Clinical trial results:
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

Summary

EudraCT number	2008-001429-32
Trial protocol	Outside EU/EEA
Global end of trial date	17 February 2011

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	CACZ885D2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00770601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clincal Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clincal Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000060-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the proportion of patients experiencing a relapse (CNS relapse and/or inflammatory relapse) during 6-month open label administration of canakinumab in patients with NOMID / CINCA syndrome.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed. The subjects were treated as in routine care. In order to avoid relapse, dose adjustments with canakinumab were allowed during the course of the study, as detailed in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	7
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	4
Adults (18-64 years)	2
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 1 centre in United States

Pre-assignment

Screening details:

A total of 7 subjects were screened and 6 subjects were randomised into the study, as one subject withdrew consent before dosing.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open label, hence no blinding was performed.

Arms

Arm title	Canakinumab

Arm description:

Subjects received body-weight stratified dosage of canakinumab treatment at 300 mg (for subjects weighing more than 40 kg) and at 4 mg/kg (in children with body weight less than or equal to 40 kg) s.c. every 4-8 weeks as per investigator discretion for a treatment period of 6 months. The first 3 NOMID patients enrolled received a dose of 150 mg (>40 kg) and 2 mg/kg for children <40 kg. Since this dose was insufficient to fully control the symptoms of the disease the 300 mg / 4mg/kg dose was introduced by Protocol Amendment 2.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Canakinumab s.c. solution (300 mg or 4 mg/kg) was administered every 8 weeks.

Number of subjects in period 1[1]	Canakinumab
Started	6
Completed	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period (N=6) are different from the worldwide number (N=7) enrolled in the trial, as 1 subject withdrew consent before first dosing.

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab

Reporting group description:

Subjects received body-weight stratified dosage of canakinumab treatment at 300 mg (for subjects weighing more than 40 kg) and at 4 mg/kg (in children with body weight less than or equal to 40 kg) s.c. every 4-8 weeks as per investigator discretion for a treatment period of 6 months. The first 3 NOMID patients enrolled received a dose of 150 mg (>40 kg) and 2 mg/kg for children <40 kg. Since this dose was insufficient to fully control the symptoms of the disease the 300 mg / 4mg/kg dose was introduced by Protocol Amendment 2.

Reporting group values	Canakinumab	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	2	2	
Age continuous Units: years			
arithmetic mean	18.7		
standard deviation	± 8.09	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	4	4	

End points

End points reporting groups

Reporting group title	Canakinumab

Reporting group description:

Subjects received body-weight stratified dosage of canakinumab treatment at 300 mg (for subjects weighing more than 40 kg) and at 4 mg/kg (in children with body weight less than or equal to 40 kg) s.c. every 4-8 weeks as per investigator discretion for a treatment period of 6 months. The first 3 NOMID patients enrolled received a dose of 150 mg (>40 kg) and 2 mg/kg for children <40 kg. Since this dose was insufficient to fully control the symptoms of the disease the 300 mg / 4mg/kg dose was introduced by Protocol Amendment 2.

Primary: Percentage of subjects with complete remission and relapse after 6 months of cankinumab treatment

End point title	Percentage of subjects with complete remission and relapse after 6 months of cankinumab treatment[1]

End point description:

The primary endpoint of the study was the proportion of patients experiencing a relapse(CNS relapse and/or inflammatory relapse)during 6-month open label administration of canakinumab in patients with NOMID / CINCA syndrome. Complete remission consisted of inflammatory remission and CNS remission.
1) Inflammatory (systemic) remission was defined as follows (all criteria to be fulfilled):
-Serum CRP AND SAA ≤ 10 mg/L AND -daily diary score (mean score/week) ≤ 2.
2) CNS remission was defined as follows: Headache score (from the daily diary, mean score/week) < 0.5 AND, when a lumbar puncture was performed: Normal values of white cell count (WBC) (≤15 cells/mm3) in CSF. The primary analysis was performed on all subjects randomised and received at least one dose of study drug. No patient was in stable full remission state as defined by the protocol.

End point type	Primary

End point timeframe:

Month 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: Percentage of subjects				

Notes:

[2] - No patient was in stable full remission state as defined by the protocol

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Canakinumab

Reporting group description:

Subjects received bodyweight stratified dosage of canakinumab treatment at 300 mg (for subjects weighing more than 40 kg) and at 4 mg/kg (in children with body weight less than or equal to 40 kg) s.c. for every 4--8 weeks as per investigator discretion for a treatment period of 6 months.

Serious adverse events	Canakinumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Canakinumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Investigations			
Blood albumin increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood albumin decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Basophil count increased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood chloride increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood creatine phosphokinase decreased			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		

Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood creatinine decreased				
subjects affected / exposed	5 / 6 (83.33%)			
occurrences (all)	6			
Blood glucose increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood triglycerides increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood uric acid decreased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
C-reactive protein increased				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	4			
CSF protein increased				
subjects affected / exposed	4 / 6 (66.67%)			
occurrences (all)	4			
CSF neutrophil count increased				
subjects affected / exposed	5 / 6 (83.33%)			
occurrences (all)	6			
Haematocrit decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Eosinophil count increased				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	4			
CSF white blood cell count increased				
subjects affected / exposed	5 / 6 (83.33%)			
occurrences (all)	6			
Haemoglobin decreased				

subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Heart rate increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
High density lipoprotein decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Monocyte count increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Lymphocyte count increased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Platelet count decreased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Neutrophil count increased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	3			
Platelet count increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
White blood cell count increased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Red blood cell sedimentation rate increased				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Red blood cell count increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Injury, poisoning and procedural complications				

Joint injury subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Sinus headache subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all)	 3 / 6 (50.00%) 3 4 / 6 (66.67%) 8 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2		
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		

Vision blurred			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pityriasis rosea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Joint stiffness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Costochondritis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Localised infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2009	The starting dose of canakinumab treatment in NOMID subjects was modified (300 mg for subjects > 40 kg and 4 mg/kg for children ≤ 40 kg), and the treatment period was extended by additional 6 months.
09 December 2009	Reduction of the dosing interval from every 8 weeks to every 4 to 8 weeks.
09 February 2010	Extension period was prolonged from 6 months to 18 months, resulted in a total of 24 months treatment period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated prematurely due to multiple protocol amendments for change in study design; limited number of subjects; availability of sufficient clinical data for higher doses of drug and lack of severe NOMID subjects for further evaluation.

Notes: