



Clinical trial results:

An open-label, multicenter, efficacy and safety pilot study of 6-month canakinumab treatment with up to 6-month follow-up and 24-month long-term treatment in patients with active Hyper-IgD Syndrome (HIDS)

Summary

EudraCT number	2010-020904-31
Trial protocol	ES
Global end of trial date	15 July 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	05 August 2015

Trial information

Trial identification

Sponsor protocol code	CACZ885D2402
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01303380
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	15 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess reduction of the flare frequency after administration of canakinumab in subjects with active Hyper-IgD Syndrome (HIDS) during the 6-month treatment period compared to historical period (defined as the most recent 6 months in which the subject had not received drugs other than symptomatic treatment with Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or steroids).

Protection of trial subjects:

NSAIDs and corticosteroids were used as rescue medication. NSAIDs were allowed to treat the signs and symptoms of HIDS during acute flares as per discretion of the investigator. NSAIDs were used for symptomatic treatment of the initial qualified flare. Corticosteroids 0.5 milligram/kilogram (mg/kg) were allowed for new flares after the initial qualified flare.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2011
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: 9
Worldwide total number of subjects	9
EEA total number of subjects	9

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)	3
Adolescents (12-17 years)	3
Adults (18-64 years)	3
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

The study was conducted at 3 centres in Spain.

Pre-assignment

Screening details:

A total of 10 subjects were screened, 9 of which entered in the treatment period of the study, one subject was considered to be a screening failure.

Period 1

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

Blinding implementation details:

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

Arms

Arm title	Canakinumab
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Arm description:

Subjects received body -weight stratified dosage of canakinumab (4 mg/kg for subjects less than or equal to (\leq) 40 kg or 300 mg for subjects more than ($>$) 40 kg) as starting dose s.c. injection every 6 weeks during 6 months of treatment. The dose was escalated to additional 150 mg (2 mg/kg for subjects \leq 40 kg) dose at the moment of flare, and 450 mg (6 mg/kg for subjects \leq 40 kg) every 6 weeks, thereafter starting at Week 6 in subjects who experienced a new HIDS flare between baseline and Week 4 as per investigator's discretion. If the flare occurred between Weeks 5-6, the subjects received rescue medication and waited up to Week 6 to receive a total of 450 mg of canakinumab.

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 4 mg/kg (2 mg/kg - 6 mg/kg) for subjects \leq 40 kg or 300 mg for subjects $>$ 40 kg was injected via s.c. route every 6 weeks during 6 months of treatment.

Number of subjects in period 1	Canakinumab
Started	9
Completed	8
Not completed	1
Lack of compliance to the study procedures	1

Baseline characteristics

Reporting groups

Reporting group title	Canakinumab
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Reporting group description:

Subjects received body -weight stratified dosage of canakinumab (4 mg/kg for subjects less than or equal to (\leq) 40 kg or 300 mg for subjects more than ($>$) 40 kg) as starting dose s.c. injection every 6 weeks during 6 months of treatment. The dose was escalated to additional 150 mg (2 mg/kg for subjects \leq 40 kg) dose at the moment of flare, and 450 mg (6 mg/kg for subjects \leq 40 kg) every 6 weeks, thereafter starting at Week 6 in subjects who experienced a new HIDS flare between baseline and Week 4 as per investigator's discretion. If the flare occurred between Weeks 5-6, the subjects received rescue medication and waited up to Week 6 to receive a total of 450 mg of canakinumab.

Reporting group values	Canakinumab	Total	
Number of subjects	9	9	
Age categorical			
Units: Subjects			
Children (2-11 years)	3	3	
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	3	3	
Age continuous			
Units: years			
median	17.3		
full range (min-max)	5 to 29	-	
Gender categorical			
Units: Subjects			
Female	6	6	
Male	3	3	

End points

End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Subjects received body -weight stratified dosage of canakinumab (4 mg/kg for subjects less than or equal to (\leq) 40 kg or 300 mg for subjects more than ($>$) 40 kg) as starting dose s.c. injection every 6 weeks during 6 months of treatment. The dose was escalated to additional 150 mg (2 mg/kg for subjects \leq 40 kg) dose at the moment of flare, and 450 mg (6 mg/kg for subjects \leq 40 kg) every 6 weeks, thereafter starting at Week 6 in subjects who experienced a new HIDS flare between baseline and Week 4 as per investigator's discretion. If the flare occurred between Weeks 5-6, the subjects received rescue medication and waited up to Week 6 to receive a total of 450 mg of canakinumab.	

Primary: Number of flares per subject during historical period and treatment period

End point title	Number of flares per subject during historical period and treatment period ^[1]
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End point description:

A flare was defined as Physician Global Assessment of HIDS flare severity score of ≥ 2 and a C-reactive protein (CRP) value > 10 mg/L. Flares during a historical period were defined as most recent 6-months in which the subject has not received treatment for their HIDS other than symptomatic treatment with NSAIDs and/or corticosteroids. The primary analysis was performed in the Full Analysis set (FAS) population defined as all subjects who received at least one dose of study treatment and had at least one post-baseline assessment.

End point type	Primary
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End point timeframe:

Historical period, Month 6 (Treatment period)

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	9			
Units: Number of flares				
median (full range (min-max))				
Historical period	5 (0 to 2)			
6 Month treatment period	0 (3 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of flares per subject at Month 24

End point title	Number of flares per subject at Month 24
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End point description:

A flare was defined as Physician Global Assessment of HIDS flare severity score of ≥ 2 and a CRP value > 10 mg/L. The analysis was performed in the FAS population.

End point type	Secondary
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End point timeframe:
Month 12 to Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of flares				
median (full range (min-max))				
24 Month treatment period	0 (0 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who flared at treatment period, Month 12 and Month 24

End point title	Number of subjects who flared at treatment period, Month 12 and Month 24
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End point description:

A flare was defined as Physician Global Assessment of HIDS flare severity score of ≥ 2 and a CRP value > 10 mg/L. The analysis was performed in the FAS population.

End point type	Secondary
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End point timeframe:

Month 6 (Treatment period), Month 12 (Long-term treatment period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of subjects				
Baseline to Month 6	2			
Month 6 to Month 12	4			
Month 12 to Month 24	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with flare events based on physician assessed HIDS flare severity score

End point title	Number of subjects with flare events based on physician assessed HIDS flare severity score
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End point description:

Physician global assessment of severity of HIDS after each flare was based on HIDS flare severity score, a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3= Moderate; 4 = Severe. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Any flare event [Day 1 (Baseline) to Month 24 (End of study)]

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of subjects				
Day 45, Absent (n=9)	0			
Day 45, Minimal (n=9)	0			
Day 45,Mild (n=9)	0			
Day 45,Moderate (n=9)	1			
Day 45,Severe (n=9)	0			
Flare/Unscheduled visit 1, Absent (n=4)	2			
Flare/Unscheduled visit 1, Minimal (n=4)	0			
Flare/Unscheduled visit 1, Mild (n=4)	1			
Flare/Unscheduled visit 1, Moderate (n=4)	1			
Flare/Unscheduled visit 1, Severe (n=4)	0			
Flare/Unscheduled visit 2, Absent (n=2)	1			
Flare/Unscheduled visit 2, Minimal (n=2)	0			
Flare/Unscheduled visit 2, Mild (n=2)	1			
Flare/Unscheduled visit 2, Moderate (n=2)	0			
Flare/Unscheduled visit 2, Severe (n=2)	0			
Flare/Unscheduled visit 3, Absent (n=2)	1			
Flare/Unscheduled visit 3, Minimal (n=2)	0			
Flare/Unscheduled visit 3, Mild (n=2)	0			
Flare/Unscheduled visit 3, Moderate (n=2)	1			
Flare/Unscheduled visit 3, Severe (n=2)	0			
End of Treatment period, Absent (n=7)	0			
End of Treatment period, Minimal (n=7)	0			
End of Treatment period, Mild (n=7)	4			
End of Treatment period, Moderate (n=7)	3			
End of Treatment period, Severe (n=7)	0			
End of Follow-up period, Absent (n=8)	0			
End of Follow-up period, Minimal (n=8)	1			
End of Follow-up period, Mild (n=8)	0			
End of Follow-up period, Moderate (n=8)	0			
End of Follow-up period, Severe (n=8)	0			

Long-term 12 M period, Flare 1, Absent (n=3)	0			
Long-term 12 M period, Flare 1, Minimal (n=3)	1			
Long-term 12 M period, Flare 1, Mild (n=3)	1			
Long-term 12 M period, Flare 1, Moderate (n=3)	1			
Long-term 12 M period, Flare 1, Severe (n=3)	0			
Long-term 12 M period, Flare 2, Absent (n=1)	0			
Long-term 12 M period, Flare 2, Minimal (n=1)	0			
Long-term 12 M period, Flare 2, Mild (n=1)	1			
Long-term 12 M period, Flare 2, Moderate (n=1)	0			
Long-term 12 M period, Flare 2, Severe (n=1)	0			
Long-term 12 M period, Flare 3, Absent (n=1)	0			
Long-term 12 M period, Flare 3, Minimal (n=1)	0			
Long-term 12 M period, Flare 3, Mild (n=1)	1			
Long-term 12 M period, Flare 3, Moderate (n=1)	0			
Long-term 12 M period, Flare 3, Severe (n=1)	0			
Long-term 24 M period, Absent (n=2)	1			
Long-term 24 M period, Minimal (n=2)	0			
Long-term 24 M period, Mild (n=2)	1			
Long-term 24 M period, Moderate (n=2)	0			
Long-term 24 M period, Severe (n=2)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with flare events based on subject assessed HIDS flare severity score

End point title	Number of subjects with flare events based on subject assessed HIDS flare severity score
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End point description:

Subject's global assessment of severity of HIDS after each flare was based on HIDS flare severity score, a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3 = Moderate; 4 = Severe. Same investigator assessed the same subject throughout the study to ensure consistency between assessments. Investigators reviewed every subject's diary at each visit after their own clinical assessment. The analysis was performed in the FAS population.

End point type	Secondary
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End point timeframe:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of subjects				
Treatment period, Absent	0			
Treatment period, Minimal	0			
Treatment period, Mild	1			
Treatment period, Moderate	1			
Treatment period, Severe	0			
Follow-up period, Absent	0			
Follow-up period, Minimal	0			
Follow-up period, Mild	0			
Follow-up period, Moderate	2			
Follow-up period, Severe	0			
12-month long-term treatment period, Absent	0			
12-month long-term treatment period, Minimal	1			
12-month long-term treatment period, Mild	1			
12-month long-term treatment period, Moderate	2			
12-month long-term treatment period, Severe	0			
24-month long-term treatment period, Absent	0			
24-month long-term treatment period, Minimal	1			
24-month long-term treatment period, Mild	0			
24-month long-term treatment period, Moderate	0			
24-month long-term treatment period, Severe	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with defined grades of subjects assessed symptom control

End point title	Percentage of subjects with defined grades of subjects assessed symptom control
End point description:	
Subjects were assessed by subject/parent (subjects aged 6-18 years) for control of signs and symptoms associated with HIDS based on 5-point scale: 0 = No control; 1 = Poor control; 2 = Somewhat control; 3 = Good control; and 4= Excellent control. The analysis was performed in the FAS 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:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, No control (n=9)	0			
Treatment period, Poor control (n=9)	0			
Treatment period, Somewhat control (n=9)	0			
Treatment period, Good control (n=9)	44.44			
Treatment period, Excellent control (n=9)	55.56			
Follow-up period, No control (n=9)	0			
Follow-up period, Poor control (n=9)	0			
Follow-up period, Somewhat control (n=9)	11.11			
Follow-up period, Good control (n=9)	33.33			
Follow-up period, Excellent control (n=9)	55.56			
Long-term 12 month period, No control (n=8)	0			
Long-term 12 month period, Poor control (n=8)	0			
Long-term 12 month period, Somewhat control (n=8)	12.5			
Long-term 12 month period, Good control (n=8)	25			
Long-term 12 month period, Excellent control (n=8)	62.5			
Long-term 24 month period, No control (n=8)	0			
Long-term 24 month period, Poor control (n=8)	0			
Long-term 24 month period, Somewhat control (n=8)	0			
Long-term 24 month period, Good control (n=8)	12.5			
Long-term 24 month period, Excellent control (n=8)	87.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with defined grades of physician assessed symptom control

End point title	Percentage of subjects with defined grades of physician
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End point description:

Subjects were assessed by physician for control of signs and symptoms associated with HIDS based on 5-point scale: 0 = No control; 1 = Poor control; 2 = Somewhat control; 3 = Good control; and 4= Excellent control. The analysis was performed in the FAS 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:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, No control (n=9)	0			
Treatment period, Poor control (n=9)	0			
Treatment period, Somewhat control (n=9)	0			
Treatment period, Good control (n=9)	44.44			
Treatment period, Excellent control (n=9)	55.56			
Follow-up period, No control (n=9)	0			
Follow-up period, Poor control (n=9)	0			
Follow-up period, Somewhat control (n=9)	0			
Follow-up period, Good control (n=9)	33.33			
Follow-up period, Excellent control (n=9)	66.67			
Long-term 12 month period, No control (n=8)	0			
Long-term 12 month period, Poor control (n=8)	0			
Long-term 12 month period, Somewhat control (n=8)	12.5			
Long-term 12 month period, Good control (n=8)	25			
Long-term 12 month period, Excellent control (n=8)	62.5			
Long-term 24 month period, No control (n=8)	0			
Long-term 24 month period, Poor control (n=8)	0			
Long-term 24 month period, Somewhat control (n=8)	0			
Long-term 24 month period, Good control (n=8)	0			
Long-term 24 month period, Excellent control (n=8)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing fever as assessed by physician's global assessment

End point title	Percentage of subjects experiencing fever as assessed by physician's global assessment
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End point description:

Fever severity was assessed by physician after each flare using a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, Absent (n=9)	88.89			
Treatment period, Minimal (n=9)	11.11			
Treatment period, Mild (n=9)	0			
Treatment period, Moderate (n=9)	0			
Treatment period, Severe (n=9)	0			
Follow-up period, Absent (n=9)	100			
Follow-up period, Minimal (n=9)	0			
Follow-up period, Mild (n=9)	0			
Follow-up period, Moderate (n=9)	0			
Follow-up period, Severe (n=9)	0			
Long-term 12 month period, Absent (n=8)	75			
Long-term 12 month period, Minimal (n=8)	12.5			
Long-term 12 month period, Mild (n=8)	12.5			
Long-term 12 month period, Moderate (n=8)	0			
Long-term 12 month period, Severe (n=8)	0			
Long-term 24 month period, Absent (n=8)	100			
Long-term 24 month period, Minimal (n=8)	0			
Long-term 24 month period, Mild (n=8)	0			
Long-term 24 month period, Moderate (n=8)	0			
Long-term 24 month period, Severe (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing aphthous ulcers as assessed by physician's global assessment

End point title	Percentage of subjects experiencing aphthous ulcers as assessed by physician's global assessment
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End point description:

Aphthous ulcers were assessed by physician after each flare using a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, Absent (n=9)	88.89			
Treatment period, Minimal (n=9)	0			
Treatment period, Mild (n=9)	11.11			
Treatment period, Moderate (n=9)	0			
Treatment period, Severe (n=9)	0			
Follow-up period, Absent (n=9)	100			
Follow-up period, Minimal (n=9)	0			
Follow-up period, Mild (n=9)	0			
Follow-up period, Moderate (n=9)	0			
Follow-up period, Severe (n=9)	0			
Long-term 12 month period, Absent (n=8)	100			
Long-term 12 month period, Minimal (n=8)	0			
Long-term 12 month period, Mild (n=8)	0			
Long-term 12 month period, Moderate (n=8)	0			
Long-term 12 month period, Severe (n=8)	0			
Long-term 24 month period, Absent (n=8)	100			

Long-term 24 month period, Minimal (n=8)	0			
Long-term 24 month period, Mild (n=8)	0			
Long-term 24 month period, Moderate (n=8)	0			
Long-term 24 month period, Severe (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing lymphadenopathy as assessed by physician's global assessment

End point title	Percentage of subjects experiencing lymphadenopathy as assessed by physician's global assessment
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End point description:

Lymphadenopathy severity was assessed by physician after each flare using a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, Absent (n=9)	88.89			
Treatment period, Minimal (n=9)	11.11			
Treatment period, Mild (n=9)	0			
Treatment period, Moderate (n=9)	0			
Treatment period, Severe (n=9)	0			
Follow-up period, Absent (n=9)	77.78			
Follow-up period, Minimal (n=9)	22.22			
Follow-up period, Mild (n=9)	0			
Follow-up period, Moderate (n=9)	0			
Follow-up period, Severe (n=9)	0			
Long-term 12 month period, Absent (n=8)	87.5			
Long-term 12 month period, Minimal (n=8)	12.5			
Long-term 12 month period, Mild (n=8)	0			
Long-term 12 month period, Moderate (n=8)	0			

Long-term 12 month period, Severe (n=8)	0			
Long-term 24 month period, Absent (n=8)	100			
Long-term 24 month period, Minimal (n=8)	0			
Long-term 24 month period, Mild (n=8)	0			
Long-term 24 month period, Moderate (n=8)	0			
Long-term 24 month period, Severe (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects experiencing abdominal pain as assessed by physician's global assessment

End point title	Percentage of subjects experiencing abdominal pain as assessed by physician's global assessment
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End point description:

Abdominal pain was assessed by physician after each flare using a 5-point scale: 0 = Absent signs/symptoms; 1 = Minimal signs/symptoms; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary
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End point timeframe:

Month 6 (End of treatment period), Month 6 (End of follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)				
Treatment period, Absent (n=9)	100			
Treatment period, Minimal (n=9)	0			
Treatment period, Mild (n=9)	0			
Treatment period, Moderate (n=9)	0			
Treatment period, Severe (n=9)	0			
Follow-up period, Absent (n=9)	100			
Follow-up period, Minimal (n=9)	0			
Follow-up period, Mild (n=9)	0			
Follow-up period, Moderate (n=9)	0			
Follow-up period, Severe (n=9)	0			
Long-term 12 month period, Absent (n=8)	87.5			
Long-term 12 month period, Minimal (n=8)	12.5			

Long-term 12 month period, Mild (n=8)	0			
Long-term 12 month period, Moderate (n=8)	0			
Long-term 12 month period, Severe (n=8)	0			
Long-term 24 month period, Absent (n=8)	100			
Long-term 24 month period, Minimal (n=8)	0			
Long-term 24 month period, Mild (n=8)	0			
Long-term 24 month period, Moderate (n=8)	0			
Long-term 24 month period, Severe (n=8)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to resolution of the initial flare after first canakinumab treatment

End point title	Time to resolution of the initial flare after first canakinumab treatment
End point description: Time to resolution of the initial flare after first dose of canakinumab was determined. The analysis was performed in the FAS population.	
End point type	Secondary
End point timeframe: Day 1 (Baseline), Day 28	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Days				
median (full range (min-max))	3 (1 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in inflammation markers over time up to Month 24

End point title	Change from baseline in inflammation markers over time up to Month 24
End point description: The C--reactive Protein (CRP) and/or Serum amyloid A protein (SAA) were used as inflammatory markers. The normal range of CRP was 0-10 mg/L. The analysis was performed in the FAS 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 (Baseline), Month 6 (End to treatment period), Month 6 (End to follow-up period), Month 12 (Long term period) and Month 24 (End of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Milligram(s)/litre				
median (full range (min-max))				
CRP- 6 month (Treatment period), (n=6)	-120.5 (-164 to -23)			
CRP- 6 month (Follow-up period), (n=9)	-111 (-164 to -23)			
CRP- 12-month (Long-term period), (n=8)	-113.55 (-159.5 to -49.9)			
CRP- 24 month (End of study), (n=8)	-125.2 (-164 to -34.1)			
SAA- 6 month (Treatment period), (n=1)	-624.2 (-624.2 to -624.2)			
SAA- 6 month (Follow-up period), (n=2)	-685.95 (-748.2 to -623.7)			
SAA- 12-month (Long-term period), (n=2)	-684.1 (-749.2 to -619)			
SAA- 24 month (End of study), (n=2)	-686.7 (-747.7 to -625.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Assessment Questionnaire (HAQ) global score in adults over time

End point title	Health Assessment Questionnaire (HAQ) global score in adults over time
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End point description:

Subjects were assessed for health-related quality of life (HRQoL) based on Health Assessment Questionnaire (HAQ). HAQ was an eight 8 categories questionnaire representing all activities related to physical function. Each category has various sub-categories, which were rated by the subject on a 4-point difficulty scale: 0 = any difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. The total score was the mean of the 8 scores, and ranged from 0 (no disability) to 3 (completely disabled). The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group respectively. Here "Number of subjects analysed" signifies the subjects assessed for HAQ during study.

