Clinical trial results:
A multicenter, randomized, double-blind, placebo-controlled study of the safety, tolerability and effects on arterial structure and function of ACZ885 in patients with intermittent claudication.

Summary

EudraCT number	2012-001427-12
Trial protocol	DE
Global end of trial date	04 August 2016

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	CACZ885M2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01731990
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	04 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of ACZ885 on peripheral artery wall morphometry using MRI techniques at 12 months

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.
Wherever possible, patients were maintained on a stable medical regimen throughout the study, so that medication changes did not confound the study results.
Medications like analgesics, opioids, pentoxyfylline or cilostazol, which are used to manage the pain of intermittent claudication were allowed, but were optimized prior to enrollment in the treatment phase of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2012
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	Germany: 8
Country: Number of subjects enrolled	Jordan: 5
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	38
EEA total number of subjects	8

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)	17
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 38 patients were enrolled into the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab (ACZ885)

Arm description:

Monthly subcutaneous doses of Canakinumab 150 mg/1 mL for 12 months

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage form: solution for injection
Strength: 150 mg/1 mL
Mode of administration: subcutaneous use.

Arm title	Placebo

Arm description:

Monthly subcutaneous doses of placebo of Canakinumab 150 mg/1 mL for 12 months

Arm type	Placebo
Investigational medicinal product name	Placebo of Canakinumab
Investigational medicinal product code	Placebo of ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo of Canakinumab

Number of subjects in period 1	Canakinumab (ACZ885)	Placebo
Started	18	20
Completed	14	12
Not completed	4	8
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	5
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab (ACZ885)
Reporting group description:	
Monthly subcutaneous doses of Canakinumab 150 mg/1 mL for 12 months	
Reporting group title	Placebo
Reporting group description:	
Monthly subcutaneous doses of placebo of Canakinumab 150 mg/1 mL for 12 months	

Reporting group values	Canakinumab (ACZ885)	Placebo	Total
Number of subjects	18	20	38
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: years			
arithmetic mean	66	63.5	
standard deviation	± 8.64	± 7.98	-
Gender, Male/Female Units: Subjects			
Female	4	7	11
Male	14	13	27

End points

End points reporting groups

Reporting group title	Canakinumab (ACZ885)
Reporting group description:	
Monthly subcutaneous doses of Canakinumab 150 mg/1 mL for 12 months	
Reporting group title	Placebo
Reporting group description:	
Monthly subcutaneous doses of placebo of Canakinumab 150 mg/1 mL for 12 months	

Primary: Mean vessel wall area ratio of 12 months to baseline

End point title	Mean vessel wall area ratio of 12 months to baseline
End point description:	
Peripheral artery wall area (superficial femoral artery) measured using Magnetic Resonance Imaging (MRI) cross-section slices. Mean vessel wall area (mm^2) was derived by converting total plaque volume (TPV) (mL) of the vessel to mm^3 by multiplying by 1000, dividing by the number of slices used for the volume calculation, and dividing by the thickness of a slice (3 mm). Least squares mean for ratio of 12 months to baseline was measured from repeated measures mixed effect model with visit, treatment, the treatment-by-visit interaction, baseline and the visit-by-baseline interaction as fixed effects. The pharmacodynamics (PD) analysis set included all patients with available PD data and no protocol deviations with relevant impact on PD data. Patients who underwent iliac/femoral stenting were removed from all data points that occurred after this procedure in the analysis.	
End point type	Primary
End point timeframe:	
Baseline, 12 months post-dose	

End point values	Canakinumab (ACZ885)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Ratio				
least squares mean (standard error)	1.05 (± 0.03)	0.99 (± 0.04)		

Statistical analyses

Statistical analysis title	ratio of mean vessel wall area to baseline
Comparison groups	Canakinumab (ACZ885) v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.284
Method	Mixed models analysis
Parameter estimate	Treatment effect for ratio to placebo
Point estimate	1.06

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	1.15

Secondary: Number of patients with adverse events in 12 months

End point title	Number of patients with adverse events in 12 months

End point description:

Summary statistics on adverse event is reported. It is categorized as number of patients in total adverse events (non serious and serious AEs), serious adverse event, death. All patients that received any study drug were included in the safety analysis set.

End point type	Secondary

End point timeframe:

Baseline to 12 months post-dose

End point values	Canakinumab (ACZ885)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: Patients				
Total Adverse events	16	20		
Serious Adverse events	10	10		
Death	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum amyloid A (SAA) level ratio of 12 months to baseline

End point title	Serum amyloid A (SAA) level ratio of 12 months to baseline

End point description:

Least squares mean for ratio of 12 months to baseline was measured from repeated measures mixed effect model with visit, treatment, treatment-by-visit interaction, baseline and the visit-by-baseline interaction as fixed effects. The PD analysis set included all patients with available PD data and no protocol deviations with relevant impact on PD data. Patients with baseline and 12 month data are included in this analysis.

End point type	Secondary

End point timeframe:

Baseline, 12 months post-dose

End point values	Canakinumab (ACZ885)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Ratio				
least squares mean (standard error)	0.62 (± 0.12)	0.79 (± 0.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: High sensitivity C-reactive protein (hsCRP) ratio of 12 months to baseline

End point title	High sensitivity C-reactive protein (hsCRP) ratio of 12 months to baseline

End point description:

Least squares mean for ratio of 12 months to baseline was measured from repeated measures mixed effect model with visit, treatment, treatment-by-visit interaction, baseline and the visit-by-baseline interaction as fixed effects. The PD analysis set included all patients with available PD data and no protocol deviations with relevant impact on PD data. Patients with baseline and 12 month data are included in this analysis.

End point type	Secondary

End point timeframe:

Baseline, 12 months post-dose

End point values	Canakinumab (ACZ885)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: Ratio				
least squares mean (standard error)	0.62 (± 0.14)	0.83 (± 0.2)		

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	19.1

Reporting groups

Reporting group title	Canakinumab (ACZ885)

Reporting group description:

Monthly subcutaneous doses of Canakinumab 150 mg/1 mL for 12 months

Reporting group title	Placebo

Reporting group description:

Monthly subcutaneous doses of placebo of Canakinumab 150 mg/1 mL for 12 months

Serious adverse events	Canakinumab (ACZ885)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	10 / 20 (50.00%)	
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)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 18 (16.67%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (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			
Chest pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric arterial occlusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric arteriosclerosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
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 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary vascular disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Canakinumab (ACZ885)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	17 / 20 (85.00%)	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Aortic aneurysm			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	2	2	
Intermittent claudication			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Peripheral ischaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Feeling cold			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza like illness			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Genital pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Prostatitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pulmonary mass			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood pressure increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oesophagogastroduodenoscopy abnormal			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Platelet count decreased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Excoriation			

subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Laceration			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Muscle strain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Atrioventricular block first degree			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Coronary artery disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Areflexia			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Muscle contractions involuntary			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Plasma cell disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Deafness unilateral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vertigo			

subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 18 (11.11%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	3 / 18 (16.67%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Diverticulum			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Erosive oesophagitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gingival bleeding			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hiatus hernia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Large intestine polyp			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 18 (16.67%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Oesophageal mucosa erythema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oesophageal stenosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pancreatic cyst			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	

Dermatitis				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Dermatitis contact				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Drug eruption				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	2		
Ecchymosis				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Eczema				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Eczema asteatotic				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Hyperhidrosis				
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)		
occurrences (all)	1	0		
Hyperkeratosis				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	1	1		
Lichen nitidus				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Nail discolouration				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Photosensitivity reaction				
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)		
occurrences (all)	0	1		
Rash				
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)		
occurrences (all)	1	1		

Skin lesion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin plaque			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Renal artery stenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal cyst			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 18 (27.78%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Back pain			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	3	2	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Muscle spasms			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	2 / 18 (11.11%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Plantar fasciitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Conjunctivitis viral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	2 / 18 (11.11%)	4 / 20 (20.00%)	
occurrences (all)	3	4	
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 18 (22.22%)	4 / 20 (20.00%)	
occurrences (all)	6	6	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 18 (5.56%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypochloraemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Hyponatraemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2014	The purpose of the amendment was to utilize new information about PAD patient characteristics derived from the ongoing trial to more appropriately and inclusively enroll patients consistent with the originally intended patient population. Expanding the upper/lower bound of the ABI inclusion criteria to 0.9 and 0.4, respectively, and adding alternative criteria, including a drop in ABI or ankle pressure with exercise or a decreased TBI, allowed Investigators to readily identify more completely the intended patients of interest with physiologically significant PAD. Thus, this amendment maximized inclusiveness while maintaining the originally intended patient population.
07 April 2015	The purpose of the amendment was to utilize new information about PAD patient characteristics derived from the ongoing trial to more appropriately and inclusively enroll patients consistent with the originally intended patient population. The removal of the mandatory exercise run-in period eased patient compliance with the protocol without altering the intention of outcome of the trial. Removal of the exercise run-in in turn decreased the minimum total run-in period. The acceptable inclusion criteria for glucose control in diabetics was increased to allow more diabetics to participate. In addition, the exclusion criteria for patients with a history of cancer was clarified such that if a patient had been cancer-free for a period of five years, they would not be excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported