Sponsor

Novartis

Generic Drug Name

Canakinumab (ACZ885)

Therapeutic Area of Trial

Rheumatoid Arthritis

Approved Indication

United States of America:
indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:
• Familial Cold Autoinflammatory Syndrome (FCAS)
• Muckle-Wells Syndrome (MWS)

Europe and Switzerland:
indicated for the treatment of adults, and of children 4 years of age and older, with cryopyrin-associated periodic syndromes (CAPS), including:

- Familial cold autoinflammatory syndrome (FCAS) / familial cold urticaria (FCU)
- Muckle-Wells syndrome (MWS)

•Neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular (CINCA) syndrome

Study Number

CACZ885A2211

Title

A 54-week, phase II, multi-center, open-label extension study to evaluate the efficacy, safety and tolerability of ACZ885 (anti-interleukin-1β monoclonal antibody) in patients with rheumatoid arthritis

Phase of Development

Phase II

Study Start/End Dates

11-Oct-2007 to 13-Aug-2009

Study Design/Methodology

Multicenter, open label, uncontrolled, non-randomized 54-week extension study to the core studies CACZ885A2204, CACZ885A2206, and CACZ885A2207 to assess the long-term safety and tolerability of ACZ885, long-term efficacy through ACR, SDAI and DAS28 scoring, long-term preservation and/or improvement of joint structure and bone mineral density (in CACZ885A2204 completer patients), as well as long term maintenance of health-related quality of life, in patients with RA who completed the treatment period of one of the core studies.

Centres

29 centres in 9 countries: Germany (5), Turkey (3), Spain (3), Russia (3), Italy (1), Belgium (2), United States of America (8), Netherlands (3), and Switzerland (1).

Publication

None.

Objectives

Primary objective(s)

To assess the long-term safety and tolerability (and in particular the infection occurrence) of ACZ885 in patients with rheumatoid arthritis (RA) who participated in the core CACZ885A2204, CACZ885A2206, or CACZ885A2207 studies.

Secondary objective(s)

- To evaluate the efficacy of ACZ885 by assessing the time course of the response to treatment according to ACR20, ACR50, ACR70, and ACR90 criteria, and by using the Simplified Disease Activity Index (SDAI) and Disease Activity Score 28 (DAS28).
- To assess the effect of ACZ885 on ACR components, including a marker of inflammation (C-reactive protein).
- To assess the long-term immunogenicity of ACZ885.
- To evaluate the long-term pharmacokinetics (PK) of ACZ885.
- To assess the long term maintenance of health-related quality of life (HRQoL) by using the Medical Outcome Short Form (36) Health Survey (SF-36®).

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

ACZ885 (canakinumab) 150 mg lyophilized cake for reconstitution of solution for intravenous infusion.

One single dose of 600 mg i.v. on Day 1 and from then on every 6 weeks (± 5 days), for a total planned treatment period of 54 weeks.

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

Not applicable.

Criteria for Evaluation

Primary variables: Safety and tolerability

Safety and tolerability of ACZ885 as assessed by:

- Adverse events (AEs), with particular focus on occurrence of infections; serious adverse events (SAEs), with their severity and relationship to study drug; and pregnancies.
- Regular monitoring of hematology, blood chemistry, and urine (performed by a central laboratory)
- Regular assessments of vital signs, 12-lead ECG, physical condition and body weight.

Secondary variables

- Clinical response to treatment (ACR 20, 50, 70, 90), assessed at each visit
- SDAI and DAS28, assessed at each visit
- MRI of the most swollen wrist (determined at baseline by the investigator site), performed at Week 18 (± 1 week) using a whole body MRI system with image acquisition according to the OMERACT recommendation (applicable only for patients who completed the core study CACZ885A2204)
- BMD, measured at Week 18 (± 1 week) by DXA of the hand with the most swollen wrist (determined at baseline by the investigator site), lumbosacral (LS) spine and hip (applicable only for patients who completed the core study CACZ885A2204)
- Evaluation of radiographic bone erosions (numeric count), modified Sharp/van der Heijde score from digital radiographic (X-ray) assessment of both hands and both feet, performed at Week 18 (± 1 week) (applicable only for patients who completed the core study CACZ885A2204)
- Change in HRQoL assessed at baseline and every 12 weeks using HAQ®and SF-36® questionnaires
- Immunogenicity: measurement of anti-ACZ885 antibodies

Pharmacokinetics

Canakinumab concentrations in serum by competitive ELISA.

Pharmacodynamics

Total interleukin 1beta (IL-1β) in serum by ELISA.

Other – Special clinical laboratory evaluations

- Antinuclear antibodies (ANA)
- Bone markers: CTX-I (C-terminal cross-linking telopeptide of type I collagen) in serum, CTX-II (C-terminal cross-linking telopeptide of type II collagen) in urine, and glucosyl-galactosyl-pyridinoline (Glc-Gal-PYD) in urine.
- Rheumatoid factor (RF)
- Anti-cyclic citrullinated peptide antibodies (anti-CCP)

Statistical Methods

No statistical analyses were performed.

Depending on the type of data, different groupings were used to summarize the data. The following groupings were used:

- Across all subjects
- Grouped by whether or not the subject received ACZ885 treatment in the core trial
- Grouped by core trial
- Grouped by core trial and whether or not the subject received ACZ885 treatment in the core trial

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients (male and non-pregnant, non-lactating females) who completed the core CACZ885A2204, CACZ885A2206, or CACZ885A2207 study without serious or severe drug-related adverse effects could enter the extension study upon signing informed consent. A patient was defined as completing the study if he/she completed the core CACZ885A2204 study up to and including visit 18 (Week 30), or the core CACZ885A2206 study up to and including visit 7 (Day 43 / Week 6), or the core CACZ885A2207 study up to and including visit 7 (Day 85 / Week 12).

Exclusion criteria

- Patients for whom continued treatment in the extension was not considered appropriate by the treating physician.
- Patients who were non-compliant or who demonstrated a major protocol violation in the core study.
- Patients who did not complete / discontinued from the core study.
- Patients with drug related serious adverse events or severe adverse events.

Number of Subjects

	Novartis product	**Comparator**
Planned N	Up to 179	All N/A
Randomised n	115	
Intent-to-treat population (ITT) n (%)	N/A	
Completed n (%)	30 (26%)	
Withdrawn n (%)	85 (74%)	
Withdrawn due to adverse events n (%)	6 (5%)	
Withdrawn due to lack of efficacy n (%)	14 (12%)	
Withdrawn for other reasons n (%)	65 (57%)	

Demographic and Background Characteristics

	Novartis product	Comparator
N (ITT)	115	All N/A
Females : males	93 (80.9%) : 22 (19.1%)	
Mean age, years (SD)	52.3 (13.16)	
Mean weight, kg (SD)	72.61 (13.141)	
Race White n (%) Black n (%) Asian n (%) Native American n (%) Other n (%)	 109 (94.8%) 2 (1.7%) 2 (1.7%) 1 (0.9%) 1 (0.9%)	

Primary Objective Result(s)

See Safety Results.

Secondary Objective Result(s)

The percentage of ACR20 responders did not significantly change over time in the groups. This was not surprising given the uncontrolled design (lack of placebo), patients, heterogeneous cohorts and treatment schedules. Changes in the ACR based efficacy parameters were mirrored by trends in the analysis of DAS28, SDAI, EULAR response criteria, patients achieving clinical remission, CRP, and the PRO questionnaires: HAQ® and SF-36®.

The majority of the patients had zero or low edema, erosion and synovitis scores on MRI and erosion and joint space narrowing Sharp/van der Heijde scores on X-ray. There were few patients with BMD assessment to allow any robust conclusion.

Safety Results

Eight patients experienced SAEs and one patient died during the study. The death and most of the SAEs were not suspected to be study drug related. Most of the infections were mild, and all infections resolved either spontaneously or following antibiotic treatment. Laboratory values showed some changes during the course of the study but were void of clinical significance. No clinically relevant changes were observed for total white blood cell counts, or neutrophils counts. Good local tolerability at the injection site was documented and no immunogenicity developed. The AE profile for ACZ885 observed in this study does not indicate target organ toxicity. Overall ACZ885 was safe and well tolerated.

Adverse Events by System Organ Class

	Novartis product N (%)	Comparator N (%)
Patients studied		
Randomized patients	115	All N/A
Patients with AEs	91 (79%)	
Drug-related AEs by primary system organ class		
Infections and infestations	50 (43%)	
Musculoskeletal and connective tissue disorders	31 (27%)	
Gastrointestinal disorders	23 (20%)	
Investigations	18 (16%)	
Nervous system disorders	18 (16%)	
Skin and subcutaneous tissue disorders	15 (13%)	
Injury, poisoning, and procedural complications	13 (11%)	
General disorders and administration site conditions	10 (9%)	
Respiratory, thoracic and mediastinal disorders	9 (8%)	
Blood and lymphatic system disorders	6 (5%)	
Renal and urinary disorders	6 (5%)	
Cardiac disorders	5 (4%)	
Eye disorders	5 (4%)	
Metabolism and nutrition disorders	5 (4%)	
Vascular disorders	5 (4%)	
Ear and labyrinth disorders	3 (3%)	
Hepatobiliary disorders	3 (3%)	
Immune system disorders	3 (3%)	
Psychiatric disorders	3 (3%)	
Reproductive system and breast disorders	3 (3%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2%)	
Congenital, familial and genetic disorders	1 (1%)	
Endocrine disorders	1 (1%)	
Social circumstances	1 (1%)	
Surgical and medical procedures	1 (1%)	

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

	Novartis product	Comparator
Nasopharyngitis	12 (10%)	All N/A
Headache	11 (10%)	
Bronchitis	8 (7%)	
Pain in extremity	7 (6%)	
Respiratory tract infection viral	7 (6%)	
Back pain	6 (5%)	
Rheumatoid arthritis	6 (5%)	
Arthralgia	5 (4%)	
Nausea	5 (4%)	
Abdominal pain upper	4 (3%)	

Serious Adverse Events and Deaths

	Novartis product	Comparator
No. (%) of subjects studied	115	All N/A
No. (%) of subjects with AE(s)	91 (79%)	
Number (%) of subjects with serious or other significant events	n (%)	
Death	1 (1%)	
SAE(s)	9 (8%)	
Discontinued due to SAE(s)	3 (3%)	

SAEs: 1 hip fracture (leading to death), 1 osteoarthritis, 1 radius fracture, 1 intermediate uveitis and sarcoidosis, 1 back pain and spinal fracture, 1 rheumatoid arthritis, 1 colon neoplasm, 1 cholelithiasis, 1 lower respiratory tract infection.

Other Relevant Findings

The population-based PK-binding model captures the kinetics of canakinumab as well as the increase in the total IL-1β concentrations. The PK parameters of canakinumab estimated from the binding model were very similar to a human IgG1-type antibody. The mean total distribution volume (VD+VP) in adult patients was approximately 6.13 L, which is close to the serum volume and typical for the distribution of large macromolecules. Mean total serum clearance (CL) was slow, estimated to be 0.210 L/day in adult patients. An increase in total IL-1β levels was observed following canakinumab dosing, signifying the binding of IL-1β to canakinumab. The mean equilibrium dissociation constant for binding of canakinumab to IL-1β was estimated to be 0.557 nM.

Date of Clinical Trial Report 01-Nov-2010
Date Inclusion on Novartis Clinical Trial Results Database 26-Nov-2010
Date of Latest Update