Clinical trial results:
Dual Antiplatelet Therapy to Inhibit Coronary Atherosclerosis and Myocardial Injury in Patients with Necrotic High-risk Coronary Plaque Disease

Summary

EudraCT number	2014-000952-26
Trial protocol	GB
Global end of trial date	03 April 2018

Results information

Result version number	v1 (current)
This version publication date	27 March 2019
First version publication date	27 March 2019

Trial information

Trial identification

Sponsor protocol code	14/SS/0089

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02110303
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh & NHS Lothian
Sponsor organisation address	Old College, South Bridge, Edinburgh, United Kingdom, EH8 9YL
Public contact	Professor David Newby, University of Edinburgh, d.e.newby@ed.ac.uk
Scientific contact	Professor David Newby, University of Edinburgh, d.e.newby@ed.ac.uk

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	31 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if ticagrelor (a blood thinning medication) reduces the levels of plasma high-sensitivity cardiac troponin I (a protein in the blood that is associated with increased risk of heart attacks in the future) in patients with stable heart disease but evidence of high-risk features on heart scans.

Protection of trial subjects:

This clinical trial was carried out with the approval of the national research ethics committee in accordance with the Declaration of Helsinki (2000), under a Clinical Trial Authorisation from the Medicine and Healthcare Products Regulatory Authority (MHRA, United Kingdom), and the written informed consent of all participants.

The CT and PET scans involved the administration of contrast 'dye' which can cause kidney problems or allergic reactions so patients who had significant kidney disease or a history of allergic reactions to contrast dye were excluded from the trial. The PET scan involved the administration of a injected radioactive tracer chemical (18F-NaF). This type of chemical tracer is routinely used in PET-CT scans and a well developed protocol was in place to minimise radiation exposure to the patient and to ensure safe handling and administration of the tracer. To avoid an excessive risk of bleeding patients who were already taking blood thinning medications other than aspirin (e.g. warfarin, clopidogrel) were excluded from the study. There is a small bleeding risk associated with taking ticagrelor so patients who were at high risk or had a history of serious bleeding problems were also excluded from the trial.

Background therapy:

All subjects in both arms were receiving aspirin on recruitment to the trial. They were mandated in the protocol to be maintained on aspirin 75 mg once daily during the trial and were also to be maintained on the maximally tolerated dose of statin. Subjects were encouraged to be maintained on maximally tolerated doses of angiotensin-converting enzyme inhibition and beta-blocker therapy as clinically indicated and in accordance with local guidelines.

Evidence for comparator:

A matched placebo comparator was used to ensure blinding in the trial and so avoid potential for systematic biases in outcome measures.

Actual start date of recruitment	13 March 2015
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	United Kingdom: 202
Worldwide total number of subjects	202
EEA total number of subjects	202

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)	79
From 65 to 84 years	123
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with stable coronary disease were recruited from Royal Infirmary of Edinburgh, Scotland. Recruitment to the study commenced on the 13th March 2015. The first participant was randomised on the 30th March 2015 and the last patient was randomised on 25th April 2017.

Pre-assignment

Screening details:

A total of 361 patients were approached to participate in the study and 220 were consented. The other 141 patients declined to participate, were ineligible, or were already taking part in another CTIMP. Eighteen of those who were consented subsequently changed their mind about participating or became ineligible, so 202 patients were randomised.

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, Monitor

Blinding implementation details:

A matched placebo comparator was supplied by the drug manufacturer to ensure the subject and clinical research team were blinded to the allocated treatment. An indication of treatment allocation could have potentially been apparent from the platelet-monocyte aggregate testing, so this testing was performed by an unblinded technician who was distinct from the clinical team and the results were not released to the research team until the end of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ticagrelor

Arm description:

Ticagrelor 90 mg tablet twice daily for 12 months

Arm type	Experimental
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	ATC Code: B01AC24
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 90 mg tablet twice daily for 12 months

Arm title	Placebo

Arm description:

Matched placebo tablet twice daily for 12 months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet twice daily for 12 months

Number of subjects in period 1	Ticagrelor	Placebo
Started	101	101
Completed	94	95
Not completed	7	6
Deceased	1	-
Consent withdrawn by subject	4	4
Physician decision	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Ticagrelor
Reporting group description:	
Ticagrelor 90 mg tablet twice daily for 12 months	
Reporting group title	Placebo
Reporting group description:	
Matched placebo tablet twice daily for 12 months	

Reporting group values	Ticagrelor	Placebo	Total
Number of subjects	101	101	202
Age categorical Units: Subjects			
18-64 years	41	38	79
65-84 years	60	63	123
Age continuous Units: years			
arithmetic mean	65.5	66.4	
standard deviation	± 8.3	± 8.1	-
Gender categorical Units: Subjects			
Female	20	20	40
Male	81	81	162
Increased coronary 18F-NaF uptake on PET-CT scan Units: Subjects			
Yes	63	65	128
No	38	36	74
Plasma high sensitivity cardiac troponin I concentration Units: ng/L			
median	3.5	3.0	
inter-quartile range (Q1-Q3)	2.0 to 6.0	1.7 to 6.0	-

Subject analysis sets	
Subject analysis set title	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects in sub-group of the per protocol population who had increased coronary 18F-NaF uptake on baseline PET-CT scan and received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.	
Subject analysis set title	Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects in sub-group of the per protocol population who had increased coronary 18F-NaF uptake on baseline PET-CT scan and received placebo. Per protocol population pre-specified as subjects with	

measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who did not have increased coronary 18F-NaF uptake on baseline PET-CT scan and received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who did not have increased coronary 18F-NaF uptake on baseline PET-CT scan and received placebo. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Ticagrelor (Per Protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in per protocol population who received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Placebo (Per Protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in per protocol population who received placebo. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Reporting group values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)
Number of subjects	59	61	35
Age categorical Units: Subjects			
18-64 years			
65-84 years			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female			
Male			

Increased coronary 18F-NaF uptake on PET-CT scan Units: Subjects			
Yes	59	61	0
No	0	0	35
Plasma high sensitivity cardiac troponin I concentration Units: ng/L			
median	4.0	4.0	2.6
inter-quartile range (Q1-Q3)	2.2 to 6.6	1.8 to 7.0	1.4 to 4.0

Reporting group values	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)	Ticagrelor (Per Protocol)	Placebo (Per Protocol)
Number of subjects	36	94	97
Age categorical Units: Subjects			
18-64 years		38	36
65-84 years		56	61
Age continuous Units: years			
arithmetic mean		65.5	66.3
standard deviation	±	± 8.4	± 8.1
Gender categorical Units: Subjects			
Female		20	19
Male		74	78
Increased coronary 18F-NaF uptake on PET-CT scan Units: Subjects			
Yes	0	59	61
No	36	35	36
Plasma high sensitivity cardiac troponin I concentration Units: ng/L			
median	2.2	3.5	3.0
inter-quartile range (Q1-Q3)	1.5 to 4.1	2.0 to 6.0	1.7 to 6.0

End points

End points reporting groups

Reporting group title	Ticagrelor

Reporting group description:

Ticagrelor 90 mg tablet twice daily for 12 months

Reporting group title	Placebo

Reporting group description:

Matched placebo tablet twice daily for 12 months

Subject analysis set title	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who had increased coronary 18F-NaF uptake on baseline PET-CT scan and received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who had increased coronary 18F-NaF uptake on baseline PET-CT scan and received placebo. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who did not have increased coronary 18F-NaF uptake on baseline PET-CT scan and received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from the pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in sub-group of the per protocol population who did not have increased coronary 18F-NaF uptake on baseline PET-CT scan and received placebo. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Ticagrelor (Per Protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in per protocol population who received ticagrelor. Per protocol population pre-specified as subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Subject analysis set title	Placebo (Per Protocol)
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects in per protocol population who received placebo. Per protocol population pre-specified as

subjects with measurement of plasma high sensitivity cardiac troponin I at 30 day visit and ≥80% compliance as calculated from pill count at 30 day visit. If a subject forgot to bring their pill bottles to 30 day visit then compliance was calculated from pill count at 3 month visit or based on other information and pill counts at subsequent visits.

Primary: Plasma high sensitivity cardiac troponin I concentration at 30 days

End point title	Plasma high sensitivity cardiac troponin I concentration at 30 days

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Primary

End point timeframe:

Concentration from blood sample at 30 day visit

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	59	61		
Units: ng/L				
geometric mean (standard deviation)	4.05 (± 2.50)	3.23 (± 2.94)		

Statistical analyses

Statistical analysis title	Troponin at 30 days (PP with 18F-NaF uptake)

Statistical analysis description:

General linear model for log transformed troponin concentrations at 30 days with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed values at 30 days.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.36

Secondary: Plasma high sensitivity cardiac troponin I concentration at 30 days	
End point title	Plasma high sensitivity cardiac troponin I concentration at 30 days

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Concentration from blood sample at 30 day visit

End point values	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)	Ticagrelor (Per Protocol)	Placebo (Per Protocol)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	35	36	94	97
Units: ng/L				
geometric mean (standard deviation)	2.43 (± 2.82)	2.31 (± 2.58)	3.35 (± 2.69)	2.85 (± 2.83)

Statistical analyses

Statistical analysis title	Troponin at 30 days (PP without 18F-NaF uptake)

Statistical analysis description:

general linear model for log transformed troponin concentrations at 30 days with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed values at 30 days.

Comparison groups	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake) v Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.31

Statistical analysis title	Troponin at 30 days (PP)

Statistical analysis description:

General linear model for log transformed troponin concentrations at 30 days with age, sex, log transformed troponin concentration, increased coronary 18F-NaF uptake, and treatment as covariates.

Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed values at 30 days.

Comparison groups	Ticagrelor (Per Protocol) v Placebo (Per Protocol)
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.37
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.26

Secondary: Area under plasma high sensitivity cardiac troponin I concentration curve over 1 year

End point title	Area under plasma high sensitivity cardiac troponin I concentration curve over 1 year

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Concentrations from blood samples at 30 day, 3 month, 6 month, 9 month, and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	33	35
Units: ng.year/L				
geometric mean (standard deviation)	3.93 (± 2.25)	4.16 (± 3.36)	2.46 (± 2.51)	2.31 (± 2.22)

End point values	Ticagrelor (Per Protocol)	Placebo (Per Protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	92		
Units: ng.year/L				
geometric mean (standard deviation)	3.31 (± 2.41)	3.33 (± 3.02)		

Statistical analyses

Statistical analysis title	AUC over 1 year (PP with 18F-NaF uptake)

Statistical analysis description:

General linear model for log transformed area under troponin concentration curve over 1 year with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed values of AUC.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.17

Statistical analysis title	AUC over 1 year (PP without 18F-NaF uptake)

Statistical analysis description:

General linear model for log transformed area under troponin concentration curve over 1 year with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed values of AUC.

Comparison groups	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake) v Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.28

Statistical analysis title	AUC over 1 year (PP)

Statistical analysis description:

General linear model for log transformed area under troponin concentration curve over 1 year with age, sex, log transformed baseline troponin concentration, increased coronary 18F-NaF uptake, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log

transformed values of AUC.

Comparison groups	Ticagrelor (Per Protocol) v Placebo (Per Protocol)
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.13

Secondary: Ratio of total calcium mass in coronary arteries at 1 year to baseline

End point title	Ratio of total calcium mass in coronary arteries at 1 year to baseline

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Calcium mass from CT scans at baseline and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake)	Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	55	33	34
Units: Ratio				
geometric mean (standard deviation)	1.22 (± 1.23)	1.29 (± 1.24)	1.29 (± 1.42)	1.45 (± 1.62)

Statistical analyses

Statistical analysis title	Total calcium mass (PP with 18F-NaF uptake)

Statistical analysis description:

General linear model for log transformed ratio of mass at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.02

Statistical analysis title	Total calcium mass (PP without 18F-NaF uptake)

Statistical analysis description:

General linear model for log transformed ratio of mass at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol Without Coronary 18F-NaF Uptake) v Placebo (Per Protocol Without Coronary 18F-NaF Uptake)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.09

Secondary: Ratio of calcium mass at 1 year to baseline in coronary artery segment with increased 18F-NaF uptake at baseline

End point title	Ratio of calcium mass at 1 year to baseline in coronary artery segment with increased 18F-NaF uptake at baseline

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Calcium mass from CT scans at baseline and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	54		
Units: Ratio				
geometric mean (standard deviation)	1.55 (± 1.40)	1.68 (± 1.78)		

Statistical analyses

Statistical analysis title	Calcium mass in segment with 18F-NaF uptake

Statistical analysis description:

General linear model for log transformed ratio of mass at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.11

Secondary: Ratio of calcium mass at 1 year to baseline in coronary artery segment without increased 18F-NaF uptake at baseline

End point title	Ratio of calcium mass at 1 year to baseline in coronary artery segment without increased 18F-NaF uptake at baseline

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Calcium mass on CT scans at baseline and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	53		
Units: Ratio				
geometric mean (standard deviation)	1.10 (± 1.48)	1.09 (± 1.57)		

Statistical analyses

Statistical analysis title	Calcium mass in segment without 18F-NaF uptake

Statistical analysis description:

General linear model for log transformed ratio of mass at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.95
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.18

Secondary: Ratio of calcium volume at 1 year to baseline in coronary artery segment with increased 18F-NaF uptake at baseline

End point title	Ratio of calcium volume at 1 year to baseline in coronary artery segment with increased 18F-NaF uptake at baseline

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Calcium volume from CT scans at baseline and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	54		
Units: Ratio				
geometric mean (standard deviation)	1.47 (± 1.39)	1.59 (± 1.69)		

Statistical analyses

Statistical analysis title	Calcium volume in segment with 18F-NaF uptake

Statistical analysis description:

General linear model for log transformed ratio of volume at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.08

Secondary: Ratio of calcium volume at 1 year to baseline in coronary artery segment without increased 18F-NaF uptake at baseline

End point title	Ratio of calcium volume at 1 year to baseline in coronary artery segment without increased 18F-NaF uptake at baseline

End point description:

Measure of dispersion reported below is actually geometric standard deviation rather than standard deviation.

End point type	Secondary

End point timeframe:

Calcium volume from CT scans at baseline and 12 month visits

End point values	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake)	Placebo (Per Protocol With Coronary 18F-NaF Uptake)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	53		
Units: Ratio				
geometric mean (standard deviation)	1.08 (± 1.44)	1.05 (± 1.53)		

Statistical analyses

Statistical analysis title	Calcium volume in segment without 18F-NaF uptake

Statistical analysis description:

General linear model for log transformed ratio of volume at 1 year to baseline with age, sex, log transformed baseline troponin concentration, and treatment as covariates. Estimate of ratio of geometric means (ticagrelor divided by placebo) and 95% confidence limits obtained by exponentiation of difference in means and confidence limits for log transformed ratio.

Comparison groups	Ticagrelor (Per Protocol With Coronary 18F-NaF Uptake) v Placebo (Per Protocol With Coronary 18F-NaF Uptake)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 77
Method	ANCOVA
Parameter estimate	Ratio of geometric means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred from consent until the last study visit were reported on the case report forms, but only those which started after randomisation have been included in these results.

Adverse event reporting additional description:

Subjects were asked about the occurrence of AEs at each study visit through open-ended and non-leading verbal questioning. Any AEs which were identified via information from support departments, e.g. safety blood results, were also reported. All reported AEs were followed up until resolution of the event or until no longer medically indicated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Ticagrelor (Safety)

Reporting group description:

Subjects who received any ticagrelor study medication, regardless of the group they were originally allocated to.

Reporting group title	Placebo (Safety)

Reporting group description:

Subjects who received some study medication but this was all placebo, regardless of the group they were originally allocated to.

Serious adverse events	Ticagrelor (Safety)	Placebo (Safety)	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 100 (7.00%)	12 / 101 (11.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
All vascular disorders			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
All cardiac disorders			
subjects affected / exposed	4 / 100 (4.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
All surgical and medical procedures			

subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
All general disorders and administration site conditions			
subjects affected / exposed	0 / 100 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
All gastrointestinal disorders			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
All hepatobiliary disorders			
subjects affected / exposed	0 / 100 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
All respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	0 / 100 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
All psychiatric disorders			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
All musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 100 (1.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
All infections and infestations			
subjects affected / exposed	2 / 100 (2.00%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ticagrelor (Safety)	Placebo (Safety)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 100 (86.00%)	75 / 101 (74.26%)	
Vascular disorders			
All vascular disorders			
subjects affected / exposed	2 / 100 (2.00%)	3 / 101 (2.97%)	
occurrences (all)	2	3	
Surgical and medical procedures			
All surgical and medical procedures			
subjects affected / exposed	6 / 100 (6.00%)	2 / 101 (1.98%)	
occurrences (all)	7	2	
General disorders and administration site conditions			
All general disorders and administrative site conditions			
subjects affected / exposed	10 / 100 (10.00%)	13 / 101 (12.87%)	
occurrences (all)	12	14	
Reproductive system and breast disorders			
All reproductive system and breast disorders			
subjects affected / exposed	2 / 100 (2.00%)	1 / 101 (0.99%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
All respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	34 / 100 (34.00%)	11 / 101 (10.89%)	
occurrences (all)	43	11	
Investigations			
All investigations			
subjects affected / exposed	3 / 100 (3.00%)	1 / 101 (0.99%)	
occurrences (all)	3	1	

Injury, poisoning and procedural complications			
All injury, poisoning and procedural complications			
subjects affected / exposed	61 / 100 (61.00%)	14 / 101 (13.86%)	
occurrences (all)	79	15	
Cardiac disorders			
All cardiac disorders			
subjects affected / exposed	4 / 100 (4.00%)	8 / 101 (7.92%)	
occurrences (all)	4	9	
Nervous system disorders			
All nervous system disorders			
subjects affected / exposed	3 / 100 (3.00%)	10 / 101 (9.90%)	
occurrences (all)	3	12	
Blood and lymphatic system disorders			
All blood and lymphatic system disorders			
subjects affected / exposed	2 / 100 (2.00%)	2 / 101 (1.98%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
All ear and labyrinth disorders			
subjects affected / exposed	1 / 100 (1.00%)	2 / 101 (1.98%)	
occurrences (all)	1	2	
Eye disorders			
All eye disorders			
subjects affected / exposed	3 / 100 (3.00%)	1 / 101 (0.99%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
All gastrointestinal disorders			
subjects affected / exposed	18 / 100 (18.00%)	14 / 101 (13.86%)	
occurrences (all)	20	15	
Skin and subcutaneous tissue disorders			
All skin and subcutaneous tissue disorders			
subjects affected / exposed	6 / 100 (6.00%)	5 / 101 (4.95%)	
occurrences (all)	6	5	
Renal and urinary disorders			
All renal and urinary disorders			
subjects affected / exposed	4 / 100 (4.00%)	2 / 101 (1.98%)	
occurrences (all)	4	2	
Musculoskeletal and connective tissue			

disorders			
All musculoskeletal and connective tissue disorders			
subjects affected / exposed	11 / 100 (11.00%)	11 / 101 (10.89%)	
occurrences (all)	13	11	
Infections and infestations			
All infections and infestations			
subjects affected / exposed	30 / 100 (30.00%)	26 / 101 (25.74%)	
occurrences (all)	35	33	
Metabolism and nutrition disorders			
All metabolism and nutrition disorders			
subjects affected / exposed	3 / 100 (3.00%)	7 / 101 (6.93%)	
occurrences (all)	3	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2016	Substantial Amendment 5: The Ticagrelor SPC was updated on 18 February 2016 to include new information from a large clinical trial involving the use of ticagrelor in patients with a history of prior myocardial infarction. The changes to the SPC resulted in an update to the reference safety information for the DIAMOND study. The study protocol was updated to remove the SPC link from Appendix 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported