72
Week 8: Was pain increased due to bent needle? : Missing	1	3	3

Week 8: Was there breakage of device observed? : Yes	0	0	0
Week 8: Was there breakage of device observed? : No	73	73	72
Week 8: Was there breakage of device observed? : Missing	1	3	3
Week 8:Was swallowing of debris observed? : Yes	0	0	0
Week 8:Was swallowing of debris observed? : No	73	73	72
Week 8:Was swallowing of debris observed? : Missing	1	3	3
Week 8:Was any other problem observed? : Yes	1	0	0
Week 8:Was any other problem observed? : No	72	73	72
Week 8:Was any other problem observed? : Missing	1	3	3
Week 8:Was less than the full dose administered : Yes	0	0	0
Week 8:Was less than the full dose administered : No	73	73	72
Week 8:Was less than the full dose administered : Missing	1	3	3
Week 12: Was needle stick in a critical area? : Yes	0	0	0

Week 12: Was needle stick in a critical area? : No	74	75	72
Week 12: Was needle stick in a critical area? : Missing	0	1	3
Week 12: Was needle stick in a non-critical area? : Yes	1	4	3
Week 12: Was needle stick in a non-critical area? : No	73	71	69
Week 12: Was needle stick in a non-critical area? : Missing	0	1	3
Week 12: Was any part of the device swallowed? : Yes	0	0	0
Week 12: Was any part of the device swallowed? : No	74	75	72
Week 12: Was any part of the device swallowed? : Missing	0	1	3
Week 12: Was allergic reaction to device noticed? : Yes	0	0	0
Week 12: Was allergic reaction to device noticed? : No	74	75	72
Week 12: Was allergic reaction to device noticed? : Missing	0	1	3
Week 12: Was pain increased due to bent needle? : Yes	0	0	0

Week 12: Was pain increased due to bent needle? : No	74	75	72
Week 12: Was pain increased due to bent needle? : Missing	0	1	3
Week 12: Was there breakage of device observed? : Yes	0	0	0
Week 12: Was there breakage of device observed? : No	74	75	72
Week 12: Was there breakage of device observed? : Missing	0	1	3
Week 12: Was swallowing of debris observed? : Yes	0	0	0
Week 12: Was swallowing of debris observed? : No	74	75	72
Week 12: Was swallowing of debris observed? : Missing	0	1	3
Week 12: Was any other problem observed? : Yes	1	1	0
Week 12: Was any other problem observed? : No	73	74	72
Week 12: Was any other problem observed? : Missing	0	1	3
Week 12: Was less than the full dose administered? : Yes	0	0	0
Week 12: Was less than the full dose administered? : No	74	75	72

Week 12: Was less than the full dose administered? : Missing	0	1	3

Prefilled syringe patient satisfaction assessment

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	75
Prefilled syringe patient satisfaction assessment (units: Points) Mean ± Standard Deviation			
Week 0: Feeling about injections	7.97 ± 1.946	7.66 ± 2.369	8.01 ± 1.927
Week 8: Feeling about injections	7.96 ± 2.538	7.68 ± 2.296	8.24 ± 2.082
Week 12: Feeling about injections	8.45 ± 1.968	7.93 ± 2.201	8.25 ± 1.997
Week 16: Feeling about injections	8.15 ± 2.337	7.99 ± 2.269	8.41 ± 2.037
Week 0: Self-confidence	6.27 ± 2.811	6.66 ± 2.315	6.52 ± 2.273
Week 8: Self-confidence	7.08 ± 2.520	6.66 ± 2.855	7.41 ± 2.198
Week 12: Self-confidence	7.01 ± 2.603	7.28 ± 2.231	7.42 ± 2.230
Week 16: Self-confidence	7.51 ± 2.388	7.23 ± 2.566	7.64 ± 2.192
Week 0: Satisfaction with self-injection	5.34 ± 2.692	6.12 ± 2.429	5.30 ± 2.694
Week 8: Satisfaction with self-injection	7.67 ± 1.734	7.50 ± 1.667	7.39 ± 2.002
Week 12: Satisfaction with self-injection	7.68 ± 1.483	7.50 ± 1.816	7.46 ± 1.780

