



Clinical trial results:

An Open-label, Efficacy and Safety Study of Canakinumab (Anti-interleukin-1 Monoclonal Antibody) Administered for 6 Months (24 Weeks) in Japanese Patients With the Following Cryopyrin-associated Periodic Syndromes: Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Neonatal Onset Multisystem Inflammatory Disease, Followed by an Extension Phase to Provide Canakinumab to Study Patients Until it is Approved and Marketed in Japan

Summary

EudraCT number	2015-003490-15
Trial protocol	Outside EU/EEA
Global end of trial date	29 February 2012

Results information

Result version number	v1 (current)
This version publication date	12 November 2016
First version publication date	12 November 2016

Trial information

Trial identification

Sponsor protocol code	CACZ885D2308
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00991146
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 February 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2012
Global end of trial reached?	Yes
Global end of trial date	29 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the proportion of patients who were free of relapse at week 24 including those patients who have been up-titrated.

Protection of trial subjects:

A rescue medication or adjustment medication scheme was applied to those patients who either did not achieve a complete response or relapsed prior to their next scheduled dose.

Patients who did not achieve (or maintain) complete response following canakinumab injection in any treatment period, could have received a dose adjustment. Possible step-wise up-titration regimens:

- 300 mg s.c. (or 4 mg/kg for patients with a body weight ≤ 40 kg)
- 450 mg s.c. (or 6 mg/kg for patients with a body weight ≤ 40 kg)
- 600 mg s.c. (or 8 mg/kg for patients with a body weight ≤ 40 kg)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 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	Japan: 19
Worldwide total number of subjects	19
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)	8
Adolescents (12-17 years)	7
Adults (18-64 years)	4
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patient's informed consent for patients ≥ 20 years of age, or for patients < 20 years of age, parent or legal guardian's written informed consent and child's assent was required before any assessment was performed.

Period 1

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

Arms

Arm title	ACZ885
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Arm description:

CAPS patients with a body weight > 40 kg received 150 mg of canakinumab administered s.c. per each injection, every 8 weeks.

CAPS patients with a body weight ≤ 40 kg received an equivalent of 2 mg/kg administered s.c. per each injection, every 8 weeks.

Arm type	Experimental
Investigational medicinal product name	ACZ885
Investigational medicinal product code	
Other name	canakinumab
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Investigational drug (active canakinumab) was provided in individual 6 mL glass vials each containing 150 mg canakinumab as a lyophilized cake. For patients with a body weight of ≥ 15 kg, canakinumab is reconstituted with 1.0 mL water for injection (WFI) to reach a concentration of 150mg/mL. For patients with a body weight < 15 kg, the 150 mg canakinumab lyophilized cake should be reconstituted with 2.2 mL WFI to get a canakinumab concentration of 75 mg/mL.

CAPS patients with a body weight > 40 kg received 150 mg of canakinumab administered s.c. per each injection, every 8 weeks.

CAPS patients with a body weight ≤ 40 kg received an equivalent of 2 mg/kg administered s.c. per each injection, every 8 weeks.

Number of subjects in period 1	ACZ885
Started	19
Completed	18
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	ACZ885
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Reporting group description:

CAPS patients with a body weight >40 kg received 150 mg of canakinumab administered s.c. per each injection, every 8 weeks.

CAPS patients with a body weight ≤40 kg received an equivalent of 2 mg/kg administered s.c. per each injection, every 8 weeks.

Reporting group values	ACZ885	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
Children (2-11 years)	8	8	
Adolescents (12-17 years)	7	7	
Adults (18-64 years)	4	4	
Age continuous			
Units: years			
arithmetic mean	14.8		
standard deviation	± 11.35	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	12	12	

End points

End points reporting groups

Reporting group title	ACZ885
Reporting group description: CAPS patients with a body weight >40 kg received 150 mg of canakinumab administered s.c. per each injection, every 8 weeks. CAPS patients with a body weight ≤40 kg received an equivalent of 2 mg/kg administered s.c. per each injection, every 8 weeks.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: Consisted of all 19 CAPS patients who were enrolled and received at least one dose of canakinumab during the study.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: Consisted of all 19 CAPS patients who were enrolled and received at least one dose of canakinumab during the study.	
Subject analysis set title	Absent
Subject analysis set type	Sub-group analysis
Subject analysis set description: Assessment of auto-inflammatory disease activity: Severity = Absent	
Subject analysis set title	Minimal
Subject analysis set type	Sub-group analysis
Subject analysis set description: Assessment of auto-inflammatory disease activity: Severity = Minimal	
Subject analysis set title	Mild
Subject analysis set type	Sub-group analysis
Subject analysis set description: Assessment of auto-inflammatory disease activity: Severity = Mild	
Subject analysis set title	Moderate
Subject analysis set type	Sub-group analysis
Subject analysis set description: Assessment of auto-inflammatory disease activity: Severity = Moderate	
Subject analysis set title	Severe
Subject analysis set type	Sub-group analysis
Subject analysis set description: Assessment of auto-inflammatory disease activity: Severity = Severe	

Primary: Percentage of patients who do not experience a relapse (clinical and serological relapse) at Week 24

End point title	Percentage of patients who do not experience a relapse (clinical and serological relapse) at Week 24 ^[1]
End point description: For complete responders, relapse was defined as the following criteria: A relapse consisted of clinical and serological relapse defined as follows: <ul style="list-style-type: none">• Clinical relapse: Physician's global assessment of auto-inflammatory disease >minimal or Physician's global assessment of auto-inflammatory disease ≥minimal and assessment of skin disease >minimal and• Serological relapse: Serum CRP >3 mg/dL and/or 2. SAA >30 µg/mL	

End point type	Primary
End point timeframe:	
Week 24	
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: Statistical analyses have not been performed for this primary end point.	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percent				
number (not applicable)				
Clinical relapse	66.7			
Serological relapse	66.7			
Complete response	94.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of complete responder patients

End point title	Number of complete responder patients
End point description:	
Complete response will consist of clinical and serological remission.	
End point type	Secondary
End point timeframe:	
Day 15 and Day 29	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: participants				
number (not applicable)				
Day 15	9			
Day 29	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of physician's global assessment of auto-

inflammatory disease activity

End point title	Overall assessment of physician's global assessment of auto-inflammatory disease activity
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End point description:

The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.

End point type	Secondary
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End point timeframe:

Baseline through end of study (24 months)

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	10.5	31.6	36.8	15.8
Week 24 (N=18)	33.3	38.9	27.8	0
End of core phase (N=19)	31.6	36.8	31.6	0
Week 48 (N=18)	50	33.3	11.1	5.6
End of first extension (N=19)	47.4	31.6	15.8	5.3
End of study (N=19)	57.9	36.8	5.3	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	5.3			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of skin disease

End point title	Overall assessment of skin disease
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End point description:

The physician's global assessment of autoinflammatory disease activity including component scores for

skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.

End point type	Secondary
End point timeframe:	
Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	31.6	26.3	15.8	15.8
Week 24 (N=18)	61.1	27.8	11.1	0
End of core phase (N=19)	57.9	26.3	15.8	0
Week 48 (N=18)	94.4	5.6	0	0
End of first extension (N=19)	89.5	5.3	5.3	0
End of study (N=19)	84.2	10.5	5.3	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	10.5			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of arthralgia

End point title	Overall assessment of arthralgia
End point description:	
The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary

End point timeframe:

Baseline through end of study (24 months)

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	84.2	10.5	5.3	0
Week 24 (N=18)	83.3	11.1	5.6	0
End of core phase (N=19)	84.2	10.5	5.3	0
Week 48 (N=18)	88.9	11.1	0	0
End of first extension (N=19)	89.5	10.5	0	0
End of study (N=19)	100	0	0	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of myalgia

End point title	Overall assessment of myalgia
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End point description:

The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.

End point type	Secondary
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End point timeframe:

Baseline through end of study (24 months)

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	100	0	0	0
Week 24 (N=18)	94.4	5.6	0	0
End of core phase (N=19)	94.7	5.3	0	0
Week 48 (N=18)	94.4	5.6	0	0
End of first extension (N=19)	94.7	5.3	0	0
End of study (N=19)	100	0	0	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of headache/migraine

End point title	Overall assessment of headache/migraine
End point description:	
The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	42.1	42.1	5.3	10.5
Week 24 (N=18)	55.6	27.8	11.1	5.6
End of core phase (N=19)	52.6	26.3	15.8	5.3
Week 48 (N=18)	61.1	22.2	11.1	5.6
End of first extension (N=19)	57.9	21.1	15.8	5.3
End of study (N=19)	73.7	21.1	5.3	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19 ^[2]			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Notes:

[2] - 1 patient had severe symptoms at V7 (Day 57)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of conjunctivitis

End point title	Overall assessment of conjunctivitis
End point description:	
The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	68.4	10.5	10.5	10.5
Week 24 (N=18)	83.3	16.7	0	0
End of core phase (N=19)	78.9	21.1	0	0
Week 48 (N=18)	100	0	0	0
End of first extension (N=19)	94.7	5.3	0	0
End of study (N=19)	94.7	5.3	0	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of fatigue/malaise

End point title	Overall assessment of fatigue/malaise
End point description:	
The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19
Units: percent				
number (not applicable)				
Baseline (N=19)	52.6	31.6	15.8	0
Week 24 (N=18)	88.9	5.6	0	5.6
End of core phase (N=19)	89.5	5.3	0	5.3
Week 48 (N=18)	94.4	0	5.6	0
End of first extension (N=19)	94.7	0	5.3	0
End of study (N=19)	100	0	0	0

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of other symptoms related to auto-inflammatory syndrome

End point title	Overall assessment of other symptoms related to auto-inflammatory syndrome
End point description: The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary
End point timeframe: Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19 ^[3]
Units: percent				
number (not applicable)				
Baseline (N=19)	94.7	5.3	0	0
Week 24 (N=18)	100	0	0	0
End of core phase (N=19)	100	0	0	0
Week 48 (N=18)	94.4	0	5.6	0
End of first extension (N=19)	94.7	0	5.3	0
End of study (N=19)	94.7	5.3	0	0

Notes:

[3] - 5 patients had moderate symptoms at following visits: 1 at V4 (Day 8), 2 at V5 (Day 15), 1 at V22

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19 ^[4]			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Notes:

[4] - 5 patients had moderate symptoms at following visits: 1 at V4 (Day 8), 2 at V5 (Day 15), 1 at V22

Statistical analyses

No statistical analyses for this end point

Secondary: Overall assessment of other symptoms not related to auto-inflammatory syndrome

End point title	Overall assessment of other symptoms not related to auto-inflammatory syndrome
End point description:	
The physician's global assessment of autoinflammatory disease activity including component scores for skin disease (urticarial skin rash), arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to autoinflammatory syndrome, and symptoms not related to autoinflammatory syndrome from start of study to the end of the study.	
End point type	Secondary
End point timeframe:	
Baseline through end of study (24 months)	

End point values	Absent	Minimal	Mild	Moderate
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	19	19 ^[5]
Units: percent				
number (not applicable)				
Baseline (N=19)	100	0	0	0
Week 24 (N=18)	94.4	0	5.6	0
End of core phase (N=19)	94.7	0	5.3	0
Week 48 (N=18)	83.3	11.1	5.6	0
End of first extension (N=19)	84.2	10.5	5.3	0
End of study (N=19)	89.5	10.5	0	0

Notes:

[5] - 1 patient had moderate symptoms at V8 (Day 85)

End point values	Severe			
Subject group type	Subject analysis set			
Number of subjects analysed	19 ^[6]			
Units: percent				
number (not applicable)				
Baseline (N=19)	0			
Week 24 (N=18)	0			
End of core phase (N=19)	0			
Week 48 (N=18)	0			
End of first extension (N=19)	0			
End of study (N=19)	0			

Notes:

[6] - 1 patient had severe symptoms at V4 (Day 8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing a relapse at week 24

End point title	Percentage of participants experiencing a relapse at week 24
End point description:	
For complete responders, relapse was defined as the following criteria: A relapse consisted of clinical and serological relapse defined as follows:	
<ul style="list-style-type: none"> Clinical relapse: Physician's global assessment of auto-inflammatory disease >minimal or Physician's global assessment of auto-inflammatory disease ≥minimal and assessment of skin disease >minimal and Serological relapse: Serum CRP >3 mg/dL and/or 2. SAA >30 µg/mL 	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: percent				
number (not applicable)				
Relapse at week 24	22.2			
Clinical relapse at week 24	33.3			
Serological relapse at week 24	33.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enter new text: 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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	ACZ885
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Reporting group description:

ACZ885

Serious adverse events	ACZ885		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 19 (26.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Sinoatrial block			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epstein-Barr virus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningitis mumps			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parvovirus infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
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	ACZ885		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Diffuse vasculitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gait disturbance			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Allergic cough			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Asthma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	3		
Nasal obstruction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	5		
Pulmonary oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	6		
Psychiatric disorders			

Head banging subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Investigations Electrocardiogram T wave amplitude decreased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all) Excoriation subjects affected / exposed occurrences (all) Joint injury subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Nervous system disorders Cerebral artery stenosis subjects affected / exposed occurrences (all) Cerebral hypoperfusion subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		

Headache subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Intracranial hypotension subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2		
Ear and labyrinth disorders Deafness subjects affected / exposed occurrences (all) Deafness neurosensory subjects affected / exposed occurrences (all) Deafness unilateral subjects affected / exposed occurrences (all) Ear pruritus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1 2 / 19 (10.53%) 2 1 / 19 (5.26%) 1 1 / 19 (5.26%) 1		
Eye disorders Chalazion subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Conjunctivitis allergic subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2 2 / 19 (10.53%) 2 3 / 19 (15.79%) 3		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		

Abdominal pain upper			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Aphthous stomatitis			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dental caries			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Enteritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Gastritis atrophic			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lip erosion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Stomatitis			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	6		
Tooth impacted			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dermatitis contact			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Dyshidrosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Erythema multiforme			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Heat rash			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash			

<p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Rash pruritic</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Urticaria</p> <p>subjects affected / exposed</p> <p>3 / 19 (15.79%)</p> <p>occurrences (all)</p> <p>3</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p> <p>Musculoskeletal pain</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p> <p>Osteochondrosis</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>3 / 19 (15.79%)</p> <p>occurrences (all)</p> <p>5</p> <p>Eczema infected</p> <p>subjects affected / exposed</p> <p>1 / 19 (5.26%)</p> <p>occurrences (all)</p> <p>1</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>7 / 19 (36.84%)</p> <p>occurrences (all)</p> <p>10</p> <p>Hand-foot-and-mouth disease</p>			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Herpes simplex			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Hordeolum			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Impetigo			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Meningitis aseptic			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Molluscum contagiosum			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nail candida			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	16		
Otitis externa			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Otitis media acute			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Parotitis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	7		
Skin infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	14 / 19 (73.68%)		
occurrences (all)	41		
Varicella			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2010	The protocol was amended to add central reading of audiograms by an independent reader and CSF-PK analysis. In addition, the amendment clarified the handling of patients for the 24-week analysis and the patients who discontinued or completed the core phase but did not continue into the extension phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported