D. Full Novartis CTRD Template

Sponsor

Novartis

Generic Drug Name

Canakinumab

Therapeutic Area of Trial

Neonatal-onset multisystem inflammatory disease (NOMID) / Chronic infantile neurologic, cutaneous, articular syndrome (CINCA)

Approved Indication

Indicated and approved in over 60 countries for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with body weight above 15 kg, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

Protocol Number

CACZ885D2201

Title

A multi-center, open label, 24-month treatment study to establish the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of canakinumab (anti-IL-1 beta antibody) in patients with NOMID / CINCA syndrome

Phase of Development

Phase III

Study Start/End Dates

26-Jan-2009 to 17-Feb-2011

This study was prematurely terminated. Reasons for a change in the scope of the study included:
• Multiple protocol amendments including a change to study design requiring higher starting and maximum maintenance dose
• Limited number of available patients at the single US site conducting Stage 1
• No execution of Stage 2 (expansion to multicenter study), due to the Ilaris® approval in Europe in June 2009 and the lack of severe NOMID patients with

evidence of CNS damage, which were since mostly enrolled in study CACZ885D2306.

Study Design/Methodology

Single center, non-randomized, open-label, uncontrolled, single group Phase III study to investigate the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of canakinumab in patients with NOMID / CINCA syndrome.
After a screening visit and a run-in period, patients entered a treatment period with a baseline evaluation prior to each drug administration and an observation period after each dose administration. All patients who completed the 6-month core treatment period were offered to enter an 18-month extension treatment period for a total of 24 months treatment period. Patients were dosed every 4 to 8 weeks and were exposed to increasing doses of canakinumab when they did not respond.

Centres

Single center in USA.

Publication

None

Outcome measures

Primary outcome measures(s)

Assessment of the proportion of patients experiencing a relapse (CNS relapse and inflammatory relapse) during the study.

Secondary outcome measures(s)

- Change in the disease diary score assessed at each visit.
- Assessment of central nervous system (CNS) disease activity, eye disease, hearing impairment, skin disease, joint disease, and kidney function at baseline and after 6 months treatment.
- Adverse events and infections occurrence throughout the study
- Vital signs and body measurements, physical examination, inflammation markers at every visit
- Pharmacokinetics (PK) and pharmacodynamics (PD) of canakinumab at each visit.
- Assessment of health-related quality of life at each visit using the PedsQL Measurement Model at baseline and after 6 months treatment.

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

Canakinumab was reconstituted to a solution for subcutaneous injection.
Patients with a body weight > 40 kg received 300 mg canakinumab subcutaneously (s.c.) every 4 to 8 weeks.
Patients with a body weight ≤ 40 kg received 2 mg/kg canakinumab s.c. every 4 to 8 weeks.
Patients were exposed to increasing doses of canakinumab (450 mg s.c. or 6 mg/kg, 600 mg s.c. or 8 mg/kg) when they did not respond.

Statistical Methods

Descriptive graphical summaries including box plots and individual patient profiles were produced. An interim analysis was performed after the first 3 patients completed at least 12 months of treatment and 2 patients completed at least 6 months of treatment.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion criteria

• Male and female patients of ≥ 2 years of age at the time of the screening visit.
• Presence, or history (prior to anakinra treatment), of at least 2 of the following clinical manifestations:
o Typical NOMID urticarial rash.
o Central nervous system (CNS) involvement: increased intracranial pressure (> 180 mm water), papilledema, cerebral spinal fluid pleiocytosis (white cell count > 6 cells/mm3), stroke, seizures, and/or sensorineural hearing loss.
o Typical arthropatic changes on X-rays: epiphysal and/or patellar overgrowth.
o Onset of NOMID/CINCA before or at 6 months of age.

Key Exclusion criteria

• Pregnant or breastfeeding women.
• Participation in any clinical trial investigation within 4 weeks prior to dosing, with the exception of trials with anakinra.
• In case of previous treatment with biologic agents or DMARDs, an appropriate washout period was required.
• Presence of active infections or a history of pulmonary TB infection.
• Presence of any additional rheumatic disease or significant systemic disease.
• Treatment with a live virus vaccine during 3 months prior to baseline visit.

Participant Flow

	Total N=7
Patients	
Completed	6 (85.7%)
Discontinued	1 (14.3%)
Subject withdrew consent	1 (14.3%)

Baseline Characteristics

Demographic characteristics:

		ACZ885 N=6
Age (years)	Mean (SD)	18.7 (8.09)
	Median	16.5
	Range	11 - 34
Gender - n(%)	Male	4 (67%)
	Female	2 (33%)
Predominant race - n(%)	Caucasian	4 (67%)
	Black	1 (17%)
	Asian	1 (17%)
Ethnicity - n(%)	Hispanic/Latino	1 (17%)
	Japanese	1 (17%)
	Mixed Ethnicity	2 (33%)
	Other	2 (33%)
Height (cm)	Mean (SD)	144.510 (26.3892)
	Median	151.880
	Range	105.70 - 171.00
Weight (kg)	Mean (SD)	57.500 (29.5469)
	Median	54.850
	Range	26.50 - 96.60
BMI (kg/m2)	Mean (SD)	25.792 (6.8596)
	Median	24.354
	Range	18.22 - 37.73

Child bearing potential - n(%)	Able to bear children	2 (33%)

Baseline disease characteristics:

	N (%)	Mean (sd)	min, median, max
NALP3 mutation	4 (67%)		
Prior and current medications			
anakinra	6 (100%)		
DMARDs	2 (33%)		
corticosteroids	4 (67%)		
NSAIDs	3 (50%)		
Investigator's clinical assessment of disease activity (VAS)	6	12.0 (18.87)	1, 4.0, 50
Patient's / Parents's assessment of clinical disease activity (VAS)	6	20.8 (30.20)	2, 11.0, 82
CRP (mg/L)	6	2.47 (3.109)	0.3, 1.71, 8.7
SAA (mg/L)	6	8.92 (9.258)	1.6, 4.35, 21.5

Outcome measures

Primary Outcome Result(s)

Despite an overall good clinical response based on symptoms (diary), only 1 out of 5 patients was in remission at the six-month assessment. Systemic remission was achieved by 3 out of 6 patients, CNS remission by 1 out of 5 patients (one additional patient was in CNS remission by clinical criteria but did not have an available lumbar puncture at 6 months). Although the patient reported clinical components of the remission criterion (global diary score ≤ 2 and headache score < 0.5) demonstrate the achievement of remission based on symptoms and diary scores most of the time, no patient was in a stable full remission state as defined by the protocol. This was mainly driven by the laboratory test components of the remission criterion (serum CRP and SAA ≤ 10 mg/L, and WBC count in CSF ≤ 15 cells/mm3). One (1) patient out of 6 was did not achieve remission during the entire study. The proportion of patients experiencing a relapse (CNS relapse and/or inflammatory relapse) during 6-month administration of canakinumab in the study was 33.3% (2 out of 6 patients).

Summary of disease remission and relapse - Primary endpoint:

Remission N (%)	Relapse N (%)
5 (83%)	2 (33%)

Secondary Outcome Result(s)

All patients enrolled in the study required a dose increase up to 600 mg (4 patients) or 8 mg/kg (2 patients), respectively. The dosing interval was reduced for all patients to 4 weeks (5 patients) or 6 weeks (1 patient). Overall, response data of the 6 patients showed canakinumab to be effective at these doses. Serum inflammatory markers (SAA and CRP) showed improved control on higher drug doses and all but one patient achieved serum inflammatory remission at the end of the study. Data on neurological, ophthalmological, and ENT/audiometry examinations as well as imaging assessments are too sparse at the time of this report to allow for firm conclusions. No change from baseline was noted in the dermatological evaluation and in the joint assessment in this cohort. In general, all bone markers decreased over time.

The PK parameters of canakinumab were in line with the expected PK characteristics of a human IgG molecule.

Mean pharmacokinetic parameters of NOMID patients (n=6):

	CL/F (L/d)	V2/F (L)	V3/F (L)	Q/F (L/d)	KA (1/d)
Mean	0.156	5.57	2.75	0.0523	0.473
Standard dev.	0.0671	1.98	2.21	0.0201	0.108

Canakinumab was able to penetrate into CSF, but at levels which are substantially lower than those achieved in serum. Canakinumab concentrations in the CSF ranged from 0 (i.e. < LLOQ) to 650 ng/mL. CSF levels were more than 100-fold lower compared to serum canakinumab concentrations.

Safety Results

Adverse Events by System Organ Class

Body system	Total N=6 nE / nS (%)
Any Body System	124 / 6 (100.0%)
Blood and lymphatic system disorders	2 / 2 (33.3%)
Ear and labyrinth disorders	2 / 2 (33.3%)
Eye disorders	3 / 3 (50.0%)
Gastrointestinal disorders	4 / 2 (33.3%)
General disorders and administration site conditions	4 / 3 (50.0%)
Infections and infestations	7 / 3 (50.0%)
Injury, poisoning and procedural complications	3 / 3 (50.0%)
Investigations	71 / 5 (83.3%)
Musculoskeletal and connective tissue disorders	6 / 3 (50.0%)
Nervous system disorders	13 / 5 (83.3%)
Reproductive system and breast disorders	1 / 1 (16.7%)
Respiratory, thoracic and mediastinal disorders	4 / 3 (50.0%)
Skin and subcutaneous tissue disorders	4 / 2 (33.3%)

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

	Total N=6 n (%)
Blood creatinine decreased	5 (83.3%)
CSF neutrophil count increased	5 (83.3%)
CSF white blood cell count increased	5 (83.3%)
CSF protein increased	4 (66.7%)
Headache	4 (66.7%)
Arthralgia	3 (50.0%)
Blood creatine phosphokinase decreased	3 (50.0%)
C-reactive protein increased	3 (50.0%)
Dizziness	3 (50.0%)
Eosinophil count increased	3 (50.0%)

Serious Adverse Events and Deaths

Number (%) of subjects with serious or other significant events	n (%)
Death	0
SAE(s)	1 (16.7)
Discontinued due to SAE(s)	0

Other Relevant Findings

Not applicable for this trial.

Date of Clinical Trial Report 24-Oct-2011
Date Inclusion on Novartis Clinical Trial Results Database **21 Feb 2012**
Date of Latest Update **21 Feb 2012**