Clinical trial results:
An open-label extension study to assess efficacy, safety and tolerability of canakinumab and the efficacy and safety of childhood vaccinations in patients with Cryopyrin Associated Periodic Syndromes (CAPS)

Summary

EudraCT number	2011-005154-57
Trial protocol	BE FR ES DE GB
Global end of trial date	13 October 2015

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	ACZ885D2307E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01576367
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)	No
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	13 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the long-term efficacy of canakinumab with respect to relapse in CAPS patients who completed the CACZ885D2307 study

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	17
EEA total number of subjects	14

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)	4

Children (2-11 years)	13
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients who complete the CACZ885D2307 study and for whom a parent or legal guardian has signed the informed consent will be eligible to continue canakinumab treatment in the extension. This single treatment arm study will not require treatment assignment of the patients.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	canakinumab

Arm description:

Patients will receive a standard dose at an equivalent of 2 mg/kg s.c. of canakinumab (ACZ885) every 8 weeks. Possible dose and/or dosing regimen adjustments that can be administered include: 4 mg/kg s.c. (every 4 to 8 weeks) 6 mg/kg s.c. (every 4 to 8 weeks) 8 mg/kg s.c. (every 4 to 8 weeks)

Arm type	Experimental
Investigational medicinal product name	canakinumab.
Investigational medicinal product code	ACZ885D
Other name	canakinumab.
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

mg/kg sc of

Number of subjects in period 1	canakinumab
Started	17
Completed	14
Not completed	3
Unsatisfactory therapeutic effect	2
Moved to commercial use after 6 months	1

Baseline characteristics

Reporting groups	
Reporting group title	canakinumab
Reporting group description:	
Patients will receive a standard dose at an equivalent of 2 mg/kg s.c. of canakinumab (ACZ885) every 8 weeks. Possible dose and/or dosing regimen adjustments that can be administered include: 4 mg/kg s.c. (every 4 to 8 weeks) 6 mg/kg s.c. (every 4 to 8 weeks) 8 mg/kg s.c. (every 4 to 8 weeks)	

Reporting group values	canakinumab	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	4	4	
Children (2-11 years)	13	13	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Age at start of extension study (years) Units: Years			
arithmetic mean	3.1		
standard deviation	± 1.7	-	
Gender, Male/Female Units: Participants			
Female	5	5	
Male	12	12	

End points

End points reporting groups

Reporting group title	canakinumab

Reporting group description:

Patients will receive a standard dose at an equivalent of 2 mg/kg s.c. of canakinumab (ACZ885) every 8 weeks. Possible dose and/or dosing regimen adjustments that can be administered include: 4 mg/kg s.c. (every 4 to 8 weeks) 6 mg/kg s.c. (every 4 to 8 weeks) 8 mg/kg s.c. (every 4 to 8 weeks)

Primary: The percentage of participants without disease relapse as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and serological inflammation markers.

End point title	The percentage of participants without disease relapse as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and serological inflammation markers.[1]

End point description:

Disease relapse following complete response is defined as inflammation markers: C-Reactive Protein (CRP) and/or Serum Amyloid A (SAA) result > 30 mg/L AND Physician's Global Assessment of Autoinflammatory Disease Activity > minimal or Physician's Global Assessment >= minimal AND Skin Disease Assessment > minimal. Physician's Global Assessment of Autoinflammatory Disease Activity and Skin Disease Assessment (urticarial skin rash) are completed by the investigator using a 5 point rating scale: absent, minimal, mild, moderate and severe. No statistical analysis was planned for this primary outcome.

End point type	Primary

End point timeframe:

Week /80, 104, 128, and 152 (A minimum of 6 months and maximum of 24 months)

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: No statistical analysis was planned for this primary outcome

End point values	canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of participants				
number (not applicable)	94.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of Canakinumab (ACZ885). Number of participants with anti-canakinumab antibodies

End point title	Immunogenicity of Canakinumab (ACZ885). Number of participants with anti-canakinumab antibodies

End point description:

Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using BIAcore system, with detection based on surface plasmon resonance technique.

End point type	Secondary

End point timeframe:

minimum of 6 months and maximum of 24 months

End point values	canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline (core study baseline) in C--Reactive Protein (CRP) and Serum Amyloid A (SAA) concentrations

End point title	Change from baseline (core study baseline) in C--Reactive Protein (CRP) and Serum Amyloid A (SAA) concentrations

End point description:

CRP and SAA were used as serologic inflammatory markers. The target level concentrations for CRP and SAA was ≤15 mg/L and ≤10 mg/L, respectively. Negative change in concentration of inflammatory markers indicated improvement.

End point type	Secondary

End point timeframe:

Week 0, 80, 104, 128 and 152, last assessment

End point values	canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: (mg/L)				
arithmetic mean (standard deviation)				
CRP at Core End of Study (last assessment) (n=14)	-5.4 (± 6.28)			
CRP at week 80 (n=16)	-14.7 (± 35.8)			
CRP at Week 104 (n=11)	-3.8 (± 14.4)			
CRP at Week 128(n=12)	-4.1 (± 10.3)			
CRP at Week 152 (n=12)	-4.3 (± 11)			
CRP at End of Study (last assessment) (n=16)	-10.4 (± 30.3)			
SAA at Core End of Study (last assessment) (n=16)	-54.4 (± 133.8)			
SAA at Week 80 (n=12)	-79.1 (± 224.1)			
SAA at week 104 (n=11)	15.8 (± 158.1)			
SAA at week 128 (n=10)	-28.2 (± 47.4)			
SAA at week 152 (n=11)	-6.4 (± 60)			
SAA at End of Study (last assessment) (n=15)	-58.5 (± 183.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency counts of physician’s global assessment of autoinflammatory disease and skin disease

End point title	Frequency counts of physician’s global assessment of autoinflammatory disease and skin disease

End point description:

Participants were assessed based by physician on Physician's Global Assessment measured on a 5--point scale for auto inflammatory disease activity as: 0 = None/absent; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Severe

End point type	Secondary

End point timeframe:

minimum of 6 months and maximum of 24 months

End point values	canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Percentage of participants				
number (not applicable)				
Assessment of autoinflammatory disease (Absent)	64.7			
Assessment of autoinflammatory disease (Minimal)	29.4			
Assessment of autoinflammatory disease (Mild)	5.9			
Assessment of autoinflammatory disease (Moderate)	0			
Assessment of autoinflammatory disease (Severe)	0			
Assessment of skin disease (Absent)	94.1			
Assessment of skin disease (Minimal)	0			
Assessment of skin disease (Mild)	5.9			
Assessment of skin disease (Moderate)	0			
Assessment of skin disease (Severe)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of vaccination cases with protective antibody levels following

immunization with inactivated vaccines

End point title	Number of vaccination cases with protective antibody levels following immunization with inactivated vaccines

End point description:

Participants who received any inactivated vaccines during the study were assessed for their ability to attain protective antibody levels against the vaccine (antigen) post immunization. Participants vaccinations were not assessed for a response if the antibody titre was already sufficient at pre-dose and maintained during the study.

End point type	Secondary

End point timeframe:

pre-vaccine dose, Day 28 post-vaccine

End point values	canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: vaccination cases				
Positive response for antibody levels	16			
No pre-dose antibody levels	3			

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	18.0

Reporting groups

Reporting group title	ACZ885

Reporting group description:

ACZ885

Serious adverse events	ACZ885		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 17 (47.06%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Papillitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			

Conductive deafness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis aseptic			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ACZ885		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 17 (94.12%)		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	6 / 17 (35.29%) 12		
Immune system disorders Milk allergy subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) Vulvovaginal burning sensation subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 5 / 17 (29.41%) 16 1 / 17 (5.88%) 1 3 / 17 (17.65%) 4 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Investigations Body temperature increased			

subjects affected / exposed occurrences (all) C-reactive protein increased subjects affected / exposed occurrences (all) CSF white blood cell count increased subjects affected / exposed occurrences (all) Serum amyloid A protein increased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all) Tympanometry abnormal subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1 1 / 17 (5.88%) 3 1 / 17 (5.88%) 1 1 / 17 (5.88%) 3 1 / 17 (5.88%) 1 2 / 17 (11.76%) 2		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Craniocerebral injury subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1 1 / 17 (5.88%) 1		
Congenital, familial and genetic disorders Cryopyrin associated periodic syndrome subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 1		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	 1 / 17 (5.88%) 3		
Nervous system disorders Burning sensation			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cerebral ventricle dilatation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	16		
Hemiplegia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Loss of consciousness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Motor developmental delay			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Pyramidal tract syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Speech disorder developmental			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Conductive deafness			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Ear pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Papilloedema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Iridocyclitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Uveitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	33		
Abdominal pain upper			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	8		
Aphthous stomatitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	7 / 17 (41.18%)		
occurrences (all)	9		
Gingival hypertrophy			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mouth ulceration			

subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	6 / 17 (35.29%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Prurigo			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Pruritus generalised			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		

Rash			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	5		
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	6		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	4		
Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Ear infection				
subjects affected / exposed	3 / 17 (17.65%)			
occurrences (all)	3			
Eczema infected				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Enterobiasis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	4 / 17 (23.53%)			
occurrences (all)	4			
Hand-foot-and-mouth disease				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Impetigo				
subjects affected / exposed	2 / 17 (11.76%)			
occurrences (all)	2			
Laryngitis				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	2			
Lice infestation				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	2			
Meningitis aseptic				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	1			
Molluscum contagiosum				
subjects affected / exposed	2 / 17 (11.76%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	7 / 17 (41.18%)			
occurrences (all)	17			
Oral herpes				
subjects affected / exposed	1 / 17 (5.88%)			
occurrences (all)	2			

Otitis media			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	12		
Tonsillitis			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Varicella			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Vulval abscess			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported