Clinical trial results:
An open-label, phase II dose titration study of ACZ885 (human anti-IL-1beta monoclonal antibody) to assess the clinical efficacy, safety, pharmacokinetics and pharmacodynamics in patients with NALP3 mutations

Summary

EudraCT number	2004-002980-26
Trial protocol	GB DE ES FR Outside EU/EEA
Global end of trial date	17 July 2008

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	CACZ885A2102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00487708
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	17 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2008
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 the efficacy of canakinumab administered through intravenous (i.v.) infusion and subcutaneous (s.c.) injection in order to improve the clinical status of the subjects with mutations in NALP3 gene.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2005
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: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	India: 2
Worldwide total number of subjects	34
EEA total number of subjects	32

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)	4
Adolescents (12-17 years)	3

Adults (18-64 years)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 centres in 5 countries.

Pre-assignment

Screening details:

A total of 34 subjects were enrolled in the study.

Period 1

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

Blinding implementation details:

As the current study was an open label study, this section was not applicable.

Arms

Arm title	Canakinumab

Arm description:

Dosage Stage 1: First dose was a single administration of 10 mg/kg i.v., the 2nd dose was a single administration of 1 mg/kg i.v. upon relapse. On second relapse, single administration of 150 mg s.c.

Dosage Stage 2: Repeat single administration of 150 mg s.c. upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg s.c.). If needed: rescue dose of 5 or 10 mg/kg i.v.

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Canakinumab powder for solution [10 mg/kg i.v infusion or 1 mg/kg i.v. infusion or 150 mg s.c. or 2 mg/kg s.c] was administered.

Number of subjects in period 1	Canakinumab
Started	34
Completed	31
Not completed	3
Adverse event, non-fatal	1
Unsatisfactory therapeutic effect	1
Administrative problems	1

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab

Reporting group description:

Dosage Stage 1: First dose was a single administration of 10 mg/kg i.v., the 2nd dose was a single administration of 1 mg/kg i.v. upon relapse. On second relapse, single administration of 150 mg s.c.

Dosage Stage 2: Repeat single administration of 150 mg s.c. upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg s.c.). If needed: rescue dose of 5 or 10 mg/kg i.v.

Reporting group values	Canakinumab	Total	
Number of subjects	34	34	
Age categorical			
Units: Subjects			
Paediatric (4-17 years)	7	7	
Adults (18-51 years)	27	27	
Age continuous			
Units: years			
arithmetic mean	30.3		
standard deviation	± 14.34	-	
Gender categorical			
Units: Subjects			
Female	21	21	
Male	13	13	

End points

End points reporting groups

Reporting group title	Canakinumab

Reporting group description:

Dosage Stage 1: First dose was a single administration of 10 mg/kg i.v., the 2nd dose was a single administration of 1 mg/kg i.v. upon relapse. On second relapse, single administration of 150 mg s.c.

Dosage Stage 2: Repeat single administration of 150 mg s.c. upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg s.c.). If needed: rescue dose of 5 or 10 mg/kg i.v.

Subject analysis set title	Canakinumab 1mg/kg i.v
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received single dose of canakinumab 1 mg/kg i.v during the study.

Subject analysis set title	Canakinumab 10 mg/kg i.v
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received single dose of canakinumab 10 mg/kg i.v during the study.

Subject analysis set title	Canakinumab 150mg sc
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received single dose of canakinumab 150mg sc during the study.

Subject analysis set title	Canakinumab 2mg/kg s.c
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received single dose of canakinumab 2mg/kg s.c during the study.

Subject analysis set title	Canakinumab rescue i.v
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who received single dose of canakinumab Rescue i.v during the study.

Primary: Time from each dose administration to relapse after achieving a complete response to treatment

End point title	Time from each dose administration to relapse after achieving a complete response to treatment[1]

End point description:

Complete response to treatment was defined as Physician global assessment of disease activity to be equal or less than(≤) minimal using a 5-point scale(0:absent, 1:minimal, 2: mild, 3:moderate and 4: severe); assessment of skin disease ≤ minimal on a 5-point scale(0: absent to 4:severe) and serum values of C-reactive protein (CRP)and/or serum amyloid A protein(SAA) to be <10 milligrams/litres (mg/L). Relapse was defined as Physician global assessment score of disease activity>minimal or Physician global assessment score to be minimal and assessment of skin disease >minimal; and CRP and/or SAA to be more than 30 mg/L compared to baseline. Subjects were grouped by combined dosing regimen where rescue dose was combined with previous dosing regimen. The analysis was performed in safety analysis set, defined as all subjects who received at least one dose of study medication. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Primary

End point timeframe:

Day 1 up to Day 29 (all 3 periods averaged)

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	34			
Units: Days				
median (confidence interval 95%)				
10 mg/kg i.v. (n=4)	156.2 (102.5 to 209.8)			
1 mg/kg i.v. (n=4)	72.8 (48 to 97.7)			
150 mg s.c. (n=29)	115.2 (94.1 to 136.4)			
150 mg s.c. + rescue i.v. (n=4)	174.5 (90.5 to 258.5)			
2 mg/kg s.c. (n=4)	48.6 (29.3 to 67.9)			
2 mg/kg s.c. + rescue i.v. (n=2)	51.7 (27 to 76.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Serum concentrations of C-Reactive Protein (CRP) and Serum Amyloid A protein (SAA)

End point title	Serum concentrations of C-Reactive Protein (CRP) and Serum Amyloid A protein (SAA)[2]

End point description:

The C-reactive protein (CRP) and Serum amyloid A protein (SAA) were used as inflammatory markers to diagnose the Muckle Wells Syndrome (MWS). The target serum level concentration of CRP and SAA was equal to or less than 10 milligrams/litres (mg/L). The analysis was performed in safety analysis set population. Here "number of subjects analysed' represents evaluable subjects in each treatment arm.

End point type	Primary

End point timeframe:

End of treatment period (all 3 periods averaged)

Notes:

[2] - 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 10 mg/kg i.v	Canakinumab 1mg/kg i.v	Canakinumab 150mg sc	Canakinumab 2mg/kg s.c
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	28	4
Units: milligram/Litre (mg/L)				
geometric mean (geometric coefficient of variation)				
CRP	26.35 (± 34.871)	27.29 (± 71.843)	10.07 (± 115.695)	3.46 (± 104.874)
SAA	102.65 (± 55.343)	92.48 (± 42.758)	21.74 (± 133.371)	9.88 (± 119.602)

End point values	Canakinumab rescue i.v			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: milligram/Litre (mg/L)				
geometric mean (geometric coefficient of variation)				
CRP	1.45 (± 98.497)			
SAA	4.63 (± 101.895)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with defined grades in physician's global assessment score

End point title	Percentage of subjects with defined grades in physician's global assessment score[3]

End point description:

Subjects were assessed by physician based on Physician's Global Assessment on 5-point scale for disease activity as: 0 = absent; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Severe. The analysis was performed in safety analysis set population.

End point type	Primary

End point timeframe:

Day 1 up to Day 29

Notes:

[3] - 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 10 mg/kg i.v	Canakinumab 1mg/kg i.v	Canakinumab 150mg sc	Canakinumab 2mg/kg s.c
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	29	5
Units: Percentage of subjects				
number (not applicable)				
Absent	0	25	3.45	0
Minimal	0	0	0	20
Mild	50	50	13.79	0
Moderate	50	25	72.41	60
Severe	0	0	3.45	0

End point values	Canakinumab rescue i.v			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage of subjects				
number (not applicable)				

Absent	0			
Minimal	0			
Mild	50			
Moderate	33.33			
Severe	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with clinically significant abnormal audiogram

End point title	Percentage of subjects with clinically significant abnormal audiogram

End point description:

Audiogram was utilized to monitor bilateral sensorineural deafness in subjects with a clinical picture of Familial Cold Autoinflammatory Syndrome (FCAS). Subjects who presented abnormal audiogram at baseline, were followed-up by the investigator for any clinically significant abnormality in the audiogram assessments. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed' signifies evaluable subjects for audiogram assessment.

End point type	Secondary

End point timeframe:

Baseline, Month 4, Month 8 and Month 12

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Percentage of subjects				
number (not applicable)				
Baseline	14			
4 months	7			
8 months	2			
12 months	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment the subject’s renal function at end of period

End point title	Assessment the subject’s renal function at end of period

End point description:

Renal function parameters like creatinine clearance values and estimated Glomerular filtration rate (eGFRs) were assessed. The eGFR was estimated from serum creatinine, using either the 4-variable Modification of Diet in Renal Disease (MDRD) formula for adults and adolescent subjects, or the Schwartz formula for pediatrics (aged minimum of 12 years). The analysis was performed in safety analysis set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (first period), Day 1 (post-dose), Week 5 (post-dose), end of period (all 3 periods averaged)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: millilitre/minute (mL/min)				
arithmetic mean (standard deviation)				
Creatinine clearance, Adults (n=15)	99.58 (± 37.484)			
eGFR, Adults (n=27)	87.85 (± 26.632)			
Creatinine clearance, Pediatric (n=4)	72.87 (± 34.957)			
eGFR, Pediatric (n=7)	152.92 (± 18.635)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL) scores in adult subjects

