NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication(s)

Tendinopathy

Protocol Number

CAIN457X2201

Protocol Title

A randomized, double-blind, placebo-controlled, parallel group, Phase II, 24-week study investigating the efficacy, safety and tolerability of AIN457 in patients with active overuse tendinopathy refractory to oral NSAIDs/acetaminophen, physiotherapy or corticosteroid injections

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: December 2017
Primary Completion Date: August 2019
Study Completion Date: October 2019

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, multi-center, Phase II study of subcutaneous secukinumab 300 mg in 98 randomized patients with overuse rotator-cuff tendinopathy without systemic inflammatory disease and refractory to NSAIDs/acetaminophen, physiotherapy or corticosteroids. Patient and investigator were blinded throughout the study, while the sponsor was blinded until after the analysis of the primary endpoint. The study consisted of a 4-week screening period, a 2-week run-in period, a 12-week treatment period and a 12-week follow-up period after last treatment.

The screening period was used to assess eligibility and to start/continue patients on physiotherapy. In the run-in period the patient had 2 weeks of stable NSAID/acetaminophen intake and standardized physiotherapy. Patients who met eligibility criteria at screening after the run-in period underwent baseline evaluations.

Eligible subjects as per inclusion/exclusion criteria were randomized to one of the two treatment arms: 7 s.c. injections of secukinumab 300 mg or placebo in a 12-week treatment period, followed by a 12-week follow-up period. Randomization was stratified by the following 2 factors: Partial tear/no tear and previous steroid injection (yes/no), in order to achieve approximate balance between these factors in the treatment groups. Primary endpoint assessments were performed at 14 weeks (2 weeks after the last injection).

Patients were required to come to the out-patient clinic approximately 2-4 hours prior to dosing for the evaluations. Dosing was on-site, except for injections at 1 and 3 weeks, which could be done either on site or by a nurse at the patient's home.

Safety assessments included physical examinations, electrocardiogram (ECG), vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), AE and SAE monitoring.

Centers

12 centers in 5 countries: Czech Republic (3), Germany (2), The Netherlands (1), The United States of America (5), The United Kingdom (1)

Objectives:

Primary Objective

The primary aim of this study is to assess the efficacy of secukinumab 300 mg s.c. vs. placebo in patients with overuse rotator cuff tendinopathy in relieving clinical symptoms at week 14.

Secondary Objectives

- Change from baseline in WORC score at weeks 2, 4, 8, 12, 18 and 24.
- Disability of Arm, Shoulder and Hand Questionnaire (QuickDASH) score at weeks 2, 4, 8, 12, 14, 18 and 24 (where available in local language/dialect).
- American Shoulder and Elbow Surgeons Shoulder Evaluation Form (ASES) score at weeks 2, 4, 8, 12, 14, 18 and 24
- EQ5D-5L your health today and index scores (see Appendix 1 for SAS code) at weeks 2, 4, 8, 12, 14, 18 and 24
- Pain score using a VAS scale (considering the last 24 hours) at weeks 2, 4, 8, 12, 14, 18 and 24
- Patient global assessment (PGA) score of disease activity, using VAS scale (considering the last 24 hours), at weeks 2, 4, 8, 12, 14, 18 & 24
- Physician global assessment (PhGA) score of disease activity, using VAS scale (considering last 24 hours), at weeks 2, 4, 8, 12, 14, 18 & 24
- MRI Sein score at weeks 8, 14 and 24

Test Product, Doses, and Mode of Administration

Group 1: Secukinumab 300 mg s.c. (2 x 150 mg subcutaneous injections)
Group 2: Placebo s.c. (2 subcutaneous injections)

Statistical Methods

The primary end-point (change from baseline in WORC score at Week 14) was analyzed by repeated measures analysis of covariance including all WORC scores available. The change at Week 14 was compared between treatments to address the primary objective.

The baseline WORC score was included as a covariate. The stratification factors partial tear/no tear and previous steroid injection (yes/no) were included in the model as fixed effects along with fixed effects for treatment, timepoint and the treatment by timepoint interaction. An unstructured within-patient covariance was considered.

The number of covariance and mean parameters may have been reduced by model comparison tools such as the BIC criterion for model fit. Missing variables were considered missing at random.

The adjusted mean of treatment effect at Week 14 as well as the difference between treatment arms were reported along with a 95% one-sided (90% two-sided) confidence interval.

The primary analysis was also repeated for patients where the affected arm was the dominant arm.

The secondary variables (except for the Sein score) have been summarized descriptively and analyzed similar to the primary analysis.

The secondary variable Sein MRI score at weeks 14 and 24 was analyzed by ordinal categorical regression. A model with an additive treatment effect on the cumulative logistic scale was used, and the common treatment effect estimated and reported together with 90% asymptotic two-sided confidence intervals. Baseline SEIN score were included as a covariate and the stratification factors, partial tear/no tear and previous steroid injection (yes/no) were included in the model as fixed effects.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Male or non-pregnant, non-lactating female patients 18 to 65 years of age at randomization
2. Presence of unilateral rotator cuff tendinopathy with:
    a. Symptoms present ≥6 weeks, but <12 months prior to randomization
    b. Tendinopathy with no more than a 50% tear as established by ultrasound at screening (historic data acceptable if not older than 3 months) and MRI at baseline: Sein MRI tendinopathy scoring system grade I-III; with no tear or partial tear [maximum 50% tendon thickness (Bauer tendon thickness score maximum 2); AP length maximum 10 mm (Bauer tendon length score max 2)]. Maximum 50% of patients with partial tear
    c. Pain in the affected shoulder (at rest or on movement) on at least 3 days out of 7 days in the past week prior to baseline and a score of ≥4 out of 10 on a VAS pain scale
    d. Positive “Painful Arc Test” on examination and/or nightly pain in the affected shoulder on at least 4 out of 7 days in the past week prior to baseline
3. The rotator-cuff tendinopathy must have been refractory to standard treatment, including NSAIDs and physiotherapy

Exclusion Criteria:

1. Rheumatologic, inflammatory diseases, including but not limited to: PsA, AS and RA
2. Previous shoulder surgery in affected shoulder

3. History of adhesive capsulitis/frozen shoulder or calcification in the tendon (in affected or contralateral shoulder) confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline
4. Symptomatic osteoarthritis of the shoulder (gleno-humeral, acromioclavicular) (in affected or contralateral shoulder confirmed by X-Ray, historic X-Rays can be used if performed within 3 months of baseline
5. Neck conditions, including but not limited to cervical spine syndrome, which in the opinion of the investigator, may explain the patient's symptoms
6. Previous platelet rich plasma injections within the last 12 months prior to randomization
7. Previous treatment with any cell-depleting therapies including but not limited to anti- CD20, investigational agents (e.g. Campath, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
8. Previous exposure to any biologic immunomodulating agents, including but not limited to TNFalpha inhibitors (including, but not limited to adalimumab, infliximab), or biologics targeting IL-17 (including, but not limited to secukinumab, ixekizumab or brodalumab) or the IL-17 receptor within the last 12 months prior to baseline
9. Any intraarticular/subacromial corticosteroid treatment within 8 weeks prior to randomization and more than 3 injections for the current tendinopathy. Oral, intramuscular or i.v. corticosteroid treatment within the last 12 months prior to randomization.

Participant Flow Table

Overall study

	secukinumab	Placebo	Total
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.	
Started	49	47	96
Completed	46	44	90
Not Completed	3	3	6
Adverse Event	1	0	1
Physician Decision	1	1	2
Withdrawal by Subject	1	2	3

Follow-up epoch

	secukinumab	Placebo	Total
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.	
Started	46	44	90
Completed	46	42	88
Not Completed	0	2	2
Withdrawal by Subject	0	2	2

Baseline Characteristics

	secukinumab	Placebo	Total
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.	
Number of Participants [units: participants]	49	47	96
Age Continuous[1] (units: years) Mean ± Standard Deviation			
	44.8±11.51	49.1±10.56	46.9±11.20
Sex: Female, Male[2] (units: Participants) Count of Participants (Not Applicable)			
Female	17	23	40
Male	32	24	56

Race/Ethnicity, Customized[3]

(units: Participants)

Asian	1	0	1
Black or African American	3	1	4
White	43	45	88
Unknown	1	0	1
Other	1	1	2

[1] Demographic summary (Safety analysis set)
[2] 41.7% of participants were female, and 58.3% were male
[3] 1% Asian, 4.2% Black or African American, 91.7% White, 1% Unknown, 2.1% Other

Primary Outcome Results

The Western Ontario Rotator Cuff (WORC) patient reported outcome (PRO) score at week 14 for All Patients - Statistical Analysis results of total WORC scores at week 14

WORC PRO score at week 14. The WORC Index consists of 21 items divided into 5 Domains: Physical Symptoms (6 items), Sport/Recreation (4 items), Work Function (4 items), Lifestyle Function (4 items) and Emotional Function (3 items). The total scores and sub scores used were the percentages of the normal scores with 0 being worst and 100 being best.
(Time Frame: Week 14 (Day 99))

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41

The Western Ontario Rotator Cuff (WORC) patient reported outcome (PRO) score at week 14 for All Patients - Statistical Analysis results of total WORC scores at week 14
(units: Scores)
Number (90% Confidence Interval)

	37.00 (30.10 to 43.90)	37.77 (30.40 to 45.15)

Statistical Analysis

Groups	secukinumab, Placebo	All Patients at day 99
P Value	0.875	
Method	LS mean	LS mean change from baseline in WORC total percentage score
Mean Difference (Final Values)	-0.77	
90% Confidence Interval 2-Sided	-8.84 to 7.30	

Secondary Outcome Results

The Western Ontario Rotator Cuff (WORC) patient reported outcome (PRO) scores over time

WORC score at Days 15, 29, 57, 85, 127, and End of Study (day 169)

(Time Frame: Days 15, 29, 57, 85, 127, and End of Study)

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
The Western Ontario Rotator Cuff (WORC) patient reported outcome (PRO) scores over time (units: Scores) Number (90% Confidence Interval)		
Day 15	12.39 (6.99 to 17.79)	8.42 (2.66 to 14.18)
Day 29	22.35 (16.38 to 28.32)	19.49 (13.11 to 25.86)

Day 57	28.74 (22.19 to 35.29)	30.11 (23.08 to 37.13)
Day 85	34.86 (28.18 to 41.53)	33.48 (26.35 to 40.61)
Day 127	41.86 (34.96 to 48.77)	38.50 (31.12 to 45.88)
End of Study	43.41 (36.21 to 50.61)	40.97 (33.27 to 48.66)

Statistical Analysis

Groups	secukinumab, Placebo	All patients at day 15
P Value	0.190	
Method	LS mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	3.97	
90% Confidence Interval 2-Sided	-1.03 to 8.97	

Statistical Analysis

Groups	secukinumab, Placebo	All patients at day 29
Method	LS Mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	3.97	
90% Confidence Interval 2-Sided	-3.39 to 9.11	

Statistical Analysis

Groups	secukinumab, Placebo	All patients at day 57
P Value	0.761	
Method	LS Mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	0.761	
90% Confidence Interval 2-Sided	-8.81 to 6.08	

Statistical Analysis

Groups	secukinumab, Placebo	All patients at day 85
P Value	0.765	
Method	LS Mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	0.765	
90% Confidence Interval 2-Sided	-6.27 to 9.03	

Statistical Analysis

Groups	secukinumab, Placebo	All patients at day 127
P Value	0.491	
Method	LS Mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	0.491	
90% Confidence Interval 2-Sided	-4.73 to 11.45	

Statistical Analysis

Groups	secukinumab, Placebo	All patients at end of study
P Value	0.639	
Method	LS Mean	LS mean change from baseline in WORC total percentage score
Difference and 90% CI versus placebo	2.44	
90% Confidence Interval 2-Sided	-6.19 to 11.07	

Disability of Arm, Shoulder and Hand Questionnaire Score (QuickDASH) over time

(Time Frame: Days 15, 29, 57, 85, 99, 127, and End of Study)

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Disability of Arm, Shoulder and Hand Questionnaire Score (QuickDASH) over time (units: Scores) Number (90% Confidence Interval)		
Day 15	-11.64 (-16.14 to -7.14)	-8.23 (-13.02 to -3.44)
Day 29	-18.31 (-23.20 to -13.41)	-16.95 (-22.18 to -11.73)
Day 57	-22.43 (-27.55 to -17.30)	-24.01 (-29.49 to -18.52)
Day 85	-28.14 (-33.55 to -22.73)	-27.22 (-32.98 to -21.45)
Day 99	-29.45 (-34.72 to -24.19)	-30.69 (-36.30 to -25.07)

Day 127	-32.86 (-38.26 to -27.46)	-31.99 (-37.75 to -26.23)
End of Study	-33.89 (-39.27 to -28.50)	-35.40 (-41.13 to -29.67)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of QuickDASH total score (PD Analysis Set) at day 99
P Value	0.735	Difference and 90% CI versus placebo
Method	LS Mean	LS mean change from baseline in QuickDASH total score
Difference and 90% CI versus Placebo	1.23	
90% Confidence Interval 2-Sided	-4.81 to 7.28	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of QuickDASH total score (PD analysis set) at End of Study
P Value	0.689	
Method	LS Mean	LS mean change from baseline in QuickDASH total score
Difference and 90% CI versus Placebo	1.51	
90% Confidence Interval 2-Sided	-4.76 to 7.79	

American Shoulder and Elbow Surgeons (ASES) Score over time

Patient Reported Outcome: American Shoulder and Elbow Surgeons Shoulder Evaluation Form (ASES) score is self-administered and has 17 questions in the areas of shoulder symptoms and functions. The ASES total score ranges from 0 to 100 (best).

(Time Frame: Days 15, 29, 57, 85, 99, 127, and End of Study)

	secukinumab	Placebo
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
American Shoulder and Elbow Surgeons (ASES) Score over time (units: Scores) Number (90% Confidence Interval)		
Day 15	8.66 (3.98 to 13.33)	5.26 (0.26 to 10.25)
Day 29	17.53 (12.35 to 22.71)	14.37 (8.82 to 19.92)
Day 57	24.15 (18.34 to 29.96)	22.56 (16.31 to 28.81)
Day 85	30.50 (24.51 to 36.50)	26.97 (20.51 to 33.43)
Day 99	31.29 (25.28 to 37.31)	27.79 (21.33 to 34.26)
Day 127	34.92 (28.80 to 41.05)	32.94 (26.33 to 39.56)
End of Study	37.29 (30.97 to 43.62)	36.15 (29.33 to 42.97)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of ASES total score (PD analysis) at day 99
P Value	0.411	
Method	LS Mean	LS mean change from baseline in ASES total percentage score
Difference and 90% CI versus placebo	3.50	

90% Confidence Interval 2-Sided	-3.54 to 10.54

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of ASES total score (PD analysis) at End of Study set)
P Value	0.804	
Method	LS Mean	LS mean change from baseline in ASES total percentage score
Difference and 90% CI versus placebo	1.14	
90% Confidence Interval 2-Sided	-6.50 to 8.78	

Your Health Today score over time

Patient Reported Outcome: Statistical analysis results of EQ-5D-5L Index score for Your health Today questionnaire, which reflects how good or bad the subjets Health is on a scale from 0 (worst health) to 100 (best health). Your health today reflects how good or bad the subjects health is on a scale from 0 (worst health) to 100 (best health)
(Time Frame: Days 15, 29, 57, 85, 99, 127, and End of Study)

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Your Health Today score over time (units: Scores) Number (90% Confidence Interval)		
Day 15	-0.22 (-4.02 to 3.58)	0.02 (-4.02 to 4.07)
Day 29	3.27 (-0.71 to 7.25)	3.56 (-0.69 to 7.81)
Day 57	3.19	9.02

	(-1.07 to 7.45)	(4.45 to 13.59)
Day 85	7.36 (2.84 to 11.89)	7.79 (2.96 to 12.62)
Day 99	8.75 (4.13 to 13.38)	10.01 (5.09 to 14.94)
Day 127	9.55 (5.29 to 13.80)	13.59 (9.05 to 18.13)
End of Study	10.22 (4.84 to 15.60)	12.13 (6.36 to 17.89)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of Your Health Today EQ-5D-5L Index score at day 99 (PD Analysis Set)
P Value	0.706	
Method	LS Mean	LS Mean change from baseline in Your Health Today Score at day 99
Difference and 90% CI versus placebo	-1.26	
90% Confidence Interval 2-Sided	-6.81 to 4.29	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of Your Health Today EQ-5D-5L Index score at End of Study
P Value	0.647	
Method	LS Mean	LS mean change from baseline in Your Health Today score
Difference and 90% CI versus placebo	-1.90	
90% Confidence Interval 2-Sided	-8.79 to 4.99	

EQ-5D-5L Index score over time

Patient Reported Outcome: Statistical analysis results of EQ-5D-5L Index score, which contains 6 items to assess Health Status (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). Overall scores range from 0 to 1 with lower scores representing a higher Level of disfunction.
(Time Frame: Days 15, 29, 57, 85, 99, 127 and End of Study)

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
EQ-5D-5L Index score over time (units: Scores) Number (90% Confidence Interval)		
Day 15	0.07 (0.05 to 0.10)	0.04 (0.01 to 0.07)
Day 29	0.10 (0.07 to 0.13)	0.09 (0.05 to 0.12)
Day 57	0.12 (0.09 to 0.15)	0.11 (0.08 to 0.15)
Day 85	0.16 (0.13 to 0.19)	0.14 (0.10 to 0.18)
Day 99	0.16 (0.13 to 0.20)	0.15 (0.11 to 0.19)
Day 127	0.19 (0.15 to 0.23)	0.17 (0.13 to 0.21)
End of Study	0.19 (0.16 to 0.23)	0.18 (0.14 to 0.22)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of of EQ-5D-5L Index score at day 99 (PD Analysis Set)
P Value	0.613	
Method	LS Mean	LS mean change from baseline in EQ-5D-5L Index score
Difference and 90% CI versus placebo	0.01	
90% Confidence Interval 2-Sided	-0.03 to 0.06	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of of EQ-5D-5L Index score at End of Study (PD Analysis Set)
P Value	0.740	
Method	LS Mean	LS mean change from baseline in EQ-5D-5L Index score
Difference and 90% CI versus placebo	0.02	
90% Confidence Interval 2-Sided	-0.04 to 0.06	

Pain score over time using a VAS scale

Pain intensity is assessed by a Visual Analog Scale (VAS) which is measured on a 10-cm line that represents a continuum between “no pain” and “worst pain"
(Time Frame: Days 15, 29, 57, 85, 99, 127 and End of Study)

	secukinumab	Placebo
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Pain score over time using a VAS scale (units: Scores) Number (90% Confidence Interval)		
Day 15	-12.11 (-19.52 to -4.70)	-9.50 (-17.30 to -1.71)
Day 29	-26.04 (-33.97 to -18.11)	-23.13 (-31.52 to -14.74)
Day 57	-35.52 (-43.67 to -27.37)	-32.83 (-41.52 to -24.15)
Day 85	-42.63 (-50.88 to -34.38)	-37.97 (-46.74 to -29.21)
Day 99	-46.11 (-54.10 to -38.12)	-40.56 (-49.00 to -32.11)
Day 127	-49.44 (-57.45 to -41.44)	-45.27 (-53.75 to -36.79)
End of Study	-52.23 (-60.31 to -44.14)	-50.74 (-59.40 to -42.08)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of pain score using VAS scale (PD Analysis Set) at day 99
P Value	0.281	
Method	LS Mean	LS Mean CFB (90% CI)
Difference and 90% CI versus placebo	-5.55	
90% Confidence Interval 2-Sided	-14.07 to 2.97	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of pain score using VAS scale (PD Analysis Set) at End of Study
P Value	0.780	
Method	LS Mean	LS Mean CFB (90% CI)
Difference and 90% CI versus placebo	-1.49	
90% Confidence Interval 2-Sided	-10.33 to 7.35	

Patient global assessment (PGA) score using a VAS scale at End of Study

The patient's global assessment of disease activity is performed using a 100 mm Visual Analog Scale (VAS) ranging from "no activity" to "most active" in the last 24 hours.
(Time Frame: Days 15, 29, 57, 85, 99, 127 and End of Study)

	secukinumab	Placebo
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Patient global assessment (PGA) score using a VAS scale at End of Study (units: Scores) Number (95% Confidence Interval)		
Day 15	-6.33 (-13.44 to 0.79)	-8.09 (-15.79 to -0.38)
Day 29	-22.25 (-29.68 to -14.82)	-16.38 (-24.43 to -8.33)
Day 57	-29.40 (-37.06 to -21.74)	-25.69 (-34.04 to -17.34)
Day 85	-37.57 (-45.01 to -30.12)	-31.75 (-39.79 to -23.72)
Day 99	-38.43 (-45.88 to -30.97)	-35.10 (-43.14 to -27.07)
Day 127	-43.78 (-51.23 to -36.33)	-38.32 (-46.37 to -30.26)
End of Study	-47.72 (-55.15 to -40.28)	-39.43 (-47.45 to -31.40)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of pain score using VAS scale (PD Analysis Set) at day 99
P Value	0.489	
Method	LS Mean	LS Mean change from baseline in VAS score
Difference and 90% CI versus placebo	-3.32	
90% Confidence Interval 2-Sided	-11.28 to 4.64	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of pain score using VAS scale at End of Study
P Value	0.087	
Method	LS Mean	LS Mean change from baseline in VAS score
Difference and 90% CI versus placebo	-8.29	
90% Confidence Interval 2-Sided	-16.26 to -0.32	

Physician global assessment (PhGA) score using a VAS scale over time

Physician global assessment (PhGA) score using a VAS scale (considering the last 24 hours)
(Time Frame: Days 15, 29, 57, 85, 99, 127 and End of Study)

	secukinumab	Placebo
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Physician global assessment (PhGA) score using a VAS scale over time (units: Score) Number (90% Confidence Interval)		
Day 15	-13.99 (-20.22 to -7.75)	-9.11 (-15.80 to -2.42)
Day 29	-25.01 (-31.51 to -18.50)	-19.42 (-26.42 to -12.43)
Day 57	-30.78 (-37.57 to -23.99)	-27.83 (-35.13 to -20.53)
Day 85	-33.42 (-40.68 to -26.16)	-37.88 (-45.66 to -30.11)
Day 99	-35.72 (-42.66 to -28.79)	-41.73 (-49.15 to -34.31)
Day 127	-41.72 (-48.32 to -35.12)	-44.18 (-51.28 to -37.08)
End of Study	-44.64 (-51.86 to -37.41)	-44.26 (-52.02 to -36.51)

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of PhGA score using VAS scale at day 99
P Value	0.210	
Method	LS Mean	LS Mean CFB (90% CI)
Difference and 99% CL versus placebo	6.10	
90% Confidence Interval 2-Sided	-1.90 to 13.91	

Statistical Analysis

Groups	secukinumab, Placebo	Statistical analysis results of PhGA score using VAS scale at End of Study
P Value	0.942	
Method	LS Mean	LS Mean CFB (90% CI)
Difference and 90% CI versus placebo	-0.37	
90% Confidence Interval 2-Sided	-8.86 to 8.11	

Pharmacokinetics – Cmin

Mean trough concentrations Cmin is a pharmacokinetics term for the minimum blood plasma concentration reached by a drug prior to administration of a second dose (mass/volume) Serum trough concentrations of secukinumab 300 mg group

(Measured at Days 1, 29, 85 and EOS)

	secukinumab
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)
Number of Participants Analyzed [units: participants]	47
Pharmacokinetics - Cmin (units: µg/mL) Mean ± Standard Deviation	
Mean trough concentration after first 4 weekly doses	90.4 ± 30.7
Week 12	13.2 ± 6.67

Immunogenicity assessment - Treatment emergent ADAs

Number of Participants with Treatment emergent Anti-secukinumab antibodies
(Time Frame: Day 1 and End of Study)

	secukinumab	**Placebo**
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Immunogenicity assessment - Treatment emergent ADAs (units: Participants)		
Day 1	0	1
End of Study	0	0

Number of participants with tendinosis grade score 1, 2 or 3 measured by magnetic resonance imaging (MRI) Sein scores

(Time Frame: Baseline and Day 99)

	secukinumab	Placebo
Arm/Group Description	AIN457 300 mg subcutaneously (s.c.)	Placebo s.c.
Number of Participants Analyzed [units: participants]	47	41
Number of participants with tendinosis grade score 1, 2 or 3 measured by magnetic resonance imaging (MRI) Sein scores (units: Score)		
Baseline grade 1	31	25
Baseline grade 2	11	10
Baseline grade 3	3	3
Day 99 grade 1	31	26
Day 99 grade 2	11	9
Day 99 grade 3	3	3

Safety Results

All-Cause Mortality

	AIN457 300 mg s.c. N = 49	Placebo N = 47
Arm/Group Description	AIN457 300 mg	Placebo s.c.
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Approximately 40 weeks: 15 Dec 2017 through 17th Oct 2019
Additional Description	Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment
Source Vocabulary for Table Default	MedDRA (22.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	AIN457 300 mg s.c. N = 49	Placebo N = 47

Arm/Group Description	AIN457 300 mg	Placebo s.c.
Total participants affected	36 (73.47%)	34 (72.34%)
Blood and lymphatic system disorders		
Neutropenia	3 (6.12%)	1 (2.13%)
Cardiac disorders		
Angina pectoris	0 (0.00%)	1 (2.13%)
Tachycardia	0 (0.00%)	1 (2.13%)
Gastrointestinal disorders		
Abdominal discomfort	2 (4.08%)	0 (0.00%)
Abdominal pain	2 (4.08%)	0 (0.00%)
Abdominal pain upper	1 (2.04%)	0 (0.00%)
Constipation	0 (0.00%)	1 (2.13%)
Diarrhoea	2 (4.08%)	1 (2.13%)
Faeces soft	1 (2.04%)	0 (0.00%)
Gastrooesophageal reflux disease	1 (2.04%)	0 (0.00%)
Irritable bowel syndrome	0 (0.00%)	1 (2.13%)
Nausea	6 (12.24%)	5 (10.64%)
Vomiting	1 (2.04%)	0 (0.00%)
General disorders and administration site conditions		
Chest pain	1 (2.04%)	0 (0.00%)
Fatigue	1 (2.04%)	2 (4.26%)
Feeling hot	0 (0.00%)	1 (2.13%)
Influenza like illness	1 (2.04%)	0 (0.00%)

Injection site erythema	1 (2.04%)	2 (4.26%)
Injection site haematoma	2 (4.08%)	1 (2.13%)
Injection site pain	0 (0.00%)	1 (2.13%)
Injection site paraesthesia	1 (2.04%)	0 (0.00%)
Injection site pruritus	1 (2.04%)	1 (2.13%)
Oedema peripheral	0 (0.00%)	1 (2.13%)
Infections and infestations		
Acute sinusitis	1 (2.04%)	0 (0.00%)
Cellulitis	1 (2.04%)	0 (0.00%)
Fungal infection	0 (0.00%)	1 (2.13%)
Fungal skin infection	3 (6.12%)	0 (0.00%)
Gastroenteritis	2 (4.08%)	1 (2.13%)
Gastroenteritis viral	0 (0.00%)	1 (2.13%)
Gastrointestinal infection	0 (0.00%)	1 (2.13%)
Gastrointestinal viral infection	1 (2.04%)	0 (0.00%)
Lymphangitis	1 (2.04%)	0 (0.00%)
Nasopharyngitis	8 (16.33%)	5 (10.64%)
Oral candidiasis	0 (0.00%)	1 (2.13%)
Oral herpes	1 (2.04%)	0 (0.00%)
Periodontitis	1 (2.04%)	0 (0.00%)
Pharyngitis	1 (2.04%)	0 (0.00%)
Pulpitis dental	0 (0.00%)	1 (2.13%)
Pustule	0 (0.00%)	1 (2.13%)
Respiratory tract infection	0 (0.00%)	1 (2.13%)
Rhinitis	0 (0.00%)	2 (4.26%)

Sinusitis	0 (0.00%)	1 (2.13%)
Upper respiratory tract infection	2 (4.08%)	4 (8.51%)
Urinary tract infection	1 (2.04%)	0 (0.00%)
Injury, poisoning and procedural complications		
Arthropod bite	0 (0.00%)	1 (2.13%)
Fall	2 (4.08%)	0 (0.00%)
Hand fracture	0 (0.00%)	1 (2.13%)
Infusion related reaction	1 (2.04%)	0 (0.00%)
Injection related reaction	1 (2.04%)	0 (0.00%)
Limb injury	1 (2.04%)	0 (0.00%)
Meniscus injury	1 (2.04%)	1 (2.13%)
Muscle strain	1 (2.04%)	0 (0.00%)
Procedural pain	0 (0.00%)	1 (2.13%)
Skin abrasion	1 (2.04%)	0 (0.00%)
Tendon rupture	1 (2.04%)	0 (0.00%)
Tooth fracture	0 (0.00%)	1 (2.13%)
Wrist fracture	0 (0.00%)	1 (2.13%)
Investigations		
Alanine aminotransferase increased	2 (4.08%)	1 (2.13%)
Aspartate aminotransferase increased	1 (2.04%)	1 (2.13%)
Blood creatine phosphokinase increased	1 (2.04%)	0 (0.00%)
Gamma-glutamyltransferase increased	1 (2.04%)	0 (0.00%)
Red blood cell sedimentation rate increased	0 (0.00%)	1 (2.13%)
Metabolism and nutrition disorders		

Diabetes mellitus	0 (0.00%)	1 (2.13%)
Gout	0 (0.00%)	1 (2.13%)
Musculoskeletal and connective tissue disorders		
Arthralgia	2 (4.08%)	2 (4.26%)
Back pain	1 (2.04%)	4 (8.51%)
Muscle spasms	1 (2.04%)	0 (0.00%)
Musculoskeletal pain	3 (6.12%)	1 (2.13%)
Musculoskeletal stiffness	0 (0.00%)	1 (2.13%)
Myalgia	1 (2.04%)	1 (2.13%)
Neck pain	3 (6.12%)	1 (2.13%)
Osteoarthritis	0 (0.00%)	1 (2.13%)
Pain in extremity	0 (0.00%)	1 (2.13%)
Patellofemoral pain syndrome	0 (0.00%)	1 (2.13%)
Spinal pain	1 (2.04%)	0 (0.00%)
Tendon disorder	0 (0.00%)	1 (2.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Benign bone neoplasm	0 (0.00%)	1 (2.13%)
Benign neoplasm of skin	1 (2.04%)	1 (2.13%)
Nervous system disorders		
Carpal tunnel syndrome	1 (2.04%)	0 (0.00%)
Dizziness	2 (4.08%)	1 (2.13%)
Dizziness postural	0 (0.00%)	1 (2.13%)
Headache	7 (14.29%)	7 (14.89%)
Paraesthesia	1 (2.04%)	1 (2.13%)

Somnolence	1 (2.04%)	0 (0.00%)
Psychiatric disorders		
Anxiety	1 (2.04%)	0 (0.00%)
Phonophobia	1 (2.04%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (2.04%)	0 (0.00%)
Oropharyngeal pain	1 (2.04%)	0 (0.00%)
Rhinorrhoea	1 (2.04%)	0 (0.00%)
Sinus congestion	0 (0.00%)	1 (2.13%)
Throat irritation	0 (0.00%)	1 (2.13%)
Skin and subcutaneous tissue disorders		
Actinic keratosis	0 (0.00%)	1 (2.13%)
Dermatitis	0 (0.00%)	1 (2.13%)
Dermatitis allergic	1 (2.04%)	0 (0.00%)
Eczema	1 (2.04%)	0 (0.00%)
Erythema	1 (2.04%)	0 (0.00%)
Keratolysis exfoliativa acquired	0 (0.00%)	1 (2.13%)
Rash	1 (2.04%)	0 (0.00%)
Skin hyperpigmentation	1 (2.04%)	0 (0.00%)
Skin ulcer	1 (2.04%)	0 (0.00%)

Conclusion:

The efficacy of secukinumab in relieving tendinopathy symptoms was not statistically different from the placebo group, and thus the primary endpoint was not met, although in most assessments and at most time points the secukinumab group had numerically better results.

Similar improvements were observed in the secondary and exploratory analyses. Considerable placebo response could be due to including too many patients with mild disease, who could benefit from physiotherapy and pain medication alone.

Twelve weeks of treatment with secukinumab 300 mg s.c. was considered safe in patients with overuse rotator cuff tendinopathy.

Date of Clinical Trial Report

4th August 2020