Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Secukinumab

Trial Indication(s)

Rheumatoid Arthritis

Protocol Number

CAIN457F2302/CAIN457F2302E1

Protocol Title

A randomized, double-blind, placebo-controlled study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the safety, tolerability and long term efficacy up to 2 years in patients with active rheumatoid arthritis who have an inadequate response to anti-TNFα agents (CAIN457F2302) and a three year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active rheumatoid arthritis (CAIN457F2302E1)

Clinical Trial Phase

Phase 3

Phase of Drug Development

III

Study Start/End Dates

Core Study Start Date: August 2011 (Actual)
Core Study Completion Date: September 2015 (Actual)
Extension Study Start Date: Sep 2013 (Actual)
Extension Study Completion Date: May 2015 (Actual) Terminated

Reason for Termination (If applicable)

This study was terminated early (unrelated to safety) due to the results of study AIN457F2309, which indicated the efficacy of AIN457 was not comparable to the currently available RA treatment, abatacept, thus leading to closing of the AIN457 RA program

Study Design/Methodology

The core study used a double-blind, randomized, parallel-group, placebo-controlled design. A screening (SCR) period of 4 weeks before randomization was used to assess eligibility followed by a treatment period of 2 years. At baseline (BSL), patients whose eligibility was confirmed were randomized to one of three treatment groups:

Group 1: secukinumab intravenously (i.v.) (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 75 mg subcutaneously (s.c.) starting at Week 8 and injected every 4 weeks,

Group 2: secukinumab i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks,

Group 3: placebo i.v. at BSL, Weeks 2 and 4 then placebo s.c. starting at Week 8 and injected every 4 weeks

At Week 24, efficacy of secukinumab treatment was assessed based on an ACR20 response. No database lock was performed and the study continued blinded, as placebo patients were rerandomized to secukinumab 75 mg or 150 mg. Blinding was kept until the end of the core study. During the extension study, all patients were switched to secukinumab 150 mg sc.c regimen.

At Week 16, patients were classified as responders (≥20% improvement from baseline in both tender and swollen joint counts) or non-responders and were re-assigned/re-randomized at Week 16 by the Interactive Response Technology (IRT) to receive treatment up to 2 years, as follows:

Patients on secukinumab 75 mg s.c. (Group 1) continued to receive secukinumab 75 mg s.c. every 4 weeks regardless of responder status,

Patients on secukinumab 150 mg s.c. (Group 2) continued to receive secukinumab 150 mg s.c. every 4 weeks regardless of responder status,

Patients on secukinumab placebo (Group 3) who were non-responders at Week 16 were reassigned at Week 16 to receive secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks,

Patients on secukinumab placebo (Group 3) who were responders at Week 16 continued to receive secukinumab placebo until Week 24. At Week 24, these patients received secukinumab 75 mg s.c. or 150 mg s.c. (1:1) every 4 weeks regardless of responder status.

Rescue medication was not allowed until Week 24. However, patients who were deemed not to be benefiting from the study drug by the Investigator or for any reason on their own accord were free to discontinue participation in the study at any time. A Follow-up visit was done 12 weeks after last study treatment administration for patients who terminated the study early or for patients who completed the study but did not enter the extension study.

Patients who completed the 2 year study were eligible to enter the open-label extension study (CAIN457F2302E1) where they received 150 mg secukinumab s.c. every 4 weeks in an open-label fashion. All patients on 75 mg who entered the extension study were switched to 150 mg. The total combined duration of treatment for the core study and the extension study was planned to be five years (at Week 260). The treatment schedule for the extension study was separated into yearly periods, 3, 4, and 5 corresponding to the third, fourth, and fifth year of treatment under the combined protocols.

Due to a decision to close the secukinumab RA program, it was decided to present in this report the primary efficacy data and all safety data collected during the core and extension studies.

Centers

174 centers in 16 countries: United States(47), Turkey(6), Thailand(7), Romania(3), Panama(2), Mexico(6), Japan(41), Italy(8), India(12), Hungary(12), Guatemala(4), United Kingdom(6), Colombia(4), Canada(3), Belgium(3), Argentina(10)

Objectives:

Primary Core study CAIN457F2302

- The primary objective of core study CAIN457F2302 was to demonstrate that the efficacy of secukinumab 75 mg or 150 mg at Week 24 is superior to placebo in patients with active RA based on the proportion of patients achieving an ACR20 response.

Primary Extension study CAIN457F2302E1

- The primary objective of the extension study CAIN457F2302E1 was to evaluate the long-term efficacy of secukinumab 150 mg with respect to ACR20, ACR50 and ACR70 response over time.

Secondary objectives of the core study CAIN457F2302

- The improvement (change) from baseline on secukinumab 75 mg or 150 mg is superior to placebo for the Health Assessment Questionnaire – Disability Index (HAQ-DI) after 24 weeks of treatment.
- The change from baseline on secukinumab (75 mg and 150 mg pooled and individual dose) is superior to placebo for the van der Heijde modified total Sharp score (vdH-mTSS) after 24 weeks of treatment.
- Secukinumab 75 mg or 150 mg is superior to placebo (as originally randomized) with regards to the proportion of patients achieving MCR (continuous six-month period of ACR70 response) at 1 year.

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

Secukinumab 150 mg LYVI for s.c. injection or i.v. infusion

Placebo matching secukinumab 150 mg LYVI for s.c. injection or i.v. infusion

Secukinumab 150 mg/1mL for s.c. injection in Pre-filled syringe (PFS), for extension study only

Statistical Methods

Due to a decision to close down the secukinumab RA program, the analysis plan was reduced compared to what was specified in the protocol. However, the changes only impacted planned secondary and exploratory efficacy objectives. Safety was analyzed for the entire study duration of CAIN457F2302 and CAIN457F2302E1.

Statistical analyses of efficacy variables were performed on an intent-to-treat basis, involving all randomized patients who were assigned to study treatment (Full Analysis Set). Baseline characteristics were analyzed for all randomized patients. Safety analyses were performed for all randomized patients 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 ACR20 criteria at Week 24. The statistical hypothesis for ACR20 being tested was that there was no difference in the proportion of patients fulfilling the ACR20 criteria at Week 24 in any of the secukinumab regimens versus the placebo regimen. The primary analysis was conducted via logistic regression with treatment as a factor and weight as a continuous covariate. Odds ratios and 95% confidence intervals (CIs) were presented comparing each secukinumab regimen to placebo.

For the continuous key secondary efficacy variables, between-treatment differences in the change from baseline in DAS28-CRP, and HAQ-DI were evaluated using a mixed-effect model repeated measures (MMRM) model with treatment group and analysis visit as factors and, as continuous covariates, the baseline value and weight. Treatment by analysis visit and the baseline value by analysis visit were included as interaction terms in the model. An unstructured covariance structure was assumed for the MMRM model.

For the binary key secondary efficacy variable ACR50, the proportion of patients meeting the criteria was evaluated using a logistic regression model with treatment as a factor and weight as a continuous covariate.

Treatment-emergent adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The crude incidence of treatment-emergent AEs was summarized by primary system organ class and preferred term. In addition, exposure time-adjusted incidence rates (per 100 patient-years) including 95% confidence intervals were provided for the entire treatment period to adjust for differences in exposure. For laboratory parameters, vital signs and ECG parameters summary tables on number and percentage of patients with newly occurring notable abnormalities were provided.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

-Male or non-pregnant, non-lactating female patients
-Presence of RA classified by American College of Rheumatology (ACR) 2010 revised criteria for at least 3 months before screening
-At Baseline: Disease activity criteria defined by ≥ 6 tender joints out of 68 and ≥6 swollen joints out of 66 with at least 1 of the following at screening:
-Anti-Cyclic Citrullinated Peptide (CCP) antibodies positive OR
Rheumatoid Factor positive and with at least 1 of the following at screening:
-High sensitivity C-reactive protein (hsCRP) ≥ 10 mg/L OR
Erythrocyte sedimentation rate (ESR) ≥ 28 mm/1st hr
-Patients must have been taking at least one anti-TNF-α agent given at an approved dose for at least 3 months before randomization and have experienced an inadequate response to treatment or have been intolerant to at least one administration of an anti-TNF-α agent
-Patients must be taking MTX for at least 3 months before randomization and have to be on a stable dose at least 4 weeks before randomization (7.5 to 25 mg/week For Japan only: 6 to 25 mg/week)

Exclusion criteria:
-Chest x-ray with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician
RA patients functional status class IV according to the ACR 1991 revised criteria
-Patients who have ever received biologic immunomodulating agents except for those targeting TNFα
-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)
-Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Core Study

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Started	210	213	214
Completed	76	81	80
Not Completed	134	132	134
Study terminated by Sponsor	47	54	46
Technical problems	1	0	0
Withdrawal by Subject	15	23	18
Protocol Violation	7	3	2
Pregnancy	0	0	1
Physician Decision	5	4	10
Non-Compliant with study treatment	0	0	1
No Longer require treatment	0	0	1
Lost to Follow-up	7	5	4
Lack of Efficacy	41	28	37

Death	1	1	1
Adverse Event	10	14	13

Extension Study, weeks 104-260

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Started	57	71	68
Completed	0	0	0
Not Completed	57	71	68
Lack of Efficacy	3	0	0
Study terminated by sponsor	52	69	63
Withdrawal by Subject	1	0	3
Physician Decision	1	0	0
Lost to Follow-up	0	0	1
Adverse Event	0	2	1

Baseline Characteristics

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo	Total
Number of Participants [units: participants]	210	213	214	637
Age, Customized (units: Particpants)				
<65	177	176	182	535
>=65	33	37	32	102
Gender, Male/Female (units: Participants)				
Female	186	188	182	556
Male	24	25	32	81

Summary of Efficacy

Primary Outcome Result(s)

Core Study: Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20) at week 24

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Number of Participants Analyzed [units: participants]	210	213	214
Core Study: Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20) at week 24 (units: Percentage of Participants)	35.2	35.2	19.6

Statistical Analysis

Groups	AIN457 10mg/kg-75mg, Placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0004
Method	Regression, Logistic
Odds Ratio (OR)	2.21
95 % Confidence Interval 2-Sided	1.4 to 3.4

Statistical Analysis

Groups	AIN457 10mg/kg-150mg, Placebo
Non-Inferiority/Equivalence Test	No
P Value	0.0004
Method	Regression, Logistic
Odds Ratio (OR)	2.21
95 % Confidence Interval 2-Sided	1.4 to 3.4

Secondary Outcome Result(s)

Change from baseline and week 24 in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Number of Participants Analyzed [units: participants]	171	188	71
Change from baseline and week 24 in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) (units: Score on a scale) Least Squares Mean ± Standard Error	-0.35 ± 0.039	-0.35 ± 0.038	-0.24 ± 0.051

Change From baseline at week 24 in van der Heijde total modified Sharp score

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Number of Participants Analyzed [units: participants]	60	67	83
Change From baseline at week 24 in van der Heijde total modified Sharp score (units: Score on a scale) Mean ± Standard Error	0.59 ± 0.62	0.83 ± 0.68	1.73 ± 0

Percentage of patients achieving major clinical response (continuous six-month period of ACR70 response) at week 52

	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Number of Participants Analyzed [units: participants]	210	213	214
Percentage of patients achieving major clinical response (continuous six-month period of ACR70 response) at week 52 (units: Participants)	2.4	0.9	1.4

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	Any AIN457 75 mg N = 301	Any AIN457 150 mg N = 392	Placebo N = 214
Total participants affected	33 (10.96%)	48 (12.24%)	9 (4.21%)
Blood and lymphatic system disorders			
Anaemia[1, †]	0 (0.00%)	3 (0.77%)	0 (0.00%)
Pancytopenia[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Thrombocytopenia[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Cardiac disorders			
Acute myocardial infarction[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Atrial fibrillation[1, †]	1 (0.33%)	0 (0.00%)	1 (0.47%)
Cardiac failure[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Cardiogenic shock[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Cardiopulmonary failure[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Coronary artery disease[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Myocardial infarction[1, †]	0 (0.00%)	1 (0.26%)	1 (0.47%)
Myocardial ischaemia[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)

Eye disorders			
Cataract[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Macular degeneration[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal hernia[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Abdominal pain[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Colitis[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Dyspepsia[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Gastritis[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Ileus[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Inguinal hernia[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Lower gastrointestinal haemorrhage[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Nausea[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Vomiting[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions			
Disease progression[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain[1, †]	1 (0.33%)	1 (0.26%)	1 (0.47%)
Sudden death[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders			
Cholecystitis[1, †]	2 (0.66%)	1 (0.26%)	0 (0.00%)
Cholelithiasis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)

Infections and infestations			
Appendicitis[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Bacteraemia[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Bronchitis[1, †]	1 (0.33%)	2 (0.51%)	0 (0.00%)
Cellulitis[1, †]	0 (0.00%)	5 (1.28%)	0 (0.00%)
Gangrene[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Gastroenteritis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Gastroenteritis bacterial[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Gastroenteritis norovirus[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Gastroenteritis viral[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Helicobacter gastritis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Herpes zoster[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Infected skin ulcer[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Influenza[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Joint tuberculosis[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Laryngitis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Peritonitis[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Pneumocystis jirovecii pneumonia[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Pneumonia[1, †]	4 (1.33%)	2 (0.51%)	2 (0.93%)
Psoas abscess[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Pyelonephritis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Sepsis[1, †]	0 (0.00%)	3 (0.77%)	0 (0.00%)
Soft tissue infection[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Staphylococcal	0 (0.00%)	1 (0.26%)	0 (0.00%)

osteomyelitis[1, †]			
Streptococcal bacteraemia[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Urosepsis[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Injury, poisoning and procedural complications			
Accidental overdose[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Animal bite[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Ankle fracture[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Contusion[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Femur fracture[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Infusion related reaction[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Jaw fracture[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Joint injury[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Radius fracture[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Tendon rupture[1, †]	0 (0.00%)	2 (0.51%)	0 (0.00%)
Ulna fracture[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Investigations			
Occult blood positive[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Transaminases increased[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Diabetes mellitus[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)

Diabetes mellitus inadequate control[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Hypoalbuminaemia[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Hypoglycaemia[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Metabolic acidosis[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Acquired claw toe[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Arthralgia[1, †]	1 (0.33%)	2 (0.51%)	0 (0.00%)
Back pain[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Foot deformity[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Joint range of motion decreased[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Osteoarthritis[1, †]	1 (0.33%)	1 (0.26%)	1 (0.47%)
Osteonecrosis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Osteoporosis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Rheumatoid arthritis[1, †]	2 (0.66%)	3 (0.77%)	1 (0.47%)
Spinal osteoarthritis[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Diffuse large B-cell lymphoma[1, †]	0 (0.00%)	2 (0.51%)	0 (0.00%)
Nervous system disorders			
Carotid artery insufficiency[1, †]	1 (0.33%)	0 (0.00%)	1 (0.47%)

Carotid artery occlusion[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Cerebellar embolism[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Cerebral artery embolism[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Cerebral haemorrhage[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Cerebral ischaemia[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Cerebrovascular insufficiency[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Dizziness[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Encephalomalacia[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Headache[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Hypoaesthesia[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Hypoxic-ischaemic encephalopathy[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Lumbar radiculopathy[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Syncope[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Transient ischaemic attack[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
VIIth nerve paralysis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders			
Acute psychosis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Anxiety[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Renal and urinary disorders			
Acute kidney injury[1, †]	0 (0.00%)	3 (0.77%)	0 (0.00%)
Calculus ureteric[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)

Haematuria[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Reproductive system and breast disorders			
Ovarian cyst[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Ovarian cyst ruptured[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea[1, †]	2 (0.66%)	1 (0.26%)	0 (0.00%)
Interstitial lung disease[1, †]	1 (0.33%)	2 (0.51%)	0 (0.00%)
Pneumonia aspiration[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)
Pulmonary oedema[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Skin ulcer[1, †]	0 (0.00%)	1 (0.26%)	0 (0.00%)
Vascular disorders			
Arteriosclerosis[1, †]	0 (0.00%)	0 (0.00%)	1 (0.47%)
Femoral artery occlusion[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Hypertension[1, †]	1 (0.33%)	1 (0.26%)	1 (0.47%)
Peripheral arterial occlusive disease[1, †]	1 (0.33%)	1 (0.26%)	0 (0.00%)
Thrombophlebitis[1, †]	1 (0.33%)	0 (0.00%)	0 (0.00%)

† Systematic Assessment
1 MedDRA 18.1

Other Adverse Events by System Organ Class

Frequent Event Reporting Threshold 2%

	Any AIN457 75 mg N = 301	Any AIN457 150 mg N = 392	Placebo N = 214
Total participants affected	184 (61.13%)	225 (57.40%)	91 (42.52%)
Blood and lymphatic system disorders			
Anaemia[1, †]	9 (2.99%)	11 (2.81%)	5 (2.34%)
Ear and labyrinth disorders			
Vertigo[1, †]	2 (0.66%)	8 (2.04%)	2 (0.93%)
Gastrointestinal disorders			
Constipation[1, †]	6 (1.99%)	13 (3.32%)	5 (2.34%)
Dental caries[1, †]	4 (1.33%)	11 (2.81%)	1 (0.47%)
Diarrhoea[1, †]	14 (4.65%)	22 (5.61%)	6 (2.80%)
Nausea[1, †]	6 (1.99%)	15 (3.83%)	6 (2.80%)
Stomatitis[1, †]	6 (1.99%)	8 (2.04%)	1 (0.47%)
Vomiting[1, †]	4 (1.33%)	8 (2.04%)	5 (2.34%)
General disorders and administration site conditions			
Oedema peripheral[1, †]	7 (2.33%)	8 (2.04%)	1 (0.47%)
Pyrexia[1, †]	8 (2.66%)	13 (3.32%)	4 (1.87%)

Infections and infestations			
Bronchitis[1, †]	15 (4.98%)	31 (7.91%)	1 (0.47%)
Conjunctivitis[1, †]	4 (1.33%)	8 (2.04%)	0 (0.00%)
Cystitis[1, †]	4 (1.33%)	15 (3.83%)	0 (0.00%)
Gastroenteritis[1, †]	4 (1.33%)	13 (3.32%)	2 (0.93%)
Herpes zoster[1, †]	8 (2.66%)	9 (2.30%)	1 (0.47%)
Influenza[1, †]	11 (3.65%)	10 (2.55%)	2 (0.93%)
Nasopharyngitis[1, †]	49 (16.28%)	63 (16.07%)	14 (6.54%)
Pharyngitis[1, †]	23 (7.64%)	18 (4.59%)	5 (2.34%)
Sinusitis[1, †]	6 (1.99%)	8 (2.04%)	3 (1.40%)
Upper respiratory tract infection[1, †]	25 (8.31%)	39 (9.95%)	10 (4.67%)
Urinary tract infection[1, †]	28 (9.30%)	33 (8.42%)	8 (3.74%)
Injury, poisoning and procedural complications			
Contusion[1, †]	5 (1.66%)	10 (2.55%)	2 (0.93%)
Investigations			
Alanine aminotransferase increased[1, †]	7 (2.33%)	10 (2.55%)	3 (1.40%)
Metabolism and nutrition disorders			
Hypercholesterolaemia[1, †]	6 (1.99%)	9 (2.30%)	2 (0.93%)
Musculoskeletal and connective tissue disorders			

Arthralgia[1, †]	19 (6.31%)	16 (4.08%)	7 (3.27%)
Back pain[1, †]	6 (1.99%)	11 (2.81%)	7 (3.27%)
Muscle spasms[1, †]	3 (1.00%)	9 (2.30%)	4 (1.87%)
Myalgia[1, †]	5 (1.66%)	8 (2.04%)	0 (0.00%)
Rheumatoid arthritis[1, †]	20 (6.64%)	17 (4.34%)	11 (5.14%)
Nervous system disorders			
Dizziness[1, †]	6 (1.99%)	8 (2.04%)	3 (1.40%)
Headache[1, †]	14 (4.65%)	18 (4.59%)	10 (4.67%)
Psychiatric disorders			
Insomnia[1, †]	3 (1.00%)	12 (3.06%)	6 (2.80%)
Respiratory, thoracic and mediastinal disorders			
Cough[1, †]	9 (2.99%)	18 (4.59%)	4 (1.87%)
Skin and subcutaneous tissue disorders			
Rash[1, †]	6 (1.99%)	8 (2.04%)	3 (1.40%)
Vascular disorders			
Hypertension[1, †]	18 (5.98%)	12 (3.06%)	5 (2.34%)

† Systematic Assessment
1 MedDRA 18.1

Other Relevant Findings

N/A

Conclusion:

This report includes Week 24 and Week 52 efficacy data from the core study CAIN457F2302 and safety data from both the core study and the extension study CAIN457F2302E1. Both studies were terminated after Novartis made the decision (unrelated to safety) to stop the development program for AIN457 in RA.

A total of 637 patients were randomized to one of the 3 treatment groups: secukinumab i.v.-75 mg (n=210), secukinumab i.v.-150 mg (n=213) and placebo (n=214). Of these, 237 (37.2%) completed 104 weeks of treatment: 76 (36.2%) in the secukinumab i.v.-75 mg group, 81 (38.0%) in the secukinumab i.v.-150 mg group and 80 patients (37.4%) in the placebo group.

The primary endpoint of ACR20 at Week 24 was met by both secukinumab dose regimens (i.v.-75 mg and i.v.-150 mg) demonstrating a better treatment effect with secukinumab compared with placebo. Both dose regimens of secukinumab were statistically superior to placebo for ACR20 response at Week 24 using the pre-defined statistical testing hierarchy. The ACR20 response rates at Week 24 were the same for both secukinumab dose regiments: 35.2% for secukinumab i.v.-75 mg (p=0.0009, adjusted) and 35.2% for secukinumab i.v.-150 mg (p=0.0009, adjusted) compared to 19.6% for placebo.

The main key secondary endpoint (HAQ-DI at Week 24) was not met for either secukinumab dose regimen and consequently neither were the remaining key secondary endpoints in the hierarchy (total vdH-mTSS and MCR at Week 24) when compared with placebo. In general, each of the secondary/exploratory endpoints tested outside of the hierarchy was numerically improved for both secukinumab regimens compared to placebo at most, if not all, time points up to Week 104.

The safety profile of secukinumab in this study showed no new or unexpected signals compared to the large safety database across psoriasis, PsA and AS. The overall safety profile of secukinumab i.v.- 75 mg and secukinumab i.v.-150 mg in this study was similar between both doses of secukinumab which were also similar to placebo.

In the short term (up to Week 16), treatment emergent AEs were reported at a similar frequency across all treatment groups (58.1% in the secukinumab i.v.-75 mg group, 54.5% in the secukinumab i.v.-150 mg group and 57.0% in the placebo group). The most frequently reported AEs were infections and infestations (28.6% in the secukinumab i.v.-75 mg

group, 23.5% in the secukinumab i.v.-150 mg group and 25.2% in the placebo group). Infections (most commonly upper respiratory tract infections) generally were of mild to moderate severity and did not lead to discontinuation.

Over the entire study, a similar AE pattern and exposure-adjusted AE incidence rate across treatments (including placebo) was observed. Infections were again the most common AE reported and, unlike short term 16-week data, occurred at a higher exposure-adjusted IR for the placebo (IR = 97.5 per 100 patient years) vs. secukinumab treatment groups, which were very similar to each other (IR = 65.5 vs. 62.5 per 100 patient years for the Any secukinumab 75 mg and Any secukinumab 150 mg, respectively).

The frequency of detectable ADAs in RA TNF inadequate responder patients in this trial was slightly higher than that observed in the studies comprising the large secukinumab safety database of patients with psoriasis PsA and AS. This may be due to factors associated with RA such as presence of RFs and ANAs which are typically absent in psoriasis and spondyloarthropathy (SpA) patients. This is further corroborated by ADA data from the RA TNF inadequate responder trials CAIN457F2309 and CAIN457F2311 where many of the ADA positive samples were seen in patients already at baseline prior to any secukinumab exposure.

No safety signals were noted when evaluating exposure-adjusted IRs for SAEs by treatment or when evaluating the exposure-adjusted IRs for the potential compound- and class-related risks. Of note was the overall low, but higher exposure-adjusted incidence rate of adjudicated major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death) in the placebo group compared to the Any secukinumab dose group (2.6 vs. 0.3 per 100 patient years, respectively) during the entire treatment period.

Date of Clinical Trial Report

25-Apr-2016 (Final clinical trial report combined core and extension results)