Sponsor

Novartis

Generic Drug Name

Secukinumab (AIN457)

Trial Indication

Ankylosing Spondylitis

Protocol Number

CAIN457A2209E1

Protocol Title

An open-label non-randomized extension study to evaluate the safety and tolerability of AIN457 (anti interleukin-17 monoclonal antibody) in patients with moderate to severe ankylosing spondylitis

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

14-Apr-2010 to 05-Dec-2012

Reason for Termination

Not applicable

Study Design/Methodology

This was a multicenter, open-label, non-randomized study without comparator, wherein active treatment (AIN457) was provided initially as 7 doses, one every 4 weeks up to 6 months (Part 1), with a possible extension of a further 7 doses, one every 4 weeks up to 6 months (Part 2) to those patients who participated in the core CAIN457A2209 study in order to collect continuous safety data over a treatment period of up to one year.

Centers

15 centers in 4 countries: Germany (4 centers), Netherlands (1 center), United Kingdom (1 center) and United States (9 centers).

Objectives:

Primary objective

- To assess the safety and tolerability of AIN457 in patients with moderate to severe ankylosing spondylitis (AS) receiving iv AIN457 initially up to 6 months (Part 1) with a possible extension of a further 6 months (Part 2) in patients, who participated in the core CAIN457A2209 phase II proof-of-concept study

Secondary objective

- To assess the immunogenicity of AIN457
- To assess the total IL-17 concentration in blood at steady state
- To assess the pharmacokinetics of AIN457 at steady state

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

All patients received AIN457 3 mg/kg intravenously every 4 weeks (q4wk) over a period of 56 weeks.

The investigational drug, AIN475 50 mg lyophilisate vials was prepared by Novartis and supplied to the Investigator as an open labeled bulk medication.

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

Not applicable.

Criteria for Evaluation

Primary variables:

- Adverse events (AEs) and Serious Adverse events (SAEs)

- Vital signs
- ECG evaluations
- Standard clinical laboratory evaluations

Secondary variables:

- Immunogenicity
- Pharmacokinetics (PK):
  - $C_{max,ss}$: The maximum (peak) observed steady-state drug concentration in the plasma, blood, serum, or other body fluids during multiple dosing [amount x volume-1]
  - $C_{min,ss}$: The minimum observed steady-state drug concentration in the plasma, blood, serum, or other body fluids at the end of the dosing interval during multiple dosing [amount x volume-1]

Statistical Methods

Categorical variables were summarized by frequency tables. Continuous variables were summarized by descriptive statistics.

The main purpose of this extension study was to provide continuous treatment with secukinumab for patients who completed the CAIN457A2209 core trial, in order to assess the safety and tolerability of secukinumab in these patients. Accordingly, not more than 60 patients were planned to participate in this extension study, and no statistical sample size rationale was provided.

Safety and tolerability variables including vital signs, AEs, ECG and laboratory variables, as well as demographic information, were summarized in a descriptive manner over time. Descriptive statistics of ASAS20, ASAS40 ASAS5/6 response criteria, partial remission, BASDAI, BASMI, BSAFI, MASES, LDI basic, HRQoL, physician's global assessment and the ASAS core components (1-6) served as exploratory efficacy assessments. Background and demographic variables such as age, weight, height, and gender were also summarized descriptively; pharmacokinetic concentrations of secukinumab were summarized descriptively over time.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients who took part and completed the core CAIN457A2209 study
- Patients who discontinued the core study due to unsatisfactory therapeutic effect at their Visit 14 (Week 16) or later could enter the extension study within 3 weeks of completing the study discontinuation visit of the core study, provided that at their discontinuation visit they fulfilled either one of the criteria below. Patients who did not enter the extension study within 3 weeks of completing the study discontinuation visit of the core study, were required to come for an additional baseline visit (Visit 17) and were required to fulfill either one of the criteria below:

- No improvement (compared with the core study baseline) in two out of the following four domains: patient global assessment, pain, BASFI and the mean of the two morning stiffness questions from the BASDAI.
  OR
- Deterioration (compared with the core study baseline) in one of the four domains (deterioration defined as >=20% worsening and an absolute worsening of >=1 unit)

Exclusion criteria

- Patients for whom continued treatment with AIN457 is not considered appropriate by the treating physician
- Patients who were non-compliant or who demonstrated a major protocol deviation in the core CAIN457A2209 study
- Patients who discontinued from the core CAIN457A2209 study before Visit 14 (Week 16), and patients who completed the core study or discontinued the core study more than 2 weeks before the baseline visit
- Pregnant or lactating women
- Presence of active infection
- Positive PPD or HIV test in patients where repeated testing was deemed appropriate due to their risk profile

Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow Table

Patient disposition (Randomized Set)

	Dose Group-(1) N=21	Dose Group-(2) N=8	Dose Group-(3) N=7	Placebo/ Secukinumab N=3	Total N=39
Patients					
Completed	13 (61.9)	6 (75.0)	6 (85.7)	3 (100.0)	28 (71.8)
Discontinued	8 (38.1)	2 (25.0)	1 (14.3)	0	11 (28.2)
Administrative problems	2 (9.5)	0	0	0	2 (5.1)
Serious Adverse Event	2 (9.5)	1 (12.5)	0	0	3 (7.7)
Lost to follow-up	1 (4.8)	0	0	0	1 (2.6)
Patient withdrew consent	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Unsatisfactory therapeutic effect	2 (9.5)	0	1 (14.3)	0	3 (7.7)

Baseline Characteristics (Safety Analysis Set)

		Dose Group-(1) N=21	Dose Group-(2) N=8	Dose Group-(3) N=7	Placebo / Secukinumab N=3	Total N=39
Age (years)	Mean (SD)	39.5 (7.56)	47.9 (11.27)	45.9 (8.61)	41.7 (11.59)	42.5 (9.25)
	Median	40.0	46.0	46.0	36.0	41.0
	Range	26 – 52	33 - 64	35 - 63	34 - 55	26 - 64
Gender - n(%)	Male	11 (52)	4 (50)	5 (71)	3 (100)	23 (59)
	Female	10 (48)	4 (50)	2 (29)		16 (41)
Predominant race - n(%)	Caucasian	18 (86)	8 (100)	6 (86)	3 (100)	35 (90)
	Other	2 (10)	0	1 (14)	0	3 (8)
	Black	1 (5)	0		0	1 (3)
Height (cm)	Mean (SD)	170.4 (8.16)	173.8 (7.40)	175.0 (7.02)	179.3 (5.13)	172.6 (7.86)
	Median	169.0	170.5	176.0	178.0	171.0
	Range	153 – 185	167 - 186	164 - 185	175 - 185	153 - 186
Weight (kg)	Mean (SD)	82.2 (19.33)	86.5 (14.64)	77.0 (18.22)	73.3 (21.03)	81.5 (18.07)
	Median	77.0	83.5	73.0	72.0	77.2
	Range	51 – 123	66 - 114	58 - 105	53 - 95	51 - 123
BMI (kg/m^2)	Mean (SD)	28.2 (6.22)	28.7 (5.32)	24.9 (4.45)	23.0 (7.26)	27.3 (5.90)
	Median	26.1	28.1	24.2	23.5	26.6
	Range	18 – 43	23 - 41	19 - 31	15 - 30	15 - 43

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Immunogenicity

Visit	Immunogenecity	AIN457 (1)/ AIN457 3mg/kg N=21	AIN457 (2)/ AIN457 3mg/kg N=8	AIN457 (3)/ AIN457 3mg/kg N=7	Placebo / AIN457 3mg/kg N=3
CEOS/BAS Ext	No	11/ 11 (100%)	6/ 6 (100%)	4/ 4 (100%)	2/ 2 (100%)
EXT SCR	No	9/ 9 (100%)		3/ 3 (100%)	1/ 1 (100%)
EWEEK0	No	20/ 20 (100%)	5/ 5 (100%)	5/ 5 (100%)	3/ 3 (100%)
EWEEK8	No	19/ 19 (100%)	7/ 7 (100%)	6/ 6 (100%)	3/ 3 (100%)
EWEEK24	No	19/ 19 (100%)	7/ 7 (100%)	6/ 6 (100%)	3/ 3 (100%)
EWEEK40	No	15/ 15 (100%)	6/ 6 (100%)	4/ 4 (100%)	3/ 3 (100%)
EEOS	No	18/ 18 (100%)	8/ 8 (100%)	6/ 6 (100%)	3/ 3 (100%)

Total IL-17 concentration in blood at steady-state

IL-17A measurements were planned for this study but could not be measured because the assay for total IL-17A, samples was not robust.

Pharmacokinetics of secukinumab at steady state

Week	N	Mean (SD) (µg/mL)	N	Mean (SD) (µg/mL)	N	Mean (SD) (µg/mL)	N	Mean (SD) (µg/mL)
	Dose Group-(1)		Dose Group-(2)		Dose Group-(3)		Placebo/Secukinumab	
0/pre-inf	21	4.73 (10.1)	7	15.0 (38.4)	5	0.043 (0.059)	3	27.1 (46.9)
0/post-inf	19	64.2 (13.5)	7	58.1 (30.5)	5	56.1 (24.1)	3	63.0 (14.6)
8/pre-inf	19	28.4 (24.3)	8	21.7 (4.20)	5	28.9 (9.31)	3	19.4 (10.7)
8 /post-inf	18	101 (61.4)	8	88.0 (19.2)	6	76.9 (21.7)	3	52.4 (16.0)
16/pre-inf	18	35.7 (34.7)	8	35.8 (20.7)	6	39.6 (25.8)	2	14.6 (8.78)
16/post-inf	17	96.6 (23.1)	8	81.8 (30.2)	6	81.1 (27.5)	2	59.0 (18.5)
20/pre-inf	19	24.9 (15.8)	7	42.1 (26.5)	6	32.6 (6.41)	3	27.2 (15.2)
20/post-inf	19	93.3 (26.2)	7	108 (23.5)	6	104 (22.1)	3	83.2 (38.5)
24/pre-inf	18	27.1 (12.4)	4	24.1 (10.9)	6	37.6 (8.74)	3	25.7 (16.5)
24/post-inf	17	99.0 (20.1)	4	101 (35.0)	6	100 (19.7)	3	83.5 (28.4)
28/pre-inf	16	40.1 (34.6)	4	28.8 (8.98)	6	33.8 (5.91)	2	18.0 (15.4)
28/post-inf	16	99.8 (22.7)	4	82.7 (12.3)	5	92.4 (12.2)	2	71.8 (14.9)
32/pre-inf	14	32.0 (19.6)	4	31.7 (3.33)	5	28.0 (9.69)	3	27.7 (18.2)
32/post-inf	14	90.0 (38.7)	4	128 (39.4)	4	83.6 (20.3)	3	92.5 (9.21)
36/pre-inf	10	41.0 (40.7)	5	26.5 (12.6)	6	34.3 (15.0)	2	26.5 (25.2)
36 /post-inf	10	110 (33.6)	5	99.7 (20.0)	6	107 (30.2)	2	80.2 (35.1)
40/pre-inf	13	26.4 (12.2)	5	27.3 (7.16)	5	33.7 (7.21)	2	13.8 (4.38)
40/post-inf	13	107 (36.4)	4	97.0 (18.5)	5	104 (32.4)	2	74.8 (6.22)
56	12	33.8 (9.62)	5	35.1 (7.62)	6	38.8 (10.3)	3	36.2 (16.9)
64	7	10.5 (3.03)	6	10.6 (3.82)	5	11.3 (4.81)	3	17.1 (10.9)

Safety Results

Incidence of AEs by primary system organ class (Safety analysis set)

	Dose Group-(1) N=21 n (%)	Dose Group-(2) N=8 n (%)	Dose Group-(3) N=7 n (%)	Placebo/ Secukinumab N=3 n (%)	Total N=39 n (%)
Patients with AE(s)	21 (100.0)	6 (75.0)	6 (85.7)	3 (100.0)	36 (92.3)
Infections and infestations	16 (76.2)	5 (62.5)	4 (57.1)	2 (66.7)	27 (69.2)
Musculoskeletal and connective tissue disorders	8 (38.1)	3 (37.5)	2 (28.6)	2 (66.7)	15 (38.5)
Gastrointestinal disorders	11 (52.4)	0	2 (28.6)	1 (33.3)	14 (35.9)
Nervous system disorders	5 (23.8)	0	3 (42.9)	1 (33.3)	9 (23.1)
Respiratory, thoracic and mediastinal disorders	5 (23.8)	3 (37.5)	1 (14.3)	0	9 (23.1)
Eye disorders	4 (19.0)	2 (25.0)	1 (14.3)	1 (33.3)	8 (20.5)
General disorders and administration site conditions	5 (23.8)	2 (25.0)	0	1 (33.3)	8 (20.5)
Injury, poisoning and procedural complications	3 (14.3)	3 (37.5)	1 (14.3)	1 (33.3)	8 (20.5)
Skin and subcutaneous tissue disorders	3 (14.3)	1 (12.5)	1 (14.3)	0	5 (12.8)
Cardiac disorders	1 (4.8)	2 (25.0)	1 (14.3)	0	4 (10.3)
Investigations	2 (9.5)	0	0	2 (66.7)	4 (10.3)
Psychiatric disorders	2 (9.5)	1 (12.5)	1 (14.3)		4 (10.3)
Vascular disorders	2 (9.5)	1 (12.5)		1 (33.3)	4 (10.3)
Renal and urinary disorders	1 (4.8)	0	1 (14.3)	1 (33.3)	3 (7.7)
Blood and lymphatic system disorders	2 (9.5)	0	0	0	2 (5.1)

	Dose Group-(1) N=21 n (%)	Dose Group-(2) N=8 n (%)	Dose Group-(3) N=7 n (%)	Placebo/ Secukinumab N=3 n (%)	Total N=39 n (%)
Reproductive system and breast disorders	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Ear and labyrinth disorders	0	1 (12.5)	0	0	1 (2.6)
Hepatobiliary disorders	1 (4.8)	0	0	0	1 (2.6)
Immune system disorders	1 (4.8)	0	0	0	1 (2.6)
Metabolism and nutrition disorders	1 (4.8)	0	0	0	1 (2.6)

Most Frequently Reported AEs (Preferred Term) Seen in more than 5% of Patients (Safety analysis set)

	Dose Group-(1) N=21 n (%)	Dose Group-(2) N=8 n (%)	Dose Group-(3) N=7 n (%)	Placebo/ Secukinumab N=3 n (%)	Total N=39
Patients with AE(s)	21 (100.0)	6 (75.0)	6 (85.7)	3 (100.0)	36 (92.3)
Nasopharyngitis	10 (47.6)	0	2 (28.6)	2 (66.7)	14 (35.9)
Fatigue	3 (14.3)	2 (25.0)		1 (33.3)	6 (15.4)
Oropharyngeal pain	3 (14.3)	2 (25.0)	1 (14.3)	0	6 (15.4)
Arthralgia	2 (9.5)	0	2 (28.6)	0	4 (10.3)
Diarrhoea	3 (14.3)	0		1 (33.3)	4 (10.3)
Headache	1 (4.8)	0	2 (28.6)	1 (33.3)	4 (10.3)
Influenza like illness	3 (14.3)	1 (12.5)	0		4 (10.3)
Iritis	2 (9.5)	1 (12.5)	0	1 (33.3)	4 (10.3)
Palpitations	1 (4.8)	2 (25.0)	1 (14.3)		4 (10.3)
Abdominal distension	2 (9.5)	0	1 (14.3)		3 (7.7)
Abdominal pain	3 (14.3)	0	0		3 (7.7)
Abdominal pain upper	2 (9.5)	0	0	1 (33.3)	3 (7.7)
Aphthous stomatitis	2 (9.5)	0	1 (14.3)		3 (7.7)
Back pain	2 (9.5)	0	0	1 (33.3)	3 (7.7)
Neck pain	1 (4.8)	1 (12.5)	0	1 (33.3)	3 (7.7)
Oedema peripheral	2 (9.5)	1 (12.5)	0	0	3 (7.7)
Sinusitis	2 (9.5)	0	1 (14.3)	0	3 (7.7)
Arthritis	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Bronchitis	2 (9.5)	0	0	0	2 (5.1)
Bursitis	0	1 (12.5)	1 (14.3)	0	2 (5.1)
Contusion	1 (4.8)	0	0	1 (33.3)	2 (5.1)

Cough	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Folliculitis	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Gastroenteritis	2 (9.5)	0	0	0	2 (5.1)
Hypertension	1 (4.8)	0	0	1 (33.3)	2 (5.1)
Infected dermal cyst	0	1 (12.5)	1 (14.3)	0	2 (5.1)
Influenza	0	2 (25.0)	0	0	2 (5.1)
Iron deficiency anaemia	2 (9.5)	0	0	0	2 (5.1)
Joint injury	0	1 (12.5)	1 (14.3)	0	2 (5.1)
Nephrolithiasis	0	0	1 (14.3)	1 (33.3)	2 (5.1)
Paraesthesia	1 (4.8)	0	1 (14.3)	0	2 (5.1)
Pyrexia	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Rash	2 (9.5)	0	0	0	2 (5.1)
Respiratory tract infection	1 (4.8)	0	0	1 (33.3)	2 (5.1)
Tendonitis	1 (4.8)	1 (12.5)	0	0	2 (5.1)
Toothache	1 (4.8)	0	1 (14.3)	0	2 (5.1)
Vomiting	2 (9.5)	0	0	0	2 (5.1)

Other Relevant Findings: N/A

Conclusion:

The primary objective of this study was to assess the safety and tolerability of the secukinumab in patients with AS. The efficacy data of this trial suggest, that continuous therapy with secukinumab in a dose of 3 mg/kg given iv every 4 weeks is effective in re-gaining and maintaining a stable response in patients with AS. This is evident by a stable and continued response as measured by ASAS20/ASAS40 and ASAS5/6. The safety data obtained in this study did not reveal any new or unexpected safety signal. The most frequently reported AEs were infections or infestations in 69.2% of the patients. Within this group, infections of the upper respiratory tract (mainly nasopharyngitis, further 3 cases of Sinusitis and 2 of bronchitis) were by far the most frequently reported events. Three (3) of the 6 SAEs reported were also infections, including folliculitis and staphylococcal abscess in 1 patient and a sinusitis leading to hospitalization in another patient. The 3 remaining SAEs were a single case each of arthritis, depression and Crohn's disease, which was not indicative of any particular signal. Type and overall frequency of adverse events including infections was generally similar to the CAIN457A2209 core trial. No immunogenicity was detected up to 1 year.

Three (3) patients were reported with protocol deviation of consuming prohibited medication, however, it was concluded that the impact on safety/PD results was rather minimal and patients were not required to be excluded from any of the analysis sets. PK assessments clearly indicated that patients were in steady-state from Week 16 onwards.

IL-17A measurements were planned for this study but could not be measured because the assay for total IL-17A, samples was not robust.

PD assessments that were part of the exploratory objectives suggest that secukinumab 3 mg/kg iv administered monthly rapidly induces and maintains clinically relevant responses in patients with active ankylosing spondylitis. CRP levels data revealed an early and maintained drop in initially elevated levels and were indicative of an anti-inflammatory activity of secukinumab in the dose administered.

Date of Clinical Study Report:

02 July 2013