End point title	Health-related quality of life (HRQoL) scores in adult subjects

End point description:

Assessment of HRQoL in adult subjects was based on three types of questionnaire: Health Assessment Questionnaire (HAQ), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) and Medical Outcome Short Form (SF-36) Health Survey summary scores as reported by subjects. In HAQ, higher score (maximum of 3) indicated a more severe disease. The FACIT-F questionnaire assessed general health status with emphasis on fatigue with maximum score of 52, and a higher score indicated less fatigue. SF-36 was separated into the physical and mental components with scores ranging from 0 to 100, and a higher score indicated a better QoL. The analysis was performed in safety analysis set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 1 (post-dose), Week 1 (post-dose), Week 5 (post dose), end of treatment period (all 3 periods averaged)

End point values	Canakinumab 150mg sc	Canakinumab rescue i.v		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	6		
Units: Units on a scale				
arithmetic mean (standard deviation)				
HAQ (n=18,3)	0.37 (± 0.693)	0.92 (± 1.277)		
FACIT-F (n=18,3)	35.65 (± 12.508)	31 (± 12.166)		

SF-36 (mental component) (n=18,3)	47.35 (± 10.379)	44.21 (± 8.728)		
SF-36 (physical component) (n=18,3)	42.69 (± 12.977)	37.44 (± 16.696)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL) scores in paediatric subjects

End point title	Health-related quality of life (HRQoL) scores in paediatric subjects

End point description:

Health¬ related quality of life was assessed in paediatric subjects by child health questionnaire (CHQ-CH87) which had 14 scales and score ranged from 0 to 100 where a higher score indicated a better quality of health. The analysis was performed in safety analysis set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Day 1 (post-dose), Week 1 (post-dose), Week 5 (post dose), end of treatment period (all 3 periods averaged)

End point values	Canakinumab 150mg sc	Canakinumab 2mg/kg s.c	Canakinumab rescue i.v	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29	5	6	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Behavior (n=2, 3, 2)	80.49 (± 13.865)	83.84 (± 9.334)	81.72 (± 10.052)	
Bodily Pain (n=2, 3, 2)	50 (± 0)	47.22 (± 22.132)	26 (± 5.657)	
Change in Health (n=2, 3, 2)	3.5 (± 0.707)	3.52 (± 0.135)	2.83 (± 0.236)	
Family Activities (n=2, 2, 2)	79.86 (± 28.481)	86.34 (± 21.876)	75 (± 23.57)	
Family Cohesion (n=2, 2, 2)	60 (± 0)	78.75 (± 6.25)	92.5 (± 10.607)	
Global Behavior Item (n=2, 3, 2)	64.17 (± 5.893)	68.33 (± 14.434)	85 (± 0)	
Global health (n=2, 3, 2)	55 (± 7.071)	44.17 (± 12.332)	22.5 (± 10.607)	
General Health Perceptions (n=2, 3, 2)	33.75 (± 17.088)	43.81 (± 12.424)	24.1 (± 1.08)	
Mental Health (n=2, 3, 2)	66.67 (± 18.414)	70.27 (± 7.631)	75.78 (± 14.363)	
Physical functioning (n=2, 3, 2)	88.27 (± 16.586)	88.27 (± 12.017)	67.28 (± 9.603)	
Role/Social Limitations – Behavioral (n=2, 3, 2)	92.59 (± 10.476)	100 (± 0)	100 (± 0)	
Role/Social Limitations – Emotional (n=2, 3, 2)	92.59 (± 10.476)	97.22 (± 2.778)	97.22 (± 3.928)	
Role/Social Limitations – Physical (n=2, 3, 2)	94.44 (± 7.857)	83.33 (± 20.031)	55.56 (± 47.14)	

Self Esteem (n=2, 3, 2)	72.02 (± 0.842)	78.32 (± 6.514)	74.66 (± 8.062)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax)

End point title	Maximum observed plasma concentration (Cmax)

End point description:

Maximum observed serum concentration following drug administration from the raw serum concentration-time data was determined. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed' in 10 mg/kg i.v arm was related to only Stage 1, adult subjects and 150 mg sc arm was related to both Stage 1 and 2 adult subjects.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 150mg sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	25		
Units: microgram/millilitre (µg/mL)				
arithmetic mean (standard deviation)	148.75 (± 45.39)	15.86 (± 3.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC from time zero to extrapolated infinite time [AUC (0 - ∞)]

End point title	AUC from time zero to extrapolated infinite time [AUC (0 - ∞)]

End point description:

Area under the plasma concentration versus time curve (AUC) from time zero (pre-dose) to extrapolated infinite time (0 - ∞). AUC(0-infinity) was estimated as AUC 0-t + C t /λ z, where λ z was the terminal elimination rate constant. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed' in 10 mg/kg i.v arm was related to only Stage 1, adult subjects and 150 mg sc arm was related to both Stage 1 and 2 adult subjects.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 150mg sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	22		
Units: microgram*day/millilitre (µg*d/mL)				
arithmetic mean (standard deviation)	3686.9 (± 1055.7)	707.9 (± 205.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent serum clearance (CL/F)

End point title	Apparent serum clearance (CL/F)

End point description:

The apparent serum clearance (CL/F) was calculated as Dose/AUC0-∞, where CL was the clearance of the drug and F was the absolute oral bioavailability. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed; signifies stage 1 and 2 adult subjects in 150 mg sc arm.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 150mg sc			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Litre/day (L/d)				
arithmetic mean (standard deviation)	0.2275 (± 0.0597)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum observed plasma concentration (Tmax)

End point title	Time to reach maximum observed plasma concentration (Tmax)

End point description:

Time required to reach peak or maximum concentration following drug administration. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed' in 10 mg/kg i.v arm was related to only Stage 1, adult subjects and 150 mg sc arm was related to both Stage 1 and 2 adult subjects.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 150mg sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	25		
Units: Days (d)				
median (full range (min-max))	0.998 (0.97 to 1.99)	6.983 (1.92 to 14.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life (T1/2)

End point title	Elimination half-life (T1/2)

End point description:

The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed' in 10 mg/kg i.v arm was related to only Stage 1, adult subjects and 150 mg sc arm was related to both Stage 1 and 2 adult subjects.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 150mg sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	22		
Units: Days (d)				
arithmetic mean (standard deviation)	31.184 (± 3.386)	26.086 (± 7.311)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution at steady state (Vss)

End point title	Apparent volume of distribution at steady state (Vss)

End point description:

Volume of distribution at steady state calculated from i.v. data. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed; signifies stage 1 adult patients in 10 mg/kg i.v arm.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Litre(L)				
arithmetic mean (standard deviation)	7.083 (± 2.117)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution during terminal phase (Vz/F)

End point title	Apparent volume of distribution during terminal phase (Vz/F)

End point description:

The apparent volume of distribution during terminal phase was estimated. The analysis was performed in safety analysis set population. Here, 'Number of subjects analysed; signifies stage 1 and 2 adult patients in 150 mg sc arm.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 150mg sc			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Litres(L)				
arithmetic mean (standard deviation)	8.335 (± 2.616)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from time zero to the last measurable concentration sampling time(AUCtlast)

End point title	Area under the concentration-time curve from time zero to the last measurable concentration sampling time(AUCtlast)

End point description:

Area under the concentration-time curve from time zero to the last measurable concentration sampling time (tlast) was estimated. The analysis was performed in safety analysis set population. Here, 'Number

of subjects analysed' in 10 mg/kg i.v arm was related to only Stage 1, adult subjects and 150 mg sc arm was related to both Stage 1 and 2 adult subjects.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 150mg sc		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	22		
Units: microgram*day/millilitre(µg*d/mL)				
arithmetic mean (standard deviation)	3634.3 (± 1028.9)	673.5 (± 188.9)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Day 1 (pre-dose), Day 2, 3, 8, 15, 22, Day 29

End point values	Canakinumab 10 mg/kg i.v	Canakinumab 1mg/kg i.v	Canakinumab 150mg sc	Canakinumab 2mg/kg s.c
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	4	29	5
Units: picograms per millilitre (pg/mL)				
arithmetic mean (standard deviation)	7.41 (± 2.171)	6.83 (± 1.997)	11.21 (± 16.32)	30.35 (± 31.805)

End point values	Canakinumab rescue i.v			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: picograms per millilitre (pg/mL)				
arithmetic mean (standard deviation)	60.66 (± 80.772)			

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)

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. The analysis was performed in safety analysis set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

From start of study treatment to 4 weeks post dose

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Number of subjects				
AEs : Adults (n=27)	27			
SAEs : Adults (n=27)	2			
AEs : Pediatrics (n=7)	7			
SAEs : Pediatrics (n=7)	1			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with anti-canakinumab antibodies at any visit

End point description:

The immunogenicity potential of canakinumab during the study was evaluated by surface plasmon resonance spectroscopy using a validated Biacore binding assay. The analysis was performed in safety analysis set population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Pre-dose, Week 4 (post dose), at each relapse before re-treatment, end of study (all 3 periods averaged)

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Number of subjects				
Adults (n=27)	0			
Pediatrics (n=7)	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 are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Pediatric
Reporting group description:	
Pediatric	
Reporting group title	Adult
Reporting group description:	
Adult	

Serious adverse events	Pediatric	Adult	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	2 / 27 (7.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pediatric	Adult	
Total subjects affected by non-serious adverse events subjects affected / exposed	7 / 7 (100.00%)	23 / 27 (85.19%)	
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	3 / 27 (11.11%) 3	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 7	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Pharyngolaryngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 3 2 / 7 (28.57%) 3	4 / 27 (14.81%) 6 1 / 27 (3.70%) 1	
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 27 (0.00%) 0	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Joint injury	1 / 7 (14.29%) 1	0 / 27 (0.00%) 0	

subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Drug exposure during pregnancy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Joint sprain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Post procedural complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	4 / 27 (14.81%)	
occurrences (all)	5	10	
Hypotonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 7 (14.29%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	7	
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 27 (7.41%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 27 (3.70%)	
occurrences (all)	4	1	
Lip dry			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	5	
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Stomach discomfort			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	1 / 27 (3.70%)	
occurrences (all)	5	1	
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	2 / 7 (28.57%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Night sweats			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	4 / 7 (57.14%)	1 / 27 (3.70%)	
occurrences (all)	7	2	
Rash pruritic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	4 / 27 (14.81%)	
occurrences (all)	0	12	
Myalgia			

subjects affected / exposed	1 / 7 (14.29%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Gastroenteritis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Localised infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	3 / 7 (42.86%)	7 / 27 (25.93%)	
occurrences (all)	6	18	
Oral herpes			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	2	
Pharyngitis			
subjects affected / exposed	3 / 7 (42.86%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Rhinitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Tonsillitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 27 (3.70%)	
occurrences (all)	1	1	

Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	5 / 7 (71.43%)	8 / 27 (29.63%)	
occurrences (all)	11	17	
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2005	Additional blood samples were added for pharmacogenomics to investigate whether the observed early gene expression changes were transient or whether they were stable throughout the remission period.
05 September 2005	A third treatment period was included in the study design in order to explore the efficacy, safety and tolerability, pharmacokinetic and pharmacodynamic of s.c.administration of canakinumab as compared with i.v administration.
21 December 2005	1. Additional s.c. treatment periods were included in the study design in order to explore the efficacy, safety and tolerability, PK and PD of repeat s.c. administration of canakinumab as compared with i.v. administration. 2. Included up to 14 additional subjects, directly starting with the s.c. dosing regimen, assessment of s.c. administration to reach remission and for how long, and, by applying the experience in the first 4 subjects, whether the 10 mg/kg infusion was to be considered as a loading dose for the induction of remission. 3. Procedures added to introduce an interim analysis, to review preliminary efficacy, safety, tolerability, PK, PD, and pharmacogenomics results related to the i.v. administration.
21 September 2006	1. New centres opened in other countries than the original UK site in order to facilitate subjects access to canakinumab. 2. Increasesd the sample size in Stage 2 to 21 additional subjects, i.e. a total number of up to 25 subjects enrolled in the study. 3. Included children aged ≥ 4 years to provide an effective treatment early in the course of this genetically driven disease. 4. Included preliminary assessment of the potency of canakinumab to modify mid to longterm disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms. 5. Included preliminary assessment of the efficacy of canakinumab to modify HRQoL. 6. Day 3 visit was removed from Period 2 onwards.
05 March 2007	Baseline and pre-dose blood sampling were revised for safety, efficacy, and pharmacogenomics.
26 April 2007	1. Allowed the enrollment of subjects even though their baseline CRP and SAA were less than 30 mg/L, on a case-by-case basis. The definition of relapse for these subjects was adapted to reflect this change. 2. Subjects with renal transplant and with history/evidence of lymphoma were excluded.
24 July 2007	1. Increased the total sample size to up to 50 subjects enrolled in the study in order to facilitate subjects access to canakinumab, based on the increasing demand by the Investigators to enroll more subjects than a maximum of 25, and to allow enrollment of so far unidentified subjects with high unmet medical need. 2. Allowed the subjects who had previously been treated with canakinumab to be enrolled in the study.
04 February 2008	Ensured that subjects with severe renal insufficiency (GFR < 30 mL/min/1.73 m^2) or planned liver transplantation would not undergo performance of an magnetic resonance imaging evaluation in order to avoid administration of a gadolinium contrast agent, based on new safety information and as requested by German Health Authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported