Clinical trial results:
A randomized, double-blind, placebo controlled multiple dose study of subcutaneous ACZ885 for the treatment of abdominal aortic aneurysm

Summary

EudraCT number	2013-002088-25
Trial protocol	SE NL DK GB DE
Global end of trial date	21 October 2015

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information

Trial identification

Sponsor protocol code	CACZ885X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02007252
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	21 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the effect of ACZ885 on AAA size and growth rate as measured with ultrasound 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2013
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	Denmark: 33
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Sweden: 21
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	10

From 65 to 84 years	53
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 65 participants were randomized in a 1:1 ratio to one of the two treatment groups. One participant discontinued prior to taking any study medication. As such, the participant flow is based on 64 randomized participants.

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	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ACZ885

Arm description:

Participants received ACZ885 150 mg subcutaneously (s.c.) once per month for 12 months.

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

Dosage and administration details:

150 mg once per month for 12 months

Arm title	Placebo

Arm description:

Participants received matching placebo to ACZ885 s.c. once per month for 12 months.

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

Dosage and administration details:

Matching placebo to ACZ885 once per month for 12 months

Number of subjects in period 1	ACZ885	Placebo
Started	31	33
Safety analysis set	31	33
Pharmacodynamic analysis set	31	33
Completed	20	22
Not completed	11	11
Abnormal laboratory value(s)	1	-
Adverse event, non-fatal	7	4
Administrative problems	3	7

Baseline characteristics

Reporting groups	
Reporting group title	ACZ885
Reporting group description:	
Participants received ACZ885 150 mg subcutaneously (s.c.) once per month for 12 months.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to ACZ885 s.c. once per month for 12 months.	

Reporting group values	ACZ885	Placebo	Total
Number of subjects	31	33	64
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	4	10
From 65-84 years	24	29	53
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	69.4	70.8	
standard deviation	± 7.44	± 5.84	-
Gender, Male/Female Units: Subjects			
Female	4	7	11
Male	27	26	53

End points

End points reporting groups

Reporting group title	ACZ885
Reporting group description:	
Participants received ACZ885 150 mg subcutaneously (s.c.) once per month for 12 months.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to ACZ885 s.c. once per month for 12 months.	

Primary: Change from baseline (BL) in Abdominal Aortic Aneurysm (AAA) size per year

End point title	Change from baseline (BL) in Abdominal Aortic Aneurysm (AAA) size per year
End point description:	
Size of the AAA was determined using an abdominal ultrasound technique at baseline, 3 months, and 12 months after treatment with study drug. Growth rate (in mm/year) was calculated from the change in AAA size compared to baseline	
End point type	Primary
End point timeframe:	
month 3, month 12	

End point values	ACZ885	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: millimeter/year				
least squares mean (confidence interval 90%)				
Month 3 (n=23,31)	0.781 (-0.942 to 5.504)	2.519 (1.03 to 4.008)		
Month 12 (n=20,23)	2.538 (1.465 to 3.612)	2.581 (1.612 to 3.549)		

Statistical analyses

Statistical analysis title	Change from BL in AAA size per year at month 3
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1037
Method	ANCOVA

Statistical analysis title	Change from BL in AAA size per year at month 12
Comparison groups	ACZ885 v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4806
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

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

Serious adverse events	ACZ885 150 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 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	ACZ885 150 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 31 (90.32%)	28 / 33 (84.85%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer stage 0, with cancer in situ			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	4 / 31 (12.90%)	3 / 33 (9.09%)	
occurrences (all)	4	3	
Aortic aneurysm			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Intermittent claudication			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Energy increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Injection site hypersensitivity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Impaired healing			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Injection site pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	0 / 31 (0.00%)	4 / 33 (12.12%)	
occurrences (all)	0	5	
Malaise			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Injection site swelling			
subjects affected / exposed	3 / 31 (9.68%)	2 / 33 (6.06%)	
occurrences (all)	4	3	
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	3 / 31 (9.68%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Haemoptysis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Epistaxis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Blood creatinine increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Occult blood positive			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Prostatic specific antigen increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Foot fracture			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Wound			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Angina pectoris			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Atrioventricular block second degree			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Transient ischaemic attack			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Syncope			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Haematochezia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Telangiectasia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	4 / 31 (12.90%)	3 / 33 (9.09%)	
occurrences (all)	4	3	
Groin pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences (all)	2	2	
Osteoarthritis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	3 / 33 (9.09%)	
occurrences (all)	8	5	

Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Vestibular neuronitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperlipidaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2013	The primary purpose of this protocol amendment was to clarify the exclusion criteria for patients with immune disorders or thrombocytopenia. An exclusion criterion was added to prevent patients with neutropenia, leukopenia, or thrombocytopenia from entering the study. Also, the individual stopping rules within this study have been modified to reflect this criterion. The other modifications were provided below: 1. A greater clarification was provided regarding the use of clopidogrel in patients with vascular stents. Specific language was added to allow the use of clopidogrel in this situation. 2. At sites in the USA where CT scans were performed, the use of historical CT scans was proposed in order to reduce the radiation exposure to patients who had recently undergone an abdominal CT scan prior to their entry into this clinical trial. The protocol was modified to allow the use of an abdominal CT scan obtained within 60 days of first dose to be used in place of the Screening CT scan. 3. Additional details regarding the planned statistical analysis of trial data were added and a few typographical inconsistencies in the protocol were corrected.

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.

This study was terminated prematurely because the results of a third interim analysis (ad hoc) indicated a lack of efficacy and futility in continuing the trial.

Notes: