Sponsor

Novartis

Generic Drug Name

Secukinumab (AIN457)

Trial Indication

Crohn's disease

Protocol Number

CAIN457A2202E1

Protocol Title

A 52-week open label extension study to evaluate the safety and tolerability of AIN457 (anti IL-17 monoclonal antibody) in patients with moderate to severe Crohn's disease

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

30-Oct-2009 to 19-Aug-2010 (Terminated)

Reason for Termination

The study was terminated early due to lack of efficacy as determined by futility analysis on occasion of a scheduled interim analysis in the core trial.

Study Design/Methodology

This was a multicenter, open-label, non-randomized trial without active comparator that provided active treatment over 48 weeks to those patients who either completed the core study, or after amendment 1 was implemented, completed at least the primary endpoint (Day 43) of the core study.

Centers

6 centers in 3 countries: Canada (1), United States (3), Poland (2).

Objectives:

Primary objective

- To assess the long-term safety and tolerability of AIN457 in patients with moderate to severe Crohn's disease who participated in the core CAIN457A2202 phase II PoC study

Secondary objective

- To assess the long term immunogenicity of AIN457
- To assess the long term concentration of IL-17 in blood
- To assess markers of disease activity CRP, calprotectin and lactoferrin in the long term
- 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 q4wk over a period of 52 weeks.

The investigational drug, AIN475 150 mg lyophilizate vials, was prepared by Novartis and supplied to the Investigator as open labeled bulk medication.

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

Not applicable.

Criteria for Evaluation

Primary variable:

- Vital signs
- ECG evaluations

- Standard clinical laboratory evaluations
- Adverse events
- Concomitant medications / Significant non-drug therapies

Secondary variable:

Efficacy:

- In the Crohn's Disease Activity Index (CDAI), higher scores represented worse disease status. Clinical remission was defined as a score of less than 150 points.

Pharmacokinetics (PK):

- Cmax,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]
- Cmin,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

Safety and tolerability variables including vital signs, AEs, ECG and laboratory variables, as well as background and demographic information, were analyzed in a descriptive manner over time. Descriptive statistics of the CDAI over time and frequency tables of the number of patients in remission (CDAI<150) over time were provided as exploratory long-term efficacy assessments. Graphs of the average CDAI time course over time were displayed. The IBDQ data were. Pharmacokinetic concentrations of AIN457 were evaluated descriptively over time.

Pharmacokinetic concentrations were evaluated graphically and descriptively over time.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients who participate and complete the core CAIN457A2202 study up to and including Visit 11 (end of study), may enter the extension study upon signing informed consent.

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 violation in the core CAIN457A2202 study
・Patients who discontinued from the core CAIN457A2202 study before Visit 8 (day 43).

Participant Flow Table

Patient disposition (Randomized Set)

Disposition Reason	AIN457 3mg/kg N=7 n (%)
Discontinued	7 (100.0)
Administrative problems	7 (100.0)

Baseline Characteristics

Demographic Variable	AIN457 3mg/kg N=7
Age (years)	
n	7
mean	44.9
SD	15.79
minimum	27
median	47.0
maximum	72
Height (cm)	
n	7
mean	176.1
SD	4.95
minimum	170
median	177.0
maximum	184
Weight (kg)	
n	7
mean	83.76
SD	13.684
minimum	59.5
median	88.80
maximum	95.5

Demographic Variable	AIN457 3mg/kg N=7
BMI (kg/m2)	
n	7
mean	27.003
SD	4.3919
minimum	18.99
median	28.119
maximum	33.04
Sex	
Male	6 (85.7 %)
Female	1 (14.3 %)
Race	
Caucasian	7 (100.0 %)
Ethnicity	
Other	7 (100.0 %)

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Disease activity C-reactive protein (CRP)

Visit	Statistic	CRP (mg/L)
SCR	n	3
	Mean (SD)	9.7 (15.01)
	CV% mean	155.3
	Geo-mean	3.0
	CV% geo-mean	603.1
	Median	1.0
	[Min; Max]	[1; 27]
BAS	n	1
	Mean (SD)	1.0 ()
	CV% mean	
	Geo-mean	1.0
	CV% geo-mean	
	Median	1.0
	[Min; Max]	[1; 1]
WK0	n	6
	Mean (SD)	6.8 (11.46)
	CV% mean	167.7
	Geo-mean	2.8
	CV% geo-mean	228.6
	Median	2.0
	[Min; Max]	[1; 30]

Visit	Statistic	CRP (mg/L)
WK4	n	7
	Mean (SD)	5.1 (5.87)
	CV% mean	114.2
	Geo-mean	3.3
	CV% geo-mean	130.8
	Median	4.0
	[Min; Max]	[1; 18]
WK8	n	5
	Mean (SD)	7.8 (9.86)
	CV% mean	126.4
	Geo-mean	4.4
	CV% geo-mean	178.3
	Median	3.0
	[Min; Max]	[1; 25]
WK12	n	2
	Mean (SD)	1.0 (0.00)
	CV% mean	0.0
	Geo-mean	1.0
	CV% geo-mean	0.0
	Median	1.0
	[Min; Max]	[1; 1]

Visit	Statistic	CRP (mg/L)
WK16	n	2
	Mean (SD)	11.5 (14.85)
	CV% mean	129.1
	Geo-mean	4.7
	CV% geo-mean	1085.3
	Median	11.5
	[Min; Max]	[1; 22]
WK20	n	2
	Mean (SD)	5.5 (6.36)
	CV% mean	115.7
	Geo-mean	3.2
	CV% geo-mean	362.9
	Median	5.5
	[Min; Max]	[1; 10]
WK24	n	2
	Mean (SD)	1.0 (0.00)
	CV% mean	0.0
	Geo-mean	1.0
	CV% geo-mean	0.0
	Median	1.0
	[Min; Max]	[1; 1]

Visit	Statistic	CRP (mg/L)
WK28	n	2
	Mean (SD)	1.0 (0.00)
	CV% mean	0.0
	Geo-mean	1.0
	CV% geo-mean	0.0
	Median	1.0
	[Min; Max]	[1; 1]
WK52	n	7
	Mean (SD)	7.1 (9.67)
	CV% mean	135.4
	Geo-mean	3.5
	CV% geo-mean	211.1
	Median	5.0
	[Min; Max]	[1; 28]
EOS	n	6
	Mean (SD)	14.2 (20.54)
	CV% mean	145.0
	Geo-mean	4.0
	CV% geo-mean	494.5
	Median	2.0
	[Min; Max]	[1; 49]

Mean serum concentrations

Treatment	Scheduled timepoint (Days)	Statistic	Concentration (ug/mL)
AIN457 3mg/kg	0.000	n	6
		Mean (SD)	14.47 (12.704)
		CV% mean	87.8
		Geo-mean	7.050
		CV% geo-mean	387.7
		Median	15.05
		[Min; Max]	[0.420; 29.4]
	0.083	n	6
		Mean (SD)	77.70 (31.866)
		CV% mean	41.0
		Geo-mean	72.27
		CV% geo-mean	44.5
		Median	75.65
		[Min; Max]	[37.2; 131]
	28.000	n	6
		Mean (SD)	23.33 (14.200)
		CV% mean	60.9
		Geo-mean	19.36
		CV% geo-mean	79.8
		Median	23.05
		[Min; Max]	[8.18; 43.5]

Treatment	Scheduled timepoint (Days)	Statistic	Concentration (ug/mL)
AIN457 3mg/kg	28.083	n	6
		Mean (SD)	95.82 (34.235)
		CV% mean	35.7
		Geo-mean	91.58
		CV% geo-mean	32.6
		Median	90.10
		[Min; Max]	[63.6; 161]
	56.000	n	5
		Mean (SD)	31.02 (13.668)
		CV% mean	44.1
		Geo-mean	28.68
		CV% geo-mean	46.5
		Median	26.10
		[Min; Max]	[18.2; 48.1]
	56.083	n	2
		Mean (SD)	83.30 (4.2426)
		CV% mean	5.1
		Geo-mean	83.25
		CV% geo-mean	5.1
		Median	83.30
		[Min; Max]	[80.3; 86.3]

Treatment	Scheduled timepoint (Days)	Statistic	Concentration (ug/mL)
AIN457 3mg/kg	84.000	n	1
		Mean (SD)	25.80
		CV% mean	
		Geo-mean	25.80
		CV% geo-mean	
		Median	25.80
		[Min; Max]	[25.8; 25.8]
	84.083	n	1
		Mean (SD)	56.90
		CV% mean	
		Geo-mean	56.90
		CV% geo-mean	
		Median	56.90
		[Min; Max]	[56.9; 56.9]
	112.000	n	1
		Mean (SD)	26.00
		CV% mean	
		Geo-mean	26.00
		CV% geo-mean	
		Median	26.00
		[Min; Max]	[26.0; 26.0]

Treatment	Scheduled timepoint (Days)	Statistic	Concentration (ug/mL)
AIN457 3mg/kg	112.083	n	1
		Mean (SD)	96.90
		CV% mean	
		Geo-mean	96.90
		CV% geo-mean	
		Median	96.90
		[Min; Max]	[96.9; 96.9]
	140.000	n	1
		Mean (SD)	26.00
		CV% mean	
		Geo-mean	26.00
		CV% geo-mean	
		Median	26.00
		[Min; Max]	[26.0; 26.0]
	140.083	n	1
		Mean (SD)	93.20
		CV% mean	
		Geo-mean	93.20
		CV% geo-mean	
		Median	93.20
		[Min; Max]	[93.2; 93.2]

Treatment	Scheduled timepoint (Days)	Statistic	Concentration (ug/mL)
AIN457 3mg/kg	168.000	n	1
		Mean (SD)	25.40
		CV% mean	
		Geo-mean	25.40
		CV% geo-mean	
		Median	25.40
		[Min; Max]	[25.4; 25.4]
	168.083	n	1
		Mean (SD)	162.0
		CV% mean	
		Geo-mean	162.0
		CV% geo-mean	
		Median	162.0
		[Min; Max]	[162; 162]
	196.000	n	1
		Mean (SD)	19.90
		CV% mean	
		Geo-mean	19.90
		CV% geo-mean	
		Median	19.90
		[Min; Max]	[19.9; 19.9]

Safety Results

Most Frequently Reported AEs Overall by Preferred Term n (%)

Body System	Preferred Term	AIN457 3mg/kg N=7 n (%)
-Any System Organ Class		
	-TOTAL	3 (42.9)
Gastrointestinal disorders		
	-TOTAL	2 (28.6)
	Abdominal distension	1 (14.3)
	Gastrooesophageal reflux disease	1 (14.3)
	Nausea	1 (14.3)
	Vomiting	1 (14.3)
General disorders and administration site conditions		
	-TOTAL	1 (14.3)
	Influenza like illness	1 (14.3)
Infections and infestations		
	-TOTAL	1 (14.3)
	Upper respiratory tract infection	1 (14.3)
Musculoskeletal and connective tissue disorders		
	-TOTAL	1 (14.3)
	Musculoskeletal pain	1 (14.3)
Psychiatric disorders		
	-TOTAL	1 (14.3)
	Depression	1 (14.3)

Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied n = number of subjects with at least one AE in that category

Other Relevant Findings: N/A

Conclusion:

The sponsor terminated the study prematurely due to unsatisfactory therapeutic effect of AIN457, as assessed by a predefined futility criterion in the core study that was applied on occasion of a scheduled interim analysis. Because of the small cohort and the variable follow-up period of the 7 patients, both due to the early study termination, no conclusions regarding a role of IL-17A blockade in the maintenance therapy of patients with Crohn's disease can be drawn. In the very limited dataset obtained in this extension study, no safety concerns were identified for this group of Crohn's patients who had low disease activity at entry and received a variable number of monthly 3mg/kg doses of secukinumab.

Date of Clinical Study Report:

19 September 2011