Sponsor

Novartis

Generic Drug Name

AIN457

Trial Indication(s)

Not Applicable

Protocol Number

CAIN457A2104

Protocol Title

A double blind, placebo controlled, parallel group study with an open label reference arm to assess the effects of intravenously administered AIN457 on ozone induced neutrophilia compared to placebo and oral corticosteroid in healthy volunteers

Clinical Trial Phases

Phase I

Study Start/End Dates

17 Mar 2009 to 24 Nov 2009

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a single centre, double blind, placebo controlled, parallel group study with an open label reference arm to assess the effects of a single dose of intravenously administered AIN457 10mg/kg on ozone induced sputum neutrophilia in healthy volunteers.

Centers

Germany (1)

Objectives:

Primary Objective:

- To assess the ability of AIN457 to inhibit ozone-induced airway neutrophilia (total neutrophil cell count in 10 6 /mL) in induced sputum at 24 hours compared to placebo.

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

AIN457 (50mg) in glass vials containing 50mg lyophilized cake for reconstitution 1.2 mL sterile water for infusion (SWFI) produced a 47 mg/mL concentrate solution which was diluted in 250 mL 5% glucose bags for infusion was administered as infusion.

Statistical Methods

The change from baseline in the primary variable was to be analyzed following a natural logarithmic transformation using an analysis of covariance model, with baseline values as a covariate. The suitability of the transformation was assessed by examining the model residuals. However, some of the changes were negative which resulted in the absolute numbers of neutrophils being analyzed (rather than change from baseline) after log transformation. Treatment effects were summarized in terms of treatment ratios which were calculated as the anti-log for the differences between the means on the logarithmic scale, 90% confidence intervals were determined using pooled estimates of variance for the means difference and then anti-logged. All statistical tests were performed with a significance interpreted at a nominal two-sided 10% significance level. The data from all subjects was included in the model and the contrast statement was used to perform pairwise comparisons. No alpha adjustments were made in this explorative study. Two interim analyses were planned and performed during the conduct of the study. At the first interim analysis, the standard deviation of the primary endpoint was estimated from blinded data and found to be close to the value that was assumed for the

sample size estimation in the study protocol. Hence, the sample size was not adjusted at the interim analysis. At the second interim analysis, the lack of effect of AIN457 on the change in sputum neutrophils following ozone challenge was identified.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Healthy male or female non-smoking subjects, aged 18 to 55 years who were in good health as determined by past medical history, physical examination, vital signs, electrocardiogram and laboratory tests at screening.
- Subjects had a body weigh of at least 50 kg and a BMI between 18 and 35 kg/m^2.
- Subjects were only included if they were able to produce sputum with normal neutrophil levels at screening and they had to have a screening FEV1 at least 80% of predicted.
- Females had to be surgically sterilized or not of child bearing potential.

Exclusion criteria

- Subjects were also excluded if they had made a donation of or lost 400 mL or more of blood within 8 weeks of dosing.
- If they had a past medical history of clinically significant ECG abnormalities.
- If they had a history of any other significant illness or hypersensitivity to any biological agents.

Participant Flow Table

Patient disposition (Safety analysis set)

	AIN 457	Placebo	OCS	Total
Subjects				
Randomized	12	6	6	24
Completed	11 (92%)	6 (100%)	6 (100%)	23 (96%)
Discontinued	1 (8%)	0	0	1 (4%)
Main cause of discontinuation				
Administrative problems	1 (8%)	0	0	1 (4%)

Baseline Characteristics

Demographic summary by treatment group (safety analysis set)

		AIN457 N = 12	Placebo N = 6	OCS N = 6	All groups N = 24
Age (years)	Mean (SD)	41 (7.2)	37 (11.0)	40 (10.5)	40 (8.8)
	Range	29, 53	26, 53	20, 49	20, 53
Gender – n (%)	Male	10 (83%)	5 (83%)	4 (67%)	19 (79%)
	Female	2 (17%)	1 (17%)	2 (33%)	5 (21%)
Race – n (%)	Caucasian	12 (100%)	6 (100%)	6 (100%)	24 (100%)
Weight (kg)	Mean (SD)	76.9 (12.91)	72.9 (13.25)	80.4 (9.33)	76.8 (12.01)
	Range	55.0, 94.0	58.5, 92.0	68.5, 89.0	55.0, 94.0
Height (cm)	Mean (SD)	176 (8.7)	178 (8.5)	180 (8.6)	178 (8.4)
	Range	158, 191	168, 189	167, 192	158, 192
BMI (kg/m^2)	Mean (SD)	24.6 (2.86)	23.0 (2.77)	24.7 (1.75)	24.2 (2.60)
	Range	18.7, 29.1	20.5, 26.4	22.0, 27.5	18.7, 29.1

Summary of Efficacy

Primary Outcome Result:

Summary of total number of neutrophils (10^6/ML) in induced sputum post ozone challenge by treatment and time-point Pharmacodynamic analysis set

Treatment	Day	Time-point post challenge	N	Mean	SD	CV% mean	Geo-mean	CV% geo-mean	Min.	Median	Max.
Placebo	2	24	6	5.911	5.7695	97.6008	3.6384	173.470	0.60	3.888	15.87
	3	48	6	5.260	5.1109	97.1645	3.0317	205.206	0.53	3.861	13.77
	16	24	5	3.755	2.5485	67.8724	2.9065	111.414	0.69	3.877	7.59
	17	48	6	1.763	1.3571	76.9597	1.2627	122.084	0.36	1.546	3.41
	37	24	3	3.311	2.9549	89.2547	2.5833	99.7769	1.49	1.724	6.72
	38	48	3	2.014	0.5266	26.1416	1.9658	28.0275	1.46	2.080	2.51
	65	24	2	1.607	0.6880	42.8269	1.5311	46.4646	1.12	1.607	2.09
	66	48	2	4.540	0.7495	16.5095	4.5090	16.6999	4.01	4.540	5.07
AIN457	2	24	12	3.323	2.4988	75.2045	2.2608	154.626	0.14	2.571	8.01
	3	48	11	3.402	2.8561	83.9485	2.4800	104.016	0.62	2.302	9.79
	16	24	12	3.869	2.8188	72.8538	2.8341	112.289	0.51	3.117	9.55
	17	48	12	3.947	4.8892	123.857	2.4677	117.963	0.96	1.792	18.04
	37	24	5	3.144	2.9490	93.7984	2.2706	114.516	0.63	2.234	8.24
	38	48	6	1.580	1.5171	95.9957	0.7779	377.456	0.04	1.089	3.83
	65	24	5	1.892	1.3214	69.8575	1.1295	297.595	0.08	2.107	3.43
	66	48	5	0.950	0.5571	58.6495	0.8189	68.3458	0.40	0.801	1.70

Summary of Safety

Safety Results

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

	AIN457 N=12 n (%)	Placebo N=6 n (%)	OCS N=6 n (%)
Subjects with AE(s)	8 (67%)	4 (67%)	1 (17%)
System organ class			
Infections and infestations	2 (17%)	3 (50%)	0
Nervous system disorders	2 (17%)	1 (17%)	1 (17%)
Respiratory, thoracic and mediastinal disorders	1 (8%)	2 (33%)	0
Cardiac disorders	1 (8%)	0	0
Gastrointestinal disorders	1 (8%)	0	0
General disorders and administration site conditions	1 (8%)	0	0
Injury, poisoning and procedural complications	1 (8%)	0	0
Musculoskeletal and connective tissue disorders	1 (8%)	0	0
Vascular disorders	0	1 (17%)	0

Serious Adverse Events and Deaths

No subject experienced SAE’s and no deaths were reported.

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report

12Jan2011