

**Clinical trial results:**

**An open-label, long-term safety and efficacy study of ACZ885 (anti-interleukin-1; monoclonal antibody) administered for at least 6 months in patients with the following cryopyrin-associated periodic syndromes: Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Muckle-Wells Syndrome with overlapping symptoms of Neonatal Onset Multisystem Inflammatory Disease**

**Summary**

EudraCT number	2007-004367-22
Trial protocol	GB DE FR ES IT BE Outside EU/EEA
Global end of trial date	29 April 2010

**Results information**

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	12 August 2015

**Trial information****Trial identification**

Sponsor protocol code	CACZ885D2306
-----------------------	--------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00685373
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical 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)	EMA-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	29 April 2010
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 April 2010
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of study was to assess the long-term safety and tolerability of canakinumab in subjects with the following cryopyrin associated periodic syndromes (CAPS): Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) or MWS with overlapping symptoms of Neonatal Onset Multisystem Inflammatory Disease (NOMID).

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. Canakinumab dose was adjusted done during the course of the study as rescue medication. A rescue dose of 300 milligram (mg) subcutaneous (s.c.) (or 4 mg/kilogram (mg/kg) for subjects with a body weight less than or equal to ( $\leq$ ) 40 kg) by Day 8. Non responders by Day 15 were treated again with same dose as rescue medication and continued with maintenance dose of 600 mg s.c. (or 8 mg/kg for subjects  $\leq$  40 kg) every 8 weeks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2008
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	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Turkey: 5
Worldwide total number of subjects	166
EEA total number of subjects	125

Notes:

<b>Subjects enrolled per age group</b>	
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)	26
Adolescents (12-17 years)	21
Adults (18-64 years)	111
From 65 to 84 years	7
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 32 centres in 8 countries.

### Pre-assignment

Screening details:

A total of 166 subjects were enrolled into the study.

### Period 1

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

### Arms

<b>Arm title</b>	Canakinumab
------------------	-------------

Arm description:

Subjects received body-weight stratified dosage of canakinumab (2 mg/kg for subjects  $\leq$  40 kg or 150 mg for subjects more than (>) 40 kg) s.c. injection every 8 weeks. The dose was escalated to 4 mg/kg or 300 mg respectively at Day 8 if dose of canakinumab was not sufficient to achieve complete response by Day 15, as per investigator's discretion.

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. injection (2 mg/kg or 150 mg) was administered every 8 weeks.

<b>Number of subjects in period 1</b>	Canakinumab
Started	166
Completed	151
Not completed	15
Consent withdrawn by subject	5
Adverse event, non-fatal	3
Subject's condition no longer requires study drug	1
Lost to follow-up	2
'Unsatisfactory therapeutic effect '	3
Protocol deviation	1

## Baseline characteristics

### Reporting groups

Reporting group title	Canakinumab
-----------------------	-------------

Reporting group description:

Subjects received body-weight stratified dosage of canakinumab (2 mg/kg for subjects  $\leq$  40 kg or 150 mg for subjects more than ( $>$ ) 40 kg) s.c. injection every 8 weeks. The dose was escalated to 4 mg/kg or 300 mg respectively at Day 8 if dose of canakinumab was not sufficient to achieve complete response by Day 15, as per investigator's discretion.

Reporting group values	Canakinumab	Total	
Number of subjects	166	166	
Age categorical Units: Subjects			
Children (2-11 years)	26	26	
Adolescents (12-17 years)	21	21	
Adults (18-64 years)	111	111	
From 65-84 years	7	7	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	30.9		
standard deviation	$\pm$ 18.43	-	
Gender categorical Units: Subjects			
Female	97	97	
Male	69	69	

## End points

### End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Subjects received body-weight stratified dosage of canakinumab (2 mg/kg for subjects $\leq$ 40 kg or 150 mg for subjects more than (>) 40 kg) s.c. injection every 8 weeks. The dose was escalated to 4 mg/kg or 300 mg respectively at Day 8 if dose of canakinumab was not sufficient to achieve complete response by Day 15, as per investigator's discretion.	

### Primary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs), discontinuation of study drug due to an AE, infections and infestations and injection site reactions

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs), discontinuation of study drug due to an AE, infections and infestations and injection site reactions <sup>[1]</sup>
-----------------	---

#### End point description:

Adverse events (AEs) were defined as any unfavorable and unintended diagnosis, symptom, sign, syndrome or disease which either occurs during study, having been absent at baseline, or, if present at baseline, appears to worsen. Serious adverse events (SAEs) were defined as any untoward medical occurrences that result in death, are life threatening, require hospitalisation, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which in judgement of investigators represent significant hazards. Discontinuation was defined as subjects with adverse events that lead to discontinuation of study drug. All infection relevant events were considered as infection by discretion of investigator. Injection site reaction involved pain, redness, swelling, induration, hemorrhage and itching. The analysis was performed in the safety set population defined as defined as subjects who received at least one dose of study drug.

End point type	Primary
----------------	---------

#### End point timeframe:

Day 1 up to Day 729

#### 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	166			
Units: Number of subjects				
Adverse events	150			
Serious adverse events	18			
Discontinuation of study drug due to an AE	4			
Infections and Infestations	109			
Any Injection Site Reactions	13			
Mild Injection Site Reactions	11			
Moderate Injection Site Reactions	2			

## Statistical analyses

No statistical analyses for this end point

---

**Secondary: Percentage of subjects without disease relapse**

---

End point title	Percentage of subjects without disease relapse
-----------------	--

End point description:

Relapse was defined as a Physician's Global Assessment of autoinflammatory disease activity score more minimal and either C reactive protein (CRP) and either Serum amyloid A (SAA) equal to or more than 30 mg/L, or Physician's Global Assessment of autoinflammatory disease activity as score more than or equal to minimal and Physician's global assessment of skin disease score as minimal Physician's global assessment. Subjects were assessed based on Physician's Global Assessment on 5-point scale for autoinflammatory disease activity as: 0 = None/absent; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in the safety set population.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 729

---

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: Percentage of subjects				
number (not applicable)	90.1			

---

**Statistical analyses**

---

No statistical analyses for this end point

---

**Secondary: Number of subjects who required canakinumab additional dose or dose frequency adjustment as assessed by investigator**

---

End point title	Number of subjects who required canakinumab additional dose or dose frequency adjustment as assessed by investigator
-----------------	--

End point description:

The number of subjects who required a dose adjustment of canakinumab or an administration frequency adjustment were defined as subjects who were not complete responders on Day 15 and treated with adjusted dose (canakinumab 300 mg or 4 mg/kg for subjects with less than 40 kg weight), continued with subsequent adjusted dose (canakinumab 600 mg or 8 mg/kg for subjects with less than 40 kg weight). Maintenance of response over time was determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and CRP and/or SAA. The analysis was performed in the safety set population.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 729

---

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	166			
Units: Number of subjects				
Subjects with dose or dose frequency adjustments	40			
Subjects with dose adjustments	36			
Subjects with frequency adjustments	19			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of subjects with anti-canakinumab antibodies

End point title	Number of subjects with anti-canakinumab antibodies
End point description:	Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using Biacore system. The analysis was performed in the safety set population.
End point type	Secondary
End point timeframe:	Day 1 to Day 729

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	156			
Units: Number of subjects	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Clearance from serum of canakinumab

End point title	Clearance from serum of canakinumab
End point description:	Clearance (CL) was defined as the total body clearance of canakinumab following an extravascular dose from the serum when the systemic bioavailability was unknown. The analysis was performed in the safety set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.
End point type	Secondary
End point timeframe:	Day 1, Day 8, Day 29, Day 57, Day 113, Day 169, Day 225, Day 281, Day 337, Day 393, Day 449, Day 505, Day 561, Day 617, Day 673 and Day 729

<b>End point values</b>	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: Litre(s)/day				
arithmetic mean (standard deviation)				
Adult subjects $\geq 18$ years (n=116)	0.179 ( $\pm$ 0.084)			
Pediatric subjects $<18$ years and $>40$ kg (n=18)	0.18 ( $\pm$ 0.145)			
Pediatric subjects $<18$ years and $\leq 40$ kg (n=29)	0.083 ( $\pm$ 0.033)			

### 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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

### Reporting groups

Reporting group title	Canakinumab
-----------------------	-------------

Reporting group description:

Subjects received body-weight stratified dosage of canakinumab (2 mg/kg for subjects  $\leq$  40 kg or 150 mg for subjects more than (>) 40 kg) s.c. injection every 8 weeks. The dose was escalated to 4 mg/kg or 300 mg respectively at Day 8 if dose of canakinumab was not sufficient to achieve complete response by Day 15, as per investigator's discretion.

<b>Serious adverse events</b>	Canakinumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 166 (10.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Hepatitis C antibody positive			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Drug exposure during pregnancy			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Forearm fracture			

subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Congenital, familial and genetic disorders</b>			
Muckle-Wells syndrome			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Surgical and medical procedures</b>			
Abortion induced			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve root compression			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Pregnancy, puerperium and perinatal conditions</b>			
Pregnancy			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Social circumstances</b>			
Miscarriage of partner			

subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders</b>			
Radicular cyst			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Psychiatric disorders</b>			
Depression			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
Nephrotic syndrome			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Tonsillitis			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
H1N1 influenza			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic tonsillitis			

subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cellulitis</b>			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Bronchitis</b>			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Appendicitis</b>			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Abdominal abscess</b>			
subjects affected / exposed	1 / 166 (0.60%)		
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 %

<b>Non-serious adverse events</b>	Canakinumab		
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	124 / 166 (74.70%)		
<b>Injury, poisoning and procedural complications</b>			
<b>Fall</b>			
subjects affected / exposed	11 / 166 (6.63%)		
occurrences (all)	12		
<b>Nervous system disorders</b>			
<b>Headache</b>			
subjects affected / exposed	33 / 166 (19.88%)		
occurrences (all)	58		
<b>General disorders and administration site conditions</b>			

Pyrexia subjects affected / exposed occurrences (all)	18 / 166 (10.84%) 36		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Abdominal pain subjects affected / exposed occurrences (all)	16 / 166 (9.64%) 18  11 / 166 (6.63%) 13  18 / 166 (10.84%) 21  13 / 166 (7.83%) 14		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	16 / 166 (9.64%) 23  14 / 166 (8.43%) 16		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Back pain subjects affected / exposed occurrences (all)  Pain in extremity subjects affected / exposed occurrences (all)	24 / 166 (14.46%) 30  12 / 166 (7.23%) 18  9 / 166 (5.42%) 9		
Infections and infestations Nasopharyngitis			

subjects affected / exposed	48 / 166 (28.92%)		
occurrences (all)	60		
Gastroenteritis			
subjects affected / exposed	12 / 166 (7.23%)		
occurrences (all)	12		
Bronchitis			
subjects affected / exposed	18 / 166 (10.84%)		
occurrences (all)	18		
Rhinitis			
subjects affected / exposed	27 / 166 (16.27%)		
occurrences (all)	29		
Upper respiratory tract infection			
subjects affected / exposed	17 / 166 (10.24%)		
occurrences (all)	22		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2008	Subjects with severe renal insufficiency (Glomerular Filtration Rate (GFR) < 30 millilitre/minute/1.73 square metre) or planned liver transplantation would not undergo administration of a gadolinium contrast agent for the performance of a magnetic resonance imaging (MRI) evaluation.
20 February 2009	The age-range of subjects was lowered (3 years or younger), so as to allow for the inclusion of subjects with Neonatal Onset Multisystem Inflammatory Disease (canakinumab naive), and to update the sample size in the protocol.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported