Clinical trial results:

A multi center, randomized, double blind, placebo-controlled, study of the safety, tolerability, and the effects on arterial structure and function of canakinumab (ACZ885) in patients with clinically evident atherosclerosis and either type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT)

Summary

EudraCT number	2009-014618-80
Trial protocol	DE GB
Global end of trial date	05 February 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	CACZ885I2206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00995930
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	05 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To assess the safety and tolerability of monthly subcutaneous (sc) administration of canakinumuab (ACZ885) in patients with atherosclerosis and type 2 diabetes mellitus (T2DM) or impaired glucose tolerance (IGT)

-To assess the effect of canakinumuab on aortic distensibility and total plaque burden

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. In addition, along with the IDMC, three Adjudication Committees were also formed to make blinded assessments of AEs related to cardiac, malignant, or infectious events. In the context of this study, rescue medications could be those medications prescribed by a caregiver or the investigator to the patient to improve the management of their diabetes or cardiovascular disease. Optimal therapy was initiated and stabilized before the subject entered the study. However, if subject's glucose, blood pressure or lipid control was considered inadequate during the study, additional medications could have been added as appropriate.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	23 December 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Israel: 66
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	189
EEA total number of subjects	80

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	113
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included individuals who had clinically evident atherosclerotic vascular disease and T2DM (diagnosed ≤ 14 years ago) or impaired glucose tolerance (IGT). Participants were randomized in a 1:1 ratio to each treatment arm.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

In addition to the pharmacist and the statistician, the PK bioanalyst, the biomarker analysts, and the pharmacokineticist received a copy of the randomization schedule to facilitate analysis of the samples. The bioanalyst provided the sample data to the analysis team under blinded conditions. All parties kept this information confidential until clinical database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Matching placebo

Arm description:

Matching placebo was administered subcutaneously monthly for a treatment period of 12 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The matching placebo lyophilizate used in this trial consisted primarily of saccharose and was reconstituted and administered in the same way as the study drug injection.

Arm title	Canakinumab (ACZ885) 150 mg

Arm description:

Canakinumab was delivered at a dose of 150 mg administered subcutaneously monthly for a treatment period of 12 months.

Arm type	Experimental
Investigational medicinal product name	canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The investigational drug was provided as lyophylized powder in glass vials containing 150 mg of canakinumuab with a 20% overfill, bringing the amount of drug in the each vial to 180 mg. The drug was reconstituted and delivered at a dose of 150 mg administered by study center personnel subcutaneously monthly for a treatment period of 12 months. Injection sites were rotated.

Number of subjects in period 1	Matching placebo	Canakinumab (ACZ885) 150 mg
Started	94	95
Completed	73	67
Not completed	21	28
Consent withdrawn by subject	3	4
Adverse Event	11	14
Death	-	1
Administrative problems	4	2
Lost to follow-up	1	2
Protocol deviation	2	5

Baseline characteristics

Reporting groups

Reporting group title	Matching placebo
Reporting group description:	
Matching placebo was administered subcutaneously monthly for a treatment period of 12 months.	
Reporting group title	Canakinumab (ACZ885) 150 mg
Reporting group description:	
Canakinumab was delivered at a dose of 150 mg administered subcutaneously monthly for a treatment period of 12 months.	

Reporting group values	Matching placebo	Canakinumab (ACZ885) 150 mg	Total
Number of subjects	94	95	189
Age categorical			
Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
Age continuous			
Units: years			
arithmetic mean	61.9	61.7	
standard deviation	± 6.92	± 7.85	-
Gender categorical			
Units: Subjects			
Female	14	13	27
Male	80	82	162

End points

End points reporting groups

Reporting group title	Matching placebo
Reporting group description:	
Matching placebo was administered subcutaneously monthly for a treatment period of 12 months.	
Reporting group title	Canakinumab (ACZ885) 150 mg
Reporting group description:	
Canakinumab was delivered at a dose of 150 mg administered subcutaneously monthly for a treatment period of 12 months.	

Primary: Number of Participants With Adverse Events, Serious Adverse Events, and Death

End point title	Number of Participants With Adverse Events, Serious Adverse Events, and Death[1]

End point description:

Participants were monitored for adverse events, serious adverse events and death throughout the study. The population for this analysis included the safety analysis set. The safety analysis set included all randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed. The number of participants having adverse events, serious adverse events, or that died, were counted.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[2]	95[3]		
Units: Participants				
Adverse events (serious and non-serious)	80	77		
Serious adverse events	14	25		
Deaths	0	1		

Notes:

[2] - Safety analysis set

[3] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Aortic Distensibility (Month 3)

End point title	Change From Baseline in Aortic Distensibility (Month 3)

End point description:

Two axial, ECG-gated, steady state free precession (SSFP) 'cine' images were acquired during breath-hold to determine aortic distensibility. The first image was obtained at the level of the right pulmonary artery through the ascending and proximal descending aorta and the second through the distal aorta

below the diaphragm. Imaging of the aorta also enabled evaluation of the plaque burden and additional vascular function measures. Only participants from the imaging analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The imaging analysis set included randomized participants who received at least one dose of study medication.

End point type	Primary
End point timeframe:	
Baseline, month 3	

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[4]	63[5]		
Units: units: mmHg^-1				
least squares mean (standard error)				
Month 3, proximal ascending region	-0.0001 (± 0.0001)	-0.0001 (± 0.0001)		

Notes:

[4] - Imaging analysis set

[5] - Imaging analysis set

Statistical analyses

Statistical analysis title	Month 3 Difference in Proximal Ascending
Statistical analysis description:	
Analysis of change from baseline in aortic distensibility at month 3 for proximal ascending difference between treatments is presented.	
Comparison groups	Matching placebo v Canakinumab (ACZ885) 150 mg
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.174 [7]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0002
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0001
upper limit	0.0004

Notes:

[6] - Analysis was assessment of effect.

[7] - Data were analyzed using an ANCOVA model with glycemic status as a classification factor and baseline as a covariate. One-sided p-value presented.

Primary: Change From Baseline to Month 3 in Plaque Burden (Aortic Vessel Wall Area)

End point title	Change From Baseline to Month 3 in Plaque Burden (Aortic Vessel Wall Area)
End point description:	

For assessment of atherosclerotic plaque burden of the aorta, vessel wall images of the aorta were acquired with an ECG gated double-inversion recovery (black blood) fast spin echo sequence applied

breath-holding. Using an oblique sagittal image of the aorta as a pilot, serial axial images were acquired to cover a section of the descending thoracic aorta. The midpoint of the right pulmonary artery in cross section was used as the anatomical reference for the first slice in baseline and follow-up scans.

End point type	Primary

End point timeframe:

Baseline, month 3.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[8]	62[9]		
Units: mm^2				
least squares mean (standard error)				
aortic, proximal ascending, month 3	14.8 (± 6.86)	-0.51 (± 6.62)		

Notes:

[8] - Imaging analysis set

[9] - Imaging analysis set

Statistical analyses

Statistical analysis title	Month 3 Proximal Ascending Wall Area Change
Comparison groups	Matching placebo v Canakinumab (ACZ885) 150 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.03 [11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.69
upper limit	-1.94

Notes:

[10] - Assessment of effect

[11] - One-sided.

Primary: Change From Baseline in Aortic Distensibility (Month 12)

End point title	Change From Baseline in Aortic Distensibility (Month 12)

End point description:

Two axial, ECG-gated, steady state free precession (SSFP) 'cine' images were acquired during breathhold to determine aortic distensibility. The first image was obtained at the level of the right pulmonary artery through the ascending and proximal descending aorta and the second through the distal aorta below the diaphragm. Imaging of the aorta also enabled evaluation of the plaque burden and additional vascular function measures. Only participants from the imaging analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline.

End point type	Primary

End point timeframe:

Baseline, month 12

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[12]	55[13]		
Units: mmHg^-1				
least squares mean (standard error)				
Month 12, proximal ascending region	-0.0001 (± 0.0001)	-0.0001 (± 0.0001)		

Notes:

[12] - Imaging analysis set

[13] - Imaging analysis set

Statistical analyses

Statistical analysis title	Month 12 Difference in Proximal Ascending
Statistical analysis description:	
Analysis of change from baseline in aortic distensibility at month 12 for proximal ascending difference between treatments is presented.	
Comparison groups	Matching placebo v Canakinumab (ACZ885) 150 mg
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.459 [15]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.0003
upper limit	0.0003

Notes:

[14] - Analysis was assessment of effect.

[15] - Data were analyzed using an ANCOVA model with glycemic status as a classification factor and baseline as a covariate. One-sided p-value presented.

Primary: Change From Baseline to Month 12 in Plaque Burden (Aortic Vessel Wall Area)

End point title	Change From Baseline to Month 12 in Plaque Burden (Aortic Vessel Wall Area)
End point description:	
For assessment of atherosclerotic plaque burden of the aorta, vessel wall images of the aorta were acquired with an ECG gated double-inversion recovery (black blood) fast spin echo sequence applied breath-holding. Using an oblique sagittal image of the aorta as a pilot, serial axial images were acquired to cover a section of the descending thoracic aorta. The midpoint of the right pulmonary artery in cross section was used as the anatomical reference for the first slice in baseline and follow-up scans.	
End point type	Primary
End point timeframe:	
Baseline, month 12	

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[16]	62[17]		
Units: mm^2				
least squares mean (standard error)				
aortic, proximal ascending, month 12	30.58 (± 10.46)	8.71 (± 10.49)		

Notes:

[16] - Imaging analysis set

[17] - Imaging analysis set

Statistical analyses

Statistical analysis title	Month 12 Proximal Ascending Wall Area Change
Comparison groups	Canakinumab (ACZ885) 150 mg v Matching placebo
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.04 [19]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-21.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	-42.35
upper limit	-1.39

Notes:

[18] - Assessment of effect

[19] - One-sided.

Secondary: Change From Baseline in Pulse Wave Velocity and Pulse Wave Velocity Error

End point title	Change From Baseline in Pulse Wave Velocity and Pulse Wave Velocity Error

End point description:

Utilizing the SphygmoCor Device, ECG leads placed at the carotid and femoral arteries provided the measure of the pulse wave at that particular arterial location. The distance between the two vascular beds divided by the pulse wave time shift provided a measure of the pulse wave velocity. Only participants from the imaging analysis set were included.

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[20]	92[21]		
Units: ms^-1				
least squares mean (standard error)				
pulse wave velocity, month 3 (n=45,38)	-0.39 (± 0.39)	-0.03 (± 0.39)		
pulse wave velocity, month 12 (n=35,31)	-0.36 (± 0.35)	-0.26 (± 0.35)		
pulse wave velocity error, month 3 (n=45,38)	-0.01 (± 0.05)	-0.03 (± 0.05)		
pulse wave velocity error, month 12 (n=35,31)	-0.01 (± 0.06)	0.06 (± 0.06)		

Notes:

[20] - Imaging analysis set

[21] - Imaging analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Plaque Composition

End point title	Change From Baseline in Plaque Composition

End point description:

During the carotid MRI acquisition, in addition to the PD weighted ECG gated double inversion fast spin echo sequences T1 and T2 weighted sequences were acquired. In combination with the PD weighted images, the multi-contrast images were analyzed to determine regions of interest with contrast patterns consistent with the presence of necrotic lipid core, calcification and fibrous tissue in participants who had complex carotid plaque present in the bifurcation region. This analysis only included participants from the imaging analysis set. 'n' signifies the patients with evaluable data at that time point . If 'n' is not provided in the category, it indicates that all the patients of imaging analyis set with N= 5, 3 provided evaluable data on each time point respectively. .

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[22]	3[23]		
Units: mm^2				
arithmetic mean (standard deviation)				
calcium composition, left carotid, month 3	0.002 (± 0.0045)	0.003 (± 0.0058)		
calcium composition, left carotid, month 12	0.002 (± 0.0045)	0.003 (± 0.0058)		
hemorrhage area, left carotid, month 3	0.006 (± 0.0114)	0 (± 0.02)		
hemorrhage area, left carotid, month 12	0.018 (± 0.0205)	0.007 (± 0.0115)		
lipid composition, left carotid, month 3	0 (± 0)	0.003 (± 0.0115)		

lipid composition, left carotid, month 12	0 (± 0.0122)	0.007 (± 0.0058)		
calcium composition,right carotid, month 3 (n=3, 4	-0.005 (± 0.0058)	-0.003 (± 0.0058)		
calcium composition,right carotid, month 12(n=3, 4	0 (± 0.0082)	0 (± 0)		
hemorrhage area,right carotid, month 3 (n=3, 4)	0.003 (± 0.0096)	0 (± 0.01)		
hemorrhage area,right carotid, month 12 (n=3, 4)	0.008 (± 0.033)	0.003 (± 0.0208)		
lipid composition, right carotid, month 3 (n=3, 4)	-0.005 (± 0.0058)	0.003 (± 0.0058)		
lipid composition, right carotid, month 12 (n=3, 4	0.008 (± 0.0171)	0.017 (± 0.0115)		

Notes:

[22] - Imaging analysis set

[23] - Imaging analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Aortic Strain

End point title	Change From Baseline in Aortic Strain

End point description:

Arterial strain was computed directly from the cine SSFP images and the change in lumen diameters over the cardiac cycle. The value was independent of pulse pressure and is unitless ratio derived from the maximum to minimum lumen diameters diastole and systole, respectively. Only participants from the imaging analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for this post baseline time point.

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[24]	92[25]		
Units: participants				
least squares mean (standard error)				
proximal ascending, month 3 (n=67,64)	-0.005 (± 0.005)	0.002 (± 0.005)		
proximal ascending, month 12 (n=59,59)	0.001 (± 0.005)	-0.002 (± 0.005)		

Notes:

[24] - Imaging analysis set

[25] - Imaging analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in High Sensitivity C-reactive Protein (hsCRP)

End point title	Change From Baseline in High Sensitivity C-reactive Protein (hsCRP)
End point description:	
Blood samples were collected to analyze high sesitivity C-reactive protein (hsCRP). Only participants from the pharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Baseline, month 3, and month 12.	

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[26]	92[27]		
Units: mg/L				
geometric mean (confidence interval 95%)				
Month 3 (n=82,79)	0.93 (0.76 to 1.14)	0.48 (0.39 to 0.58)		
Month 12 (n=73,68)	1.04 (0.83 to 1.31)	0.51 (0.41 to 0.64)		

Notes:

[26] - Pharmacodynamic analysis set

[27] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Plasma Glucose

End point title	Change From Baseline in Fasting Plasma Glucose
End point description:	
Blood samples were collected to analyze fasting plasma glucose. Only participants from the pharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.	
End point type	Secondary
End point timeframe:	
Baseline, month 3, and month 12.	

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[28]	92[29]		
Units: mmol/L				
geometric mean (confidence interval 95%)				

month 3 (n=79,75)	0.95 (0.89 to 1.01)	1 (0.94 to 1.06)		
month 12 (n=71,62)	0.95 (0.87 to 1.02)	0.99 (0.92 to 1.07)		

Notes:

[28] - Pharmacodynamic analysis set

[29] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin A1c (HbA1c)

End point title	Change From Baseline in Hemoglobin A1c (HbA1c)

End point description:

Blood samples were collected to analyze hemoglobin A1c (HbA1c). Only participants from the pharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[30]	92[31]		
Units: Percentage				
geometric mean (confidence interval 95%)				
month 3 (n=81,77)	1 (0.97 to 1.02)	0.99 (0.97 to 1.02)		
month 12 (n=72,65)	1 (0.96 to 1.04)	0.96 (0.96 to 1.03)		

Notes:

[30] - Pharmacodynamic analysis set

[31] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 2 Hour Glucose Post Oral Glucose Tolerance Test (OGTT)

End point title	Change From Baseline in 2 Hour Glucose Post Oral Glucose Tolerance Test (OGTT)

End point description:

Blood samples were collected to analyze the 2 hour glucose post oral glucose tolerance tet (OGTT). Only participants from the pharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.

End point type	Secondary

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[32]	92[33]		
Units: mmol/L				
geometric mean (confidence interval 95%)				
month 3 (n=79,74)	0.92 (0.85 to 0.99)	0.98 (0.9 to 1.05)		
monht 12 (n=71,62)	0.93 (0.84 to 1.01)	0.95 (0.88 to 1.04)		

Notes:

[32] - Pharmacodynamic analysis set

[33] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Homeostatis Model Assessments Beta Cell Function (HOMA-B)

End point title	Change From Baseline in Homeostatis Model Assessments Beta Cell Function (HOMA-B)

End point description:

Blood samples were collected to analyze beta cell function. Beta cell function was calculated by the Homeostasis Model Assessments (of beta cell function (HOMA-B) as follows: HOMA-B: The product of 20 and basal insulin (µU/mL) levels divided by the value of basal glucose (mmol/L) concentrations minus 3.5 [i.e., HOMA-B = 20*basal insulin/(basal glucose-3.5)]. Only participants from thepharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[34]	92[35]		
Units: percentage of beta cell function				
geometric mean (confidence interval 95%)				
HOMA-B, month 3 (n=77,70)	1.11 (0.91 to 1.35)	0.99 (0.82 to 1.2)		
HOMA-B, month 12 (n=71,60)	1.03 (0.84 to 1.26)	0.91 (0.75 to 1.1)		

Notes:

[34] - Pharmacodynamic analysis set

[35] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Insulin Resistance (HOMA-IR)

End point title	Change From Baseline Insulin Resistance (HOMA-IR)

End point description:

Blood samples were collected to analyze insulin resistance. Insulin resistance was calculated by the Homeostasis Model Assessments of insulin resistance (HOMA-IR)) as follows: HOMA-IR: The product of basal glucose (mmol/L) and insulin (µU/mL) levels divided by 22.5 [i.e., HOMA-IR = basal glucose*basal insulin/22.5]. Only participants from the pharmacodynamic (PD) analysis set, who had evaluable data at both baseline and the given post-baseline time point, were included in the analysis for that post baseline time point. The PD analysis set included randomized participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Baseline, month 3, and month 12.

End point values	Matching placebo	Canakinumab (ACZ885) 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92[36]	92[37]		
Units: Insulin Resisitance (IR) score				
geometric mean (confidence interval 95%)				
HOMA-R, month 3 (n=77,70)	1 (0.85 to 1.18)	1.09 (0.93 to 1.28)		
HOMA-R, month 12 (n=71,60)	0.93 (0.77 to 1.13)	0.97 (0.8 to 1.16)		

Notes:

[36] - Pharmacodynamic analysis set

[37] - Pharmacodynamic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Canakinumab Serum Concentrations

End point title	Pharmacokinetics: Canakinumab Serum Concentrations[38]

End point description:

Blood samples were collected to analyze the canakinumabserum concentrations. Only participants from the pharmacokinetic (PK) analysis set, who had evaluable data at each time point, were included in the analysis for that time point. The PK analysis set included randomized participants from the canakinumab arm who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Pre-dose, 0.167 day post dose 1, 7 days post dose 1, 14 days post dose 1, every 30 days post each dose from doses 1 through 12, 60 days post dose 12, and 90 days post dose 12.

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacokinetics on canakinumab serum concentration can only be performed on patients treated with canakinumab, therefore only the canakinumab treatment group is included in the analysis.

End point values	Canakinumab (ACZ885) 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	95[39]			
Units: ng/mL				
arithmetic mean (standard deviation)				
pre-dose (n=91)	0 (± 0)			
0.167 day post dose 1 (n=94)	480 (± 648)			
7 days post dose 1 (n=95)	10107 (± 4369)			
14 days post dose 1 (n=93)	9138 (± 3527)			
30 days post dose 1 (n=90)	5936 (± 2281)			
30 days post dose 2 (n=86)	8136 (± 3299)			
30 days post dose 3 (n=81)	9278 (± 3795)			
30 days post dose 4 (n=78)	10183 (± 4552)			
30 days post dose 5 (n=78)	10164 (± 4209)			
30 days post dose 6 (n=77)	10254 (± 3916)			
30 days post dose 7 (n=76)	10368 (± 4840)			
30 days post dose 8 (n=71)	9745 (± 4436)			
30 days post dose 9 (n=69)	10407 (± 3967)			
30 days post dose 10 (n=71)	10635 (± 4697)			
30 days post dose 11 (n=70)	10612 (± 4434)			
30 days post dose 12 (n=66)	10887 (± 4785)			
60 days post dose 12 (n=66)	4575 (± 2362)			
90 days post dose 12 (n=88)	3241 (± 2883)			

Notes:

[39] - Pharmacokinetic analysis set

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.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	ACZ885 150mg
Reporting group description:	
ACZ885 150mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	ACZ885 150mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 95 (26.32%)	14 / 94 (14.89%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myelodysplastic syndrome			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Anxiety				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Investigations				
Hepatic enzyme increased				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fall				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery restenosis				
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Subdural haematoma				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Acute myocardial infarction				

subjects affected / exposed	2 / 95 (2.11%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Angina pectoris				
subjects affected / exposed	2 / 95 (2.11%)	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Angina unstable				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Atrial fibrillation				
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bradycardia				
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cardiac failure				
subjects affected / exposed	1 / 95 (1.05%)	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Coronary artery disease				
subjects affected / exposed	0 / 95 (0.00%)	2 / 94 (2.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Myocardial ischaemia				
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nervous system disorders				
Carotid artery stenosis				

subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 95 (2.11%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia, obstructive			
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis acute		
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Skin and subcutaneous tissue disorders		
Diabetic foot		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal and urinary disorders		
Nephrolithiasis		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal failure		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders		
Lumbar spinal stenosis		
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gouty tophus		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Back pain		
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		

subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations		
Epiglottitis		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Furuncle		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	1 / 95 (1.05%)	0 / 94 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
Hypoglycaemia		
subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		

subjects affected / exposed	0 / 95 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ACZ885 150mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 95 (48.42%)	65 / 94 (69.15%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 95 (5.26%)	3 / 94 (3.19%)	
occurrences (all)	5	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 95 (3.16%)	5 / 94 (5.32%)	
occurrences (all)	3	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 95 (5.26%)	5 / 94 (5.32%)	
occurrences (all)	6	5	
Headache			
subjects affected / exposed	4 / 95 (4.21%)	5 / 94 (5.32%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 95 (2.11%)	5 / 94 (5.32%)	
occurrences (all)	2	5	
Non-cardiac chest pain			
subjects affected / exposed	3 / 95 (3.16%)	8 / 94 (8.51%)	
occurrences (all)	5	9	
Influenza like illness			
subjects affected / exposed	4 / 95 (4.21%)	5 / 94 (5.32%)	
occurrences (all)	4	6	
Fatigue			

subjects affected / exposed	2 / 95 (2.11%)	8 / 94 (8.51%)	
occurrences (all)	2	11	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 95 (0.00%)	5 / 94 (5.32%)	
occurrences (all)	0	5	
Nausea			
subjects affected / exposed	4 / 95 (4.21%)	7 / 94 (7.45%)	
occurrences (all)	9	10	
Diarrhoea			
subjects affected / exposed	5 / 95 (5.26%)	6 / 94 (6.38%)	
occurrences (all)	7	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 95 (5.26%)	2 / 94 (2.13%)	
occurrences (all)	5	2	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 95 (2.11%)	6 / 94 (6.38%)	
occurrences (all)	2	6	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 95 (2.11%)	6 / 94 (6.38%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	4 / 95 (4.21%)	7 / 94 (7.45%)	
occurrences (all)	6	7	
Back pain			
subjects affected / exposed	4 / 95 (4.21%)	5 / 94 (5.32%)	
occurrences (all)	4	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 95 (12.63%)	18 / 94 (19.15%)	
occurrences (all)	22	28	
Upper respiratory tract infection			

subjects affected / exposed	9 / 95 (9.47%)	10 / 94 (10.64%)	
occurrences (all)	11	11	
Metabolism and nutrition disorders Hypertriglyceridaemia			
subjects affected / exposed	1 / 95 (1.05%)	5 / 94 (5.32%)	
occurrences (all)	1	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2009	This amendment included the following: Allow for subjects with a negative PPD test within two months of screening to be excluded from having another placed at screening to avoid false positives from too proximate exposure to tuberculosis antigens, add for safety and efficacy reasons: lipid subfractionation and C-Peptide at visits 2, 8, and 18; soluble PD biomarkers (plasma) at Visits 3, 8, and 18; fasting plasma glucose and fasting insulin at Visit 1, add urine pregnancy testing at every dosing visit and vital sign monitoring on Day 1 every 15 minutes for the first hour post-dose and every 30 minutes for the second hour post-dose, move the 2 mL PK blood draw from visit 19 to Visit 3, 8 hours post-dose and to add the additional draws to the blood log, perform a clean catch culture in the event of a positive urine dipstick which could indicate a UTI, and allow for additional subjects to be randomized during a possible increase in cases of influenza (either seasonal or H1N1)
03 February 2010	This amendment included the following: Correct amount of blood drawn from 5 mL to 3 mL; change PK and IL1beta timepoints, clarify autoantibody analysis performed on plasma samples, add central aortic pressure language indicating that the assessment take place just prior to the MRI and to convert brachial artery imaging to an exploratory endpoint, exclude subjects who had received or were planning to receive live (attenuated) vaccination, including but not limited to live H1N1 and Seasonal Flu vaccination, and clarify inclusion/exclusion criteria and to add an exclusion criteria concerning vaccinations.
12 May 2010	This amendment included the following: The lower limit for HbA1c was reduced to 6.0% from 6.5%. Since potential subjects could be on any type of medication for diabetes (including insulin and sulfonylureas), their HbA1c values were below the current protocol limit of 6.5%. In order to be able to recruit subjects for the study, the lower limit of HbA1c as defined by the protocol was brought in line with the population. In addition, patients who have had events (secondary prevention, our target population) tend to have even more tightly controlled glycemic indices evidenced by lower HbA1cs. The upper limit of SGOT and SGPT was raised to 2 x ULN from 1.5 x ULN. Since potential subjects could be on statins, their SGOT or SGPT values were above the current protocol limit of 1.5 x ULN. In order to be able to recruit subjects for the study, the upper limit of SGOT and SGPT as defined by the protocol were brought in line with the population.
30 March 2011	This amendment included the following:Time from a major cardiovascular event to screening was reduced to ≥ 3 months from ≥ 6 months. Subjects in atrial fibrillation, having an implantable cardiac device or taking coumadin were excluded. Maximum non-steroidal use was clarified; additional information about concomitant medications was included. Additional information about hypertensive medication was included. Stopping rules were clarified to include additional information regarding concomitant medication.
31 January 2012	This amendment included the following: Planned number of patients was changed from approximately 140 patients enrolled and 120 patients completed to approximately 190 patients enrolled and 120 evaluable patients completed. Brachial artery imaging was changed to an optional assessment and endothelial function was changed to an exploratory objective. The human safety and tolerability data was updated to reflect the most recent IB version. Patients who had immunosuppressant treatment within one year prior to screening were excluded. Patients diagnosed with or who had a history of neutropenia were excluded. Patients diagnosed or had a history of an autoimmune disorder were excluded. New infections and immunosuppressant treatment was added to premature patient withdrawal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Since this is an early stage study for a new indication, a one-sided test instead of the pre-specified two-sided test was performed for between treatment comparisons of the primary imaging endpoints. Planned PK analyses and modeling not performed.

Notes: