Sponsor

Novartis

Generic Drug Name

ACZ885 (canakinumab)

Trial Indication(s)

Not applicable

Protocol Number

CACZ885A2206

Protocol Title

An exploratory, open label pharmacokinetic – pharmacodynamics study to compare subcutaneous versus intravenous administration of ACZ885 in adult patients with established rheumatoid arthritis.

Clinical Trial Phase

Phase II

Study Start/End Dates

13-Aug-2007 to 02-Jun-2009

Reason for Termination

Following a project level decision by the sponsor to stop the development of ACZ885 in RA indication, the study was terminated early after enrolling 13 patients. Hence a number of biomarker parameters were not analyzed and the planned interim analysis was not performed.

Study Design/Methodology

This was a Phase II, multi center, open label, randomized, parallel group, synovial fluid and serum PK/PD exploratory study evaluating the impact of i.v. versus s.c. administration of different doses of ACZ885 (10 mg/kg s.c. vs 5 mg/kg i.v. and 2 mg/kg s.c. vs 1 mg/kg i.v) in patients with RA.

Centers

7 centers in 3 countries: Germany (4), Belgium (2), Netherlands (1)

Objectives:

Primary objective(s)

Primary Objective: To establish a pharmacokinetic (PK) / total IL-1β pharmacodynamic (PD) relationship in joint fluids of patients with rheumatoid arthritis (RA) treated with different doses of ACZ885 and to evaluate the impact of the subcutaneous (s.c.) versus intravenous (i.v.) route of administration.

Secondary objective(s)

- to evaluate the PK/PD of ACZ885 in sera of patients with RA treated with different doses of ACZ885
- to evaluate the impact of the s.c. versus i.v. route of administration
- to evaluate the efficacy of ACZ885 by assessing the response to treatment by ACR20, 50, 70 & 90 criteria, and by using the SDAI & DAS28 scoring
- to establish a biomarker profile
- to assess overall safety and tolerability
- to assess change in health-related quality of life (HRQoL) by using health-related quality of life (HRQoL).

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

ACZ885 (canakinumab) 150 mg Lyophilized cake for reconstitution of solution for injection vials were supplied by Novartis.

Statistical Methods

A statistical analysis of each of the primary variables was planned. The concentration of ACZ885 measured in the joint fluid on Day 15 was to be log-transformed prior to analysis and a linear fixed effect model was to be fitted with the pharmacokinetic concentration as the response variable. Treatment group was to be fitted as a fixed effect. Treatment contrasts were to be calculated to compare:

- Route of administration (subcutaneous vs. intravenous)
- Dose level (i.e. high dose vs. low dose)

A similar analysis was planned for the concentration of IL-1β in joint fluid on Day 15. However, due to the low number of subjects in each of the treatment groups, these analyses were not performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female patients aged 18 - 75 years (inclusive).
- Body weight must be between 50 and 100 kg (inclusive).
- Post-menopausal or surgically sterile female patients. Women of child-bearing potential if already on a stable dose of methotrexate and are practicing effective contraception for at least 3 months prior to screening, have a negative pregnancy test at screening and baseline, and are willing to use 2 forms of contraception including at least 1 barrier method during the study and for at least 2 months following the completion/discontinuation of the study. Male patients must be willing to use an effective contraception method during the study and at least for 2 months following the completion/discontinuation of the study.
- Diagnosis of Rheumatoid Arthritis, classified by ARA (American Rheumatism Association) 1987 revised criteria (Appendix 2). Disease duration of at least 6 months prior to randomization is essential.
- Functional status class I, II or III classified according to the ACR (American College of Rheumatology) 1991 revised criteria (Appendix 3).
- Active disease at screening and baseline (Day 1 predose) evaluation (same evaluator): ≥ 6 tender and ≥ 6 swollen joints of 28 examined (including any effused joint) and either a) Westergren erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour, or b) C-reactive protein (CRP) ≥ 1.0 mg/dL.
- Prior treatment with 1-3 disease-modifying anti-rheumatic drugs (DMARDs) - Patients should have failed at least 1 DMARD but should not be deemed "refractory to all therapies". Patients should be on a current treatment with

methotrexate ≤ 25 mg/week and with the current dose stable for at least 3 months. All patients will take folic acid 1 mg daily, or 5 mg weekly post MTX dose, to minimize toxicity, according to local guidelines. In addition to methotrexate, patients may be on either a stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) and/or a stable dose of oral corticosteroids (prednisone or equivalent ≤ 10 mg daily) for at least 4 weeks prior to randomization. Patients who failed any DMARDs will be allowed.

- Negative purified protein derivative (PPD) tuberculin skin test reaction (PPD 5 tuberculin units or as according to local standard practice).
- Patients with a total white cell count and platelet count clinically acceptable for patients with RA; hemoglobin must be ≥ 10 g/dL and hematocrit ≥ 30% at screening and baseline.

Exclusion Criteria:

- Previous treatment with anti-TNF-α or anti IL-1 therapy (or other biological therapy), immunosuppressive agents such as cyclosporine, mycophenolate or tacrolimus. The following washout period will be required for such patients to be eligible to participate in the trial.
    a. 2 months washout prior to screening for etanercept or adalimumab
    b. 3 months washout prior to screening for infliximab
    c. 3 months washout prior to screening for rituximab
    d. 1 month washout prior to screening for cyclosporine, mycophenolate and tacrolimus.
- If patient has been discontinued from other DMARDs for lack of efficacy or toxicity, the patient should be at least 1 month off the agent and the effects of that agent should have dissipated according to the recognized duration of effect (e.g., sulfasalazine, hydroxychloroquine), or standard washout procedure (cholestyramine for leflunomide). Importantly, discontinuation should not be undertaken only for the purposes of participation in this study.
- Patients who have received intra-articular or systemic corticosteroid injections having been required for treatment of acute RA flare (not being part of a regular therapeutic regimen) within four weeks prior to randomization.
- Presence of or history of Major chronic inflammatory autoimmune diseases like psoriasis, psoriatic arthritis, spondyloarthropathy, inflammatory bowel disease or systemic lupus erythematosus.

Renal trauma, glomerulonephritis or patient with one kidney. Patients with congestive heart failure (New York Heart Association class > III), QT prolongation syndrome or poorly controlled diabetes mellitus. Patients with a history of QTc prolongation will be excluded. A positive HIV test result, Hepatitis B surface antigen or Hepatitis C test result. Significant illness within 2 weeks prior to dosing or any active systemic infection or medical condition that may require treatment or therapeutic intervention during the study. Hypersensitivity to any biological agents, serious allergic reaction, collagen disease, neurological disease (including demyelinating disease). Any joint surgery in past 8 weeks or planned surgery

within next 5 months. Cancer (other than basal cell cancer or adequately treated carcinoma-in-situ of the cervix). Drug or alcohol abuse within the 12 months prior to dosing or evidence of such indicated by the laboratory assays conducted during the screening or baseline evaluations. Underlying metabolic, endocrine, hematologic, pulmonary, cardiac, blood, renal, hepatic, infectious, psychiatric or gastrointestinal conditions which places the patient at unacceptable risk for participation in a study of an immunomodulatory therapy.

- Treatment with an investigational agent within 12 weeks prior to enrollment or longer if required by local regulation.
- Pregnant or breastfeeding women.
- Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing

Participant Flow Table

Patient disposition - n (%) of patients

	All subjects N=13
Patients	
Completed	12 (92%)
Discontinued	1 (8%)
Main cause of discontinuation	
Administrative problems	1 (8%)

Baseline Characteristics

Demographic summary

		All subjects N=13
Age (years)	Mean (SD)	55.8 (12.31)
	Median	57.0
	Range	35 - 70
Gender - n(%)	Male	4 (30.8 %)
	Female	9 (69.2 %)
Race - n(%)	Caucasian	13 (100 %)
Ethnicity - n(%)	Other	13 (100 %)
Body Mass Index (kg/m^2)	Mean (SD)	26.04 (4.384)
	Median	24.09
	Range	21.0 - 34.7
Weight (kg)	Mean (SD)	75.01 (15.258)
	Median	76.00
	Range	51.0 - 98.0
Height (cm)	Mean (SD)	169.4 (9.47)
	Median	169.0
	Range	154 - 190

Summary of Efficacy

Primary Outcome Result(s)

Pharmacokinetic/total IL-1beta pharmacodynamic relationship in joint fluids of patients with rheumatoid arthritis treated with different doses of ACZ885 - Impact of the subcutaneous versus intravenous administration

Due to the low number of subjects in each of the treatment groups, these analyses were not performed.

Secondary Outcome Result(s) (Only Key Secondary outcome measures not all)

ACZ885 Joint Fluid Concentrations ug/mL vs Serum Concentrations (ug/mL) Safety Population

ACZ885 Treatment	Day 1 Pre-dose Joint Fluid	Day 15 Pre-dose Joint Fluid	Day 15 Pre-dose Serum	Day 15 Ratio of Joint Fluid to Serum	Day 43 Joint Fluid	Day 43 Serum	Day 43 Ratio of Joint Fluid to Serum
10mg/kg s.c.	19.3	17.6	26.4	0.667	5.88	16.7	0.352
5mg/kg i.v.	0	10.2	23.2	0.440	NA	17.1	NA
5mg/kg i.v.	0	0.0429	21.9	0.002	NA	17.1	NA
2mg/kg s.c.	0	5.87	8.13	0.722	NA	2.23	NA
1mg/kg i.v.	0	2.92	5.83	0.501	NA	6.66	NA
1mg/kg i.v.	0	NA	3.72	NA	3.18	3.72	0.855

NA: Not available

Efficacy via response to treatment (ACR 20% improvement [ACR 20], 50, 70 & 90) Safety Population

Endpoint: ACR20

Visit	All subjects (N=13)
DAY8	1/13 (7.7%)
DAY15	4/12 (33.3%)
DAY29	6/12 (50.0%)
DAY43	5/12 (41.7%)
EOS	1/ 4 (25.0%)

Endpoint: ACR50

Visit	All subjects (N=13)
DAY8	0/13 (0.0%)
DAY15	0/12 (0.0%)
DAY29	1/12 (8.3%)
DAY43	2/12 (16.7%)
EOS	0/ 4 (0.0%)

Endpoint: ACR70

Visit	All subjects (N=13)
DAY8	0/13 (0.0%)
DAY15	0/12 (0.0%)
DAY29	0/12 (0.0%)
DAY43	1/12 (8.3%)
EOS	0/ 4 (0.0%)

Endpoint: ACR90

Visit	All subjects (N=13)
DAY8	0/13 (0.0%)
DAY15	0/12 (0.0%)
DAY29	0/12 (0.0%)
DAY43	0/12 (0.0%)
EOS	0/ 4 (0.0%)

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

No SAEs were reported during the study.

Other Adverse Events by System Organ Class

Adverse events overall and specific events - n (%) of subjects (all patients)

	All subjects N=13	
	n	(%)
Patients with AE(s)	6	(46)
Ear and labyrinth disorders		
Vertigo	1	(8)
General disorders and administration site conditions		
Injection site hematoma	1	(8)
Infections and infestations		
Localized infection	1	(8)
Tooth infection	1	(8)
Upper respiratory tract infection	1	(8)
Nervous system disorders		
Carpal tunnel syndrome	1	(8)
Headache	2	(15)
Hyperesthesia	1	(8)

Other Relevant Findings

Summary of 28-joint count (total swollen and tender count) by time (All subjects)

All subjects

Visit		Swollen joints (right & left)	Tender joints (right & left)
DAY1	n	13	13
	mean	12.7	15.9
	SD	6.72	6.41
	minimum	6	8
	median	10.0	13.0
	maximum	24	28
DAY8	n	13	13
	mean	9.2	13.5
	SD	4.92	6.52
	minimum	4	5
	median	7.3	13.0
	maximum	20	26
DAY15	n	12	12
	mean	8.8	11.8
	SD	6.46	5.46
	minimum	1	5
	median	7.5	10.0
	maximum	22	25
DAY29	n	12	12
	mean	7.9	11.5
	SD	4.66	7.25
	minimum	2	3
	median	7.1	9.0
	maximum	16	21

DAY43	n	12	12
	mean	8.3	12.4
	SD	6.42	6.78
	minimum	1	2
	median	6.5	12.2
	maximum	19	26
EOS	n	4	4
	mean	9.8	12.8
	SD	5.44	9.57
	minimum	2	4
	median	11.5	10.5
	maximum	14	26

Date of Clinical Trial Report

11-Oct-2010