Week 16: Satisfaction with self-injection	7.57 ± 1.741	7.82 ± 1.933	7.67 ± 1.577

ASAS partial remission

	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Secukinumab 10 mg/kg i.v. / 300 mg s.c.	Placebo i.v. and s.c.
Number of Participants Analyzed [units: participants]	74	76	76
ASAS partial remission (units: Participants) Count of Participants (Not Applicable)			
Week 16 : Responder	7	16	1
Week 16 : Non-Responder	67	60	75

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c., Placebo i.v. and s.c.
P Value	0.0593
Method	Regression, Logistic
Odds Ratio (OR)	7.71
95 % Confidence Interval 2-Sided	0.92 to 64.42

Statistical Analysis

Groups	Secukinumab 10 mg/kg i.v. / 300 mg s.c., Placebo i.v. and s.c.
P Value	0.0046
Method	Regression, Logistic
Odds Ratio (OR)	19.39
95 % Confidence Interval 2-Sided	2.49 to 150.79

Summary of Safety

Safety Results

All-Cause Mortality

	Any Secukinumab 150 mg N = 110	Any Secukinumab 300 mg N = 113	Any Secukinumab N = 223	Placebo N = 75
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit up to approximately 3 years.
Additional Description	Patients randomized to Placebo at Baseline are reported under Placebo for AEs starting before re-randomization to Secukinumab (Week 16) and under the respective Secukinumab arm for AEs starting after re-randomization to Secukinumab (Week 16).
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	Any Secukinumab 150 mg N = 110	Any Secukinumab 300 mg N = 113	Any Secukinumab N = 223	Placebo N = 75
Total participants affected	11 (10.00%)	11 (9.73%)	22 (9.87%)	1 (1.33%)
Cardiac disorders				
Coronary artery disease	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Myocardial infarction	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Sinus node dysfunction	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Supraventricular extrasystoles	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Supraventricular tachycardia	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Ear and labyrinth disorders				
Vertigo	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Eye disorders				
Cataract	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)

Iridocyclitis	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Vogt-Koyanagi-Harada syndrome	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Gastrointestinal disorders				
Haemorrhoids	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Nausea	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
General disorders and administration site conditions				
Fatigue	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Infections and infestations				
Pneumonia	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Pyelonephritis acute	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Urinary tract infection	1 (0.91%)	1 (0.88%)	2 (0.90%)	1 (1.33%)
Injury, poisoning and procedural complications				
Ankle fracture	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Cervical vertebral fracture	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Fall	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Hand fracture	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Limb injury	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Rib fracture	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Tibia fracture	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				

Ankylosing spondylitis	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Arthralgia	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Osteoarthritis	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Sacroiliitis	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Spinal pain	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Malignant melanoma	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Nervous system disorders				
Loss of consciousness	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Migraine	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Syncope	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Psychiatric disorders				
Schizophrenia	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Reproductive system and breast disorders				
Cervical dysplasia	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Pneumothorax	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)
Respiratory failure	0 (0.00%)	1 (0.88%)	1 (0.45%)	0 (0.00%)
Vascular disorders				
Deep vein thrombosis	1 (0.91%)	0 (0.00%)	1 (0.45%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit up to approximately 3 years.
Additional Description	Patients randomized to Placebo at Baseline are reported under Placebo for AEs starting before re-randomization to Secukinumab (Week 16) and under the respective Secukinumab arm for AEs starting after re-randomization to Secukinumab (Week 16).
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Any Secukinumab 150 mg N = 110	Any Secukinumab 300 mg N = 113	Any Secukinumab N = 223	Placebo N = 75
Total participants affected	86 (78.18%)	89 (78.76%)	175 (78.48%)	28 (37.33%)
Eye disorders				
Iritis	0 (0.00%)	3 (2.65%)	3 (1.35%)	0 (0.00%)
Uveitis	3 (2.73%)	5 (4.42%)	8 (3.59%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal pain	1 (0.91%)	3 (2.65%)	4 (1.79%)	2 (2.67%)
Abdominal pain upper	5 (4.55%)	3 (2.65%)	8 (3.59%)	1 (1.33%)
Diarrhoea	11 (10.00%)	9 (7.96%)	20 (8.97%)	0 (0.00%)
Food poisoning	2 (1.82%)	3 (2.65%)	5 (2.24%)	0 (0.00%)

Gastritis	3 (2.73%)	1 (0.88%)	4 (1.79%)	0 (0.00%)
Nausea	3 (2.73%)	4 (3.54%)	7 (3.14%)	1 (1.33%)
Toothache	3 (2.73%)	2 (1.77%)	5 (2.24%)	1 (1.33%)
Vomiting	0 (0.00%)	4 (3.54%)	4 (1.79%)	0 (0.00%)
General disorders and administration site conditions				
Fatigue	5 (4.55%)	4 (3.54%)	9 (4.04%)	0 (0.00%)
Influenza like illness	2 (1.82%)	1 (0.88%)	3 (1.35%)	2 (2.67%)
Infections and infestations				
Bronchitis	14 (12.73%)	9 (7.96%)	23 (10.31%)	1 (1.33%)
Conjunctivitis	1 (0.91%)	3 (2.65%)	4 (1.79%)	1 (1.33%)
Ear infection	0 (0.00%)	3 (2.65%)	3 (1.35%)	0 (0.00%)
Gastroenteritis viral	1 (0.91%)	3 (2.65%)	4 (1.79%)	0 (0.00%)
Influenza	3 (2.73%)	9 (7.96%)	12 (5.38%)	0 (0.00%)
Nasopharyngitis	27 (24.55%)	27 (23.89%)	54 (24.22%)	2 (2.67%)
Oral herpes	1 (0.91%)	3 (2.65%)	4 (1.79%)	1 (1.33%)
Pharyngitis	3 (2.73%)	6 (5.31%)	9 (4.04%)	1 (1.33%)
Pharyngotonsillitis	0 (0.00%)	3 (2.65%)	3 (1.35%)	0 (0.00%)
Pneumonia	1 (0.91%)	3 (2.65%)	4 (1.79%)	0 (0.00%)
Pulpitis dental	4 (3.64%)	1 (0.88%)	5 (2.24%)	2 (2.67%)
Respiratory tract infection	12 (10.91%)	10 (8.85%)	22 (9.87%)	4 (5.33%)
Rhinitis	6 (5.45%)	4 (3.54%)	10 (4.48%)	0 (0.00%)
Sinusitis	8 (7.27%)	1 (0.88%)	9 (4.04%)	2 (2.67%)
Tonsillitis	4 (3.64%)	4 (3.54%)	8 (3.59%)	0 (0.00%)

Upper respiratory tract infection	12 (10.91%)	16 (14.16%)	28 (12.56%)	2 (2.67%)
Urinary tract infection	4 (3.64%)	6 (5.31%)	10 (4.48%)	2 (2.67%)
Injury, poisoning and procedural complications				
Sunburn	0 (0.00%)	3 (2.65%)	3 (1.35%)	0 (0.00%)
Investigations				
Alanine aminotransferase increased	3 (2.73%)	2 (1.77%)	5 (2.24%)	0 (0.00%)
Metabolism and nutrition disorders				
Hypercholesterolaemia	4 (3.64%)	3 (2.65%)	7 (3.14%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Ankylosing spondylitis	5 (4.55%)	3 (2.65%)	8 (3.59%)	2 (2.67%)
Arthralgia	14 (12.73%)	13 (11.50%)	27 (12.11%)	2 (2.67%)
Arthritis	4 (3.64%)	3 (2.65%)	7 (3.14%)	0 (0.00%)
Back pain	7 (6.36%)	12 (10.62%)	19 (8.52%)	2 (2.67%)
Fibromyalgia	1 (0.91%)	3 (2.65%)	4 (1.79%)	1 (1.33%)
Muscle spasms	3 (2.73%)	5 (4.42%)	8 (3.59%)	1 (1.33%)
Myalgia	3 (2.73%)	1 (0.88%)	4 (1.79%)	0 (0.00%)
Osteoarthritis	2 (1.82%)	4 (3.54%)	6 (2.69%)	0 (0.00%)
Pain in extremity	4 (3.64%)	2 (1.77%)	6 (2.69%)	1 (1.33%)
Spinal pain	4 (3.64%)	4 (3.54%)	8 (3.59%)	0 (0.00%)
Spondylitis	0 (0.00%)	3 (2.65%)	3 (1.35%)	0 (0.00%)
Tendonitis	3 (2.73%)	1 (0.88%)	4 (1.79%)	0 (0.00%)

Nervous system disorders				
Dizziness	2 (1.82%)	4 (3.54%)	6 (2.69%)	1 (1.33%)
Headache	12 (10.91%)	14 (12.39%)	26 (11.66%)	5 (6.67%)
Hypoaesthesia	2 (1.82%)	0 (0.00%)	2 (0.90%)	2 (2.67%)
Migraine	5 (4.55%)	1 (0.88%)	6 (2.69%)	0 (0.00%)
Paraesthesia	4 (3.64%)	0 (0.00%)	4 (1.79%)	0 (0.00%)
Psychiatric disorders				
Depression	3 (2.73%)	3 (2.65%)	6 (2.69%)	1 (1.33%)
Respiratory, thoracic and mediastinal disorders				
Cough	6 (5.45%)	6 (5.31%)	12 (5.38%)	2 (2.67%)
Oropharyngeal pain	7 (6.36%)	7 (6.19%)	14 (6.28%)	0 (0.00%)
Rhinitis allergic	3 (2.73%)	1 (0.88%)	4 (1.79%)	0 (0.00%)
Skin and subcutaneous tissue disorders				
Pruritus	1 (0.91%)	3 (2.65%)	4 (1.79%)	0 (0.00%)
Vascular disorders				
Hypertension	7 (6.36%)	5 (4.42%)	12 (5.38%)	0 (0.00%)

Other Relevant Findings

None.

Conclusion:

Secukinumab demonstrated a rapid onset of response and superior efficacy over placebo in the treatment of subjects with moderate to severe active AS, as assessed by measures of clinical response, quality of life and markers of inflammation. Both the iv-150 mg and iv-300 regimens of secukinumab resulted in significantly greater responses than placebo, with respect to the primary endpoint (Assessment Of Spondyloarthritis International Society Criteria, ASAS20) and most secondary endpoints (ASAS40, ASAS 5/6, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), High Sensitivity C-Reactive Protein(hsCRP)), but only the iv-300 mg group showed superiority for ASAS partial remission at Week 16. These trends continued over the entire treatment period. Efficacy response rates with regard to multiple aspects of the disease (ASAS20, ASAS40, and change from baseline in subject's global assessment of disease activity, subject's assessment of total spinal pain, inflammation (mean of BASDAI questions 5 and 6), Bath Ankylosing Spondylitis Functional Index (BASFI), nocturnal pain, Bath Ankylosing Spondylitis Metrology Index (BASMI), and BASDAI) were sustained through 156 weeks of treatment. The degree of improvement shown through measures of clinical response, physical function, quality of life and markers of inflammation was also sustained through 156 weeks of treatment, with a trend for a greater response in the iv-300 mg group observed in a number of endpoints, with numerically higher responses in ASAS40, ASAS partial remission, Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease, ASDAS major improvement, total BASDAI, and BASDAI 50, through Week 156.

Secukinumab was efficacious through 156 weeks of treatment in both Tumor Necrosis Factor (TNF)-α naive and TNF-inadequate responder (IR) subjects. The iv-300 mg dose tended to show a better response in TNF naive and in the smaller subgroup of TNF-IR subjects than the iv-150mg dose over a number of endpoints including ASAS20, ASAS40, ASAS5/6, total BASDAI, BASDAI50 and ASAS partial remission.

The safety profile of secukinumab iv-150 mg and iv-300 mg dose regimens showed no clinically meaningful differences between treatments through Week 156. Overall, the present study confirmed the safety profile from the large secukinumab safety database across multiple indications with no new or unexpected safety findings.

Date of Clinical Trial Report

30-Jul-2018