End point type	Secondary
End point timeframe:	
Day 1 (Baseline), Month 6 (End to treatment period), Month 6 (End to follow-up period), Month 12 (Long term period) and Month 24 (End of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Score on a scale				
median (full range (min-max))				
Treatment period, (n=3)	0 (0 to 0)			
Follow-up period, (n=4)	0 (0 to 0)			
12-month (Long-term period), (n=5)	0 (0 to 1)			
24 month (End of study), (n=4)	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Childhood Health Assessment Questionnaire (CHAQ) global score in children over time

End point title	Childhood Health Assessment Questionnaire (CHAQ) global score in children over time
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End point description:

Subjects or their parents (subjects aged 6 to 17 years) were assessed for HRQoL based on Childhood Health Assessment Questionnaire (CHAQ). CHAQ was an eight domain questionnaire representing functional capacity and independence, evaluated for previous week. Each domain was rated on a 4-point difficulty scale: 0 = any difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group respectively. Here "Number of subjects analysed" signifies the subjects assessed for CHAQ during study. Here, the value 99999.9 in the field represents not estimable data.

End point type	Secondary
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End point timeframe:

Day 1 (Baseline), Month 6 (End to treatment period), Month 6 (End to follow-up period), Month 12 (Long term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Score on a scale				
median (full range (min-max))				
End to treatment period (n= 2)	0 (0 to 0)			
End to follow-up period (n=4)	0.1 (0 to 1)			
12 month- Long term period, (n=2)	0.1 (0 to 1)			
24 month- End of study (n=1)	0.1 (0 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who received dose up-titration during 6-month treatment period

End point title	Percentage of subjects who received dose up-titration during 6-month treatment period
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End point description:

Subjects who experienced a new HIDS flare between baseline and Week 4 and received an escalated dose of 450 mg of canakinumab every 6 weeks thereafter starting at Week 6 were determined. The analysis was performed in the FAS population.

End point type	Secondary
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End point timeframe:

Day 1 up to Day 167 (End of follow-up)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	22.22			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of flares experienced during the study

End point title	Duration of flares experienced during the study
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End point description:

Flare was defined as Physician Global Assessment of HIDS flare severity score of ≥ 2 and a CRP value > 10 mg/L. The change in post canakinumab treatment flare duration during the study were assessed as compared to historical period. The analysis was performed in the FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group respectively.

End point type	Secondary
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End point timeframe:

Month 6 (Treatment period), Month 6 (Follow-up period), Month 12 (Long-term period) and Month 24 (End of study)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Days				
median (full range (min-max))				
Treatment period, (n=3)	3 (2 to 4)			
Follow-up period, (n=7)	4 (2 to 10)			
12-month (Long-term period), (n=6)	3.5 (2 to 8)			
24 month (End of study), (n=2)	8.5 (6 to 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to flare after the last dose of canakinumab during the follow-up period

End point title	Time to flare after the last dose of canakinumab during the follow-up period
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End point description:

The median time to flare by the subject after administration of the last dose of canakinumab during the follow-up period was analysed using Kaplan-Meier method. The analysis was performed on the FAS population. Here "Number of subjects analysed" signifies the subjects assessed for time to flare after the last dose of canakinumab during follow-up period.

End point type	Secondary
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End point timeframe:

Last dose of canakinumab treatment in follow-up period to end of follow-up period (Day 337)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Days				
median (full range (min-max))	110 (62 to 196)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)
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End point description:

Adverse events (AEs) were defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), 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 (or prolong) 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. The analysis was performed on Safety Set (SAF) population defined as all subjects who received at least one application of study treatment and had at least one post-baseline safety assessment.

End point type	Secondary
End point timeframe:	
Day 1 (Start of study treatment) up to 24 Month (End of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of subjects				
Adverse events	9			
Serious adverse events	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who received rescue treatment

End point title	Subjects who received rescue treatment
End point description:	
Subjects who experienced flares were treated with corticosteroids and NSAIDs as rescue medication. The analysis was performed on the FAS population.	
End point type	Secondary
End point timeframe:	
Day 1 (Baseline) up to 24 Month (End of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of subjects				
number (not applicable)	11.11			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration-time profile of canakinumab

End point title	Serum concentration-time profile of canakinumab
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End point description:

Canakinumab concentrations in serum were assessed for evaluating pharmacokinetics (PK) of the drug. The analysis was performed on the FAS population.

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose), Day 4, Day 15, Day 43, Day 85, Day 127, Day 169 (End of treatment period), Day 197, Day 225, Day 253, Day 281, Day 309, and Day 337 (End of follow-up period) (Post-dose)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Microgram(s)/millilitre				
arithmetic mean (standard deviation)				
Day 4	28.8 (± 7.9)			
Day 15	26.9 (± 8)			
Day 43	12.7 (± 4.6)			
Day 85	19.4 (± 9.6)			
Day 127	23.8 (± 12.8)			
Day 169	24 (± 13.4)			
Day 197	12.6 (± 13.7)			
Day 225	11.5 (± 7.9)			
Day 253	6.5 (± 4.8)			
Day 281	1.6 (± 1.6)			
Day 309	0.9 (± 1)			
Day 337	32.6 (± 15.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentration of total Interleukin-1 β antibody (IL-1 β)

End point title	Serum concentration of total Interleukin-1 β antibody (IL-1 β)
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End point description:

Pharmacodynamics of canakinumab was assessed by total IL-1 β (sum of free and bound canakinumab) concentration, determined in serum by means of sandwich ELISA assay with limit of detection at 0.1 picogram/millilitre. The analysis was performed on the FAS population.

End point type	Secondary
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End point timeframe:

Day 1 (Pre-dose), Day 4, Day 15, Day 43, Day 85, Day 127, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, and Day 337

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Picogram(s)/millilitre				
arithmetic mean (standard deviation)				
Day 4	27.3 (± 25.2)			
Day 15	22.2 (± 14.7)			
Day 43	21.8 (± 13.9)			
Day 85	27.3 (± 14)			
Day 127	24.3 (± 12.1)			
Day 169	32.5 (± 17.9)			
Day 197	16.3 (± 5.9)			
Day 225	17 (± 8.3)			
Day 253	10.2 (± 5.8)			
Day 281	4.9 (± 3.3)			
Day 309	3.7 (± 2)			
Day 337	49.1 (± 60.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects exhibiting anti-canakinumab antibodies at any visit

End point title	Number of subjects exhibiting anti-canakinumab antibodies at any visit
End point description: Immunogenicity assessment included determination of anti-canakinumab (ACZ885) antibodies in serum samples using bridging ECLIA assay. The analysis was performed on the FAS population.	
End point type	Secondary
End point timeframe: Day 1 to Month 24 (End of study)	

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Number of subjects	0			

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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Canakinumab
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Reporting group description:

Canakinumab

Serious adverse events	Canakinumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Streptococcal bacteraemia			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 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	9 / 9 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone neoplasm			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			

Impaired healing subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2		
Pyrexia subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 11		
Eye disorders			
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Aphthous stomatitis subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Toothache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Vomiting			

subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Reproductive system and breast disorders Vaginal ulceration subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2 1 / 9 (11.11%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Erythema nodosum subjects affected / exposed occurrences (all) Hidradenitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Neck pain	2 / 9 (22.22%) 3 1 / 9 (11.11%) 1		

subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Scoliosis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Candidiasis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	4		
Pharyngotonsillitis			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	6		
Respiratory tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		

Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	2		
Tonsillitis streptococcal			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2010	Subjects with indeterminate QuantiFERON test result at investigator's discretion and subjects who received any investigational drug during the 30 days before enrolment were excluded from the study.. Assessment parameters for the clinical assessment of auto-inflammatory disease activity by the investigator and subject were reduced from 8 global HIDS-specific signs and symptoms to 4: fever, lymphadenopathy, aphthous ulcers and abdominal pain.
03 February 2011	Exclusion criterion on the use of Etanercept treatment was modified from four weeks prior to this visit to two weeks prior to the baseline visit (wash-out period).
30 September 2011	Exclusion criteria was extended to: Subjects included in the screening were stopped for biologic treatments during the screening period (Etanercept, Adalimumab, Infliximab, Kineret, other investigational biologics or other drugs as NSAID, corticosteroids). No subject received first dose of study medication without complying described timelines. Subjects received a dose of canakinumab at day 169 (Visit 8), the visit was considered as follow up period after flare occurrence at this visit (+/- 5 days). The length of follow-up treatment was increased from 6 to 30 months, to include an assessment of the long-term (24-month) efficacy, safety and tolerability of ACZ885 in the treatment of Hyper-IgD with periodic fever syndrome was added.
21 December 2011	The visit schedule was modified to follow the schedule of drug dosing frequency. Time frame of data analysis for the primary efficacy analysis was modified to the end of the treatment period.
01 March 2012	Two interim analyses were added: one interim analysis after the end of the follow-up period (maximum 6 months after the end of the subjects treatment period), and second analysis after the first year of the extension period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported