Clinical trial results:
Anti-platelet Therapy in the Primary Prevention of Cardiovascular Disease in Patients with Chronic Obstructive Pulmonary Disease.

Summary

EudraCT number	2014-005475-86
Trial protocol	GB
Global end of trial date	10 November 2017

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	7356

Additional study identifiers

ISRCTN number	ISRCTN43245574
ClinicalTrials.gov id (NCT number)	NCT03487406
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Level 1, Regent Point, Gosforth, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Newcastle Clinical Trials Unit, Newcastle University, 44 (0)191 2083820 ,
Scientific contact	Newcastle Clinical Trials Unit, Newcastle University, 44 (0)191 2083820 ,

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	18 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2017
Global end of trial reached?	Yes
Global end of trial date	10 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish if treatment with blood thinning medications such as Aspirin and Ticagrelor in patients with a lung condition called chronic obstructive pulmonary disease (COPD) who are predicted to be at an increased risk of heart disease or heart attacks, will affect the function of the blood cells called platelets. This will be measured using a bedside Multiplate platelet function test.

Protection of trial subjects:

Follow-up of participants and 1, 3 and 6 months and collection of adverse events. A Trial Oversight Committee monitored efficacy and safety endpoints and had access to unblinded study data.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 120
Worldwide total number of subjects	120
EEA total number of subjects	120

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)	43
From 65 to 84 years	74
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Start date (open to recruitment): 4th September 2015. First randomisation: 4th November 2015. Last randomisation: 4th May 2017. Last patient completed 6 month visit: 1st November 2017. End of trial: 10th November 2017

Pre-assignment

Screening details:

Participants eligible for screening into this study must have had a recorded clinical diagnosis of COPD as follows:

1. Abnormal spirometry with FEV1<80% and FEV1/FVC ratio <70% of predicted
2. Smoking history that is 10-pack years or greater (current or ex-smokers can be included)
3. Have capacity to consent.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

For purposes of blinding, placebo to match Brilique (Ticagrelor) and Aspirin tablets were manufactured.

Arms

Are arms mutually exclusive?	Yes
Arm title	Aspirin

Arm description: -

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

Dosage and administration details:

One 75mg tablet once daily

Investigational medicinal product name	Placebo (Ticagrelor)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet twice daily

Arm title	Ticagrelor

Arm description: -

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

Dosage and administration details: 90mg twice daily	
Investigational medicinal product name	Placebo (Aspirin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet daily	
Arm title	DAPT
Arm description: Dual Antiplatelet Therapy	
Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One 75mg tablet once daily	
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	Brilique
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 90mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo (Ticagrelor)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet twice daily	
Investigational medicinal product name	Placebo (Aspirin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet daily	

Number of subjects in period 1	Aspirin	Ticagrelor	DAPT
Started	31	29	29
Completed	31	29	29

Number of subjects in period 1	Placebo
Started	31
Completed	31

Period 2	
Period 2 title	6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Arms	
Are arms mutually exclusive?	Yes
Arm title	Aspirin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One 75mg tablet once daily	
Investigational medicinal product name	Placebo (Ticagrelor)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet twice daily	
Arm title	Ticagrelor
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	Brilique
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 90mg twice daily	
Investigational medicinal product name	Placebo (Aspirin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet daily	
Arm title	DAPT
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One 75mg tablet once daily	
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	Brilique
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 90mg twice daily	
Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo (Ticagrelor)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet twice daily	
Investigational medicinal product name	Placebo (Aspirin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: One tablet daily	

Number of subjects in period 2	Aspirin	Ticagrelor	DAPT
Started	31	29	29
Completed	31	29	29

Number of subjects in period 2	Placebo
Started	31
Completed	31

Baseline characteristics

Reporting groups	
Reporting group title	Aspirin
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	DAPT
Reporting group description: Dual Antiplatelet Therapy	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Aspirin	Ticagrelor	DAPT
Number of subjects	31	29	29
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	68.5	66.5	69.0
standard deviation	± 7.2	± 7.7	± 10.6
Gender categorical Units: Subjects			
Female	19	14	14
Male	12	15	15
Smoking status Units: Subjects			
Non-smoker	0	0	0
Ex-smoker	20	21	21
Light smoker (<10)	0	1	3
Moderate smoker (10-19)	9	5	4
Heavy smoker (20 or over)	2	2	1
Diabetes status Units: Subjects			
Type 1	0	2	3
Type 2	3	2	3
No diabetes	28	25	23

Angina or heart attack in a 1st degree relative <60? Units: Subjects			
Yes	6	7	9
No	25	22	20
On blood pressure treatment? Units: Subjects			
Yes	9	12	13
No	22	17	16
Rheumatoid arthritis? Units: Subjects			
Yes	1	3	1
No	30	26	28
COPD disease category*			
*NICE Clinical Guideline (June 2010)			
Units: Subjects			
Severe (<30% FEV1 predicted)	6	6	5
Moderate (30-49% FEV1 predicted)	14	7	11
Mild (50-79% FEV1 predicted)	11	16	13
Not recorded	0	0	0
Daily sputum produced >3 months in each of last 2 years Units: Subjects			
Yes	15	18	15
No	16	11	14
SCRQ-C Current Health Units: Subjects			
Very good	0	0	0
Good	5	10	8
Fair	18	12	14
Poor	7	6	6
Very Poor	0	1	1
Missing	1	0	0
QRISK2 Score Units: Scale Score			
median	19	22	24
inter-quartile range (Q1-Q3)	17 to 27	14 to 27	20 to 35
Cholesterol/HDL ratio Units: Ratio			
median	2.8	3.0	3.1
inter-quartile range (Q1-Q3)	2.4 to 4.1	2.6 to 3.6	2.4 to 3.6
Systolic blood pressure Units: mmHg			
arithmetic mean	144.6	143.1	144.5
standard deviation	± 18.2	± 14.7	± 22.1
Height Units: cm			
arithmetic mean	163.0	164.6	166.9
standard deviation	± 10.5	± 11.3	± 10.9
Weight Units: kg			
arithmetic mean	73.1	72.2	79.9

standard deviation	± 17.4	± 18.7	± 18.5
BMI			
Units: Kg/m2			
arithmetic mean	27.4	26.5	28.9
standard deviation	± 5.6	± 5.7	± 7.0
Number of acute exacerbations of COPD treated in last 12 months			
Units: Number			
arithmetic mean	3.4	2.6	2.5
standard deviation	± 3.1	± 3.1	± 2.0
Number of hospitalisations in last 12 months for COPD			
Units: Number			
arithmetic mean	0.4	0.4	0.2
standard deviation	± 1.6	± 0.9	± 1.0
Haemoglobin			
Units: G/100ml			
arithmetic mean	145.4	146.1	141.8
standard deviation	± 14.5	± 13.0	± 16.6
White blood cell count			
Units: 10^9/L			
arithmetic mean	8.6	8.8	8.3
standard deviation	± 2.3	± 2.2	± 1.9
Platelet count			
Units: 10^9/L			
arithmetic mean	280.6	284.9	281.6
standard deviation	± 61.0	± 65.7	± 71.8
Neutrophil count			
Units: 10^9/L			
arithmetic mean	5.6	5.6	5.3
standard deviation	± 2.0	± 1.8	± 1.8
Monocytes			
Units: 10^9/L			
arithmetic mean	0.64	0.7	0.67
standard deviation	± 0.21	± 0.19	± 0.23
Eosinophil count			
Units: 10^9/L			
arithmetic mean	0.2	0.18	0.24
standard deviation	± 0.15	± 0.12	± 0.19
Urea			
Units: mmol/L			
arithmetic mean	5.4	5.0	5.9
standard deviation	± 2.1	± 2.3	± 1.8
Creatinine			
Units: umol/L			
arithmetic mean	71.4	76.1	86.9
standard deviation	± 14.0	± 20.0	± 19.2
Fibrinogen			
Units: g/l			
arithmetic mean	3.7	3.9	3.7
standard deviation	± 0.7	± 0.8	± 0.9
hs CRP			

Units: mg/l			
arithmetic mean	3.6	8.2	3.8
standard deviation	± 3.5	± 16.5	± 3.8
TNF alpha			
Units: pg/ml			
arithmetic mean	2.35	1.52	1.44
standard deviation	± 2.59	± 1.23	± 1.50
IL6			
Units: pg/ml			
arithmetic mean	5.96	3.82	3.39
standard deviation	± 6.18	± 3.04	± 1.61
MPO			
Units: ng/ml			
arithmetic mean	1013.17	785.53	702.53
standard deviation	± 578.5	± 453.5	± 324.3
Vascular stiffness			
Units: m/s			
arithmetic mean	9.91	9.23	9.87
standard deviation	± 2.49	± 1.23	± 2.58
CIMT maximum			
Units: mm			
arithmetic mean	1.0	1.0	1.0
standard deviation	± 0.3	± 0.2	± 0.2
MRC dyspnoea scale			
Scale score 1 - 5			
Units: Scale score			
arithmetic mean	3.7	3.4	3.3
standard deviation	± 1.1	± 1.3	± 1.2
EQ5D 5L Index			
Units: Scale score			
arithmetic mean	0.676	0.662	0.675
standard deviation	± 0.222	± 0.221	± 0.253
EQ5D Health Score			
Units: Scale score			
arithmetic mean	59.3	66.6	60.9
standard deviation	± 16.6	± 18.1	± 17.5
SGRQ-C Symptom score			
Units: Scale score			
arithmetic mean	72.3	60.2	67.3
standard deviation	± 18.4	± 24.8	± 19.7
SGRQ-C Activity score			
Units: Scale score			
arithmetic mean	74.8	67.7	62.8
standard deviation	± 24.6	± 24.2	± 30.8
SGRQ-C Impact score			
Units: Scale score			
arithmetic mean	42.5	40.0	42.2
standard deviation	± 20.1	± 25.2	± 27.2
SGRQ-C total			
Units: Scale score			
arithmetic mean	57.7	53.0	53.0
standard deviation	± 19.1	± 21.8	± 25.2

Reporting group values	Placebo	Total	
Number of subjects	31	120	
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			
Age at randomisation			
Units: years			
arithmetic mean	66.3		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	16	63	
Male	15	57	
Smoking status Units: Subjects			
Non-smoker	0	0	
Ex-smoker	21	83	
Light smoker (<10)	3	7	
Moderate smoker (10-19)	5	23	
Heavy smoker (20 or over)	2	7	
Diabetes status Units: Subjects			
Type 1	0	5	
Type 2	2	10	
No diabetes	29	105	
Angina or heart attack in a 1st degree relative <60? Units: Subjects			
Yes	10	32	
No	21	88	
On blood pressure treatment? Units: Subjects			
Yes	10	44	
No	21	76	
Rheumatoid arthritis? Units: Subjects			
Yes	0	5	
No	31	115	
COPD disease category*			
*NICE Clinical Guideline (June 2010)			

Units: Subjects			
Severe (<30% FEV1 predicted)	8	25	
Moderate (30-49% FEV1 predicted)	10	42	
Mild (50-79% FEV1 predicted)	12	52	
Not recorded	1	1	
Daily sputum produced >3 months in each of last 2 years Units: Subjects			
Yes	22	70	
No	9	50	
SCRQ-C Current Health Units: Subjects			
Very good	2	2	
Good	4	27	
Fair	18	62	
Poor	4	23	
Very Poor	3	5	
Missing	0	1	
QRISK2 Score Units: Scale Score			
median	20		
inter-quartile range (Q1-Q3)	12 to 28	-	
Cholesterol/HDL ratio Units: Ratio			
median	3.0		
inter-quartile range (Q1-Q3)	2.2 to 4.0	-	
Systolic blood pressure Units: mmHg			
arithmetic mean	145.7		
standard deviation	± 16.1	-	
Height Units: cm			
arithmetic mean	167.5		
standard deviation	± 9.9	-	
Weight Units: kg			
arithmetic mean	74.7		
standard deviation	± 18.2	-	
BMI Units: Kg/m2			
arithmetic mean	26.5		
standard deviation	± 5.4	-	
Number of acute exacerbations of COPD treated in last 12 months Units: Number			
arithmetic mean	4.2		
standard deviation	± 4.5	-	
Number of hospitalisations in last 12 months for COPD Units: Number			
arithmetic mean	0.6		
standard deviation	± 1.2	-	

Haemoglobin Units: G/100ml arithmetic mean standard deviation	 146.4 ± 13.3	 -	
White blood cell count Units: 10^9/L arithmetic mean standard deviation	 8.6 ± 2.6	 -	
Platelet count Units: 10^9/L arithmetic mean standard deviation	 284.3 ± 77.2	 -	
Neutrophil count Units: 10^9/L arithmetic mean standard deviation	 5.7 ± 2.3	 -	
Monocytes Units: 10^9/L arithmetic mean standard deviation	 0.73 ± 0.42	 -	
Eosinophil count Units: 10^9/L arithmetic mean standard deviation	 0.24 ± 0.17	 -	
Urea Units: mmol/L arithmetic mean standard deviation	 4.7 ± 1.2	 -	
Creatinine Units: umol/L arithmetic mean standard deviation	 76.1 ± 14.9	 -	
Fibrinogen Units: g/l arithmetic mean standard deviation	 3.9 ± 0.8	 -	
hs CRP Units: mg/l arithmetic mean standard deviation	 7.8 ± 15.4	 -	
TNF alpha Units: pg/ml arithmetic mean standard deviation	 2.38 ± 2.73	 -	
IL6 Units: pg/ml arithmetic mean standard deviation	 5.81 ± 5.64	 -	
MPO Units: ng/ml arithmetic mean standard deviation	 814.38 ± 480.4	 -	

Vascular stiffness Units: m/s arithmetic mean standard deviation	 9.74 ± 1.90	 -	
CIMT maximum Units: mm arithmetic mean standard deviation	 1.0 ± 0.2	 -	
MRC dyspnoea scale			
Scale score 1 - 5			
Units: Scale score arithmetic mean standard deviation	 3.6 ± 1.0	 -	
EQ5D 5L Index Units: Scale score arithmetic mean standard deviation	 0.619 ± 0.261	 -	
EQ5D Health Score Units: Scale score arithmetic mean standard deviation	 61.8 ± 20.4	 -	
SGRQ-C Symptom score Units: Scale score arithmetic mean standard deviation	 73.6 ± 22.2	 -	
SGRQ-C Activity score Units: Scale score arithmetic mean standard deviation	 74.2 ± 27.3	 -	
SGRQ-C Impact score Units: Scale score arithmetic mean standard deviation	 45.2 ± 26.7	 -	
SGRQ-C total Units: Scale score arithmetic mean standard deviation	 59.1 ± 23.9	 -	

End points

End points reporting groups

Reporting group title	Aspirin
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	DAPT
Reporting group description: Dual Antiplatelet Therapy	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Aspirin
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	DAPT
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at baseline and 6 months for the ITT analysis set.	
Subject analysis set title	No Aspirin
Subject analysis set type	Intention-to-treat
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at baseline and 6 months for the ITT analysis set.	
Subject analysis set title	Ticagrelor
Subject analysis set type	Intention-to-treat
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at baseline and 6 months for the ITT analysis set.	
Subject analysis set title	No Ticagrelor
Subject analysis set type	Intention-to-treat
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at baseline and 6 months for the ITT analysis set.	
Subject analysis set title	Aspirin (PP)
Subject analysis set type	Per protocol
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at 6 months for the PP analysis set.	
Subject analysis set title	No Aspirin (PP)
Subject analysis set type	Per protocol
Subject analysis set description: Descriptive statistics for the primary outcome of response for the comparative groups at 6 months for the PP analysis set.	
Subject analysis set title	Ticagrelor (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Descriptive statistics for the primary outcome of response for the comparative groups at 6 months for the PP analysis set.

Subject analysis set title	No Ticagrelor (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

Descriptive statistics for the primary outcome of response for the comparative groups at 6 months for the PP analysis set.

Primary: Response in platelet function (ITT analysis set)

End point title	Response in platelet function (ITT analysis set)[1]

End point description:

Inhibition of ASPI and adenosine diphosphate (ADP)-induced platelet aggregation at baseline, reported according to the 2x2 factorial comparative groups.
Note that response is ASPI response in the Aspirin and No Aspirin columns and ADP response in the Ticagrelor and No Ticagrelor columns.
Response is reported as a percentage with the 95% CI.

End point type	Primary

End point timeframe:

Baseline

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a proof of concept study and the primary analysis is according to the Fleming A' Hern design. In the Aspirin group the number of responders (29) did not reach the critical threshold of 44 responders required to warrant further research. In the ticagrelor group, there were 24 ADP responders. This rate is lower than anticipated and did not reach the threshold to warrant further research.

End point values	Aspirin	No Aspirin	Ticagrelor	No Ticagrelor
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	58	62
Units: percent				
number (confidence interval 95%)	1.7 (0.2 to 11.3)	10 (4.5 to 20.8)	6.9 (2.6 to 17.3)	1.6 (0.2 to 10.9)

Statistical analyses

No statistical analyses for this end point

Primary: Response in platelet function (ITT analysis set)

End point title	Response in platelet function (ITT analysis set)[2]

End point description:

Inhibition of ASPI and adenosine diphosphate (ADP)-induced platelet aggregation at 6-months, reported according to the 2x2 factorial comparative groups.
Note that response is ASPI response in the Aspirin and No Aspirin columns and ADP response in the Ticagrelor and No Ticagrelor columns.
Response is reported as a percentage with the 95% CI.

End point type	Primary

End point timeframe:

6 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a proof of concept study and the primary analysis is descriptive.

End point values	Aspirin	No Aspirin	Ticagrelor	No Ticagrelor
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	58	62
Units: percent				
number (confidence interval 95%)	48.3 (35.8 to 61)	11.7 (5.6 to 22.8)	41.4 (29.3 to 54.6)	3.2 (0.8 to 12.3)

Statistical analyses

No statistical analyses for this end point

Primary: Response in platelet function (PP analysis set)

End point title	Response in platelet function (PP analysis set)[3]

End point description:

Descriptive statistics for the primary outcome of response for the comparative groups at 6 months for the per protocol analysis set.
Response is reported as a percentage with the 95% CI.

End point type	Primary

End point timeframe:

6 months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a proof of concept study and the primary analysis is descriptive.

End point values	Aspirin (PP)	No Aspirin (PP)	Ticagrelor (PP)	No Ticagrelor (PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	41	45	32	54
Units: percent				
number (confidence interval 95%)	68.3 (52.3 to 80.9)	15.6 (7.5 to 29.6)	68.8 (50.4 to 82.6)	3.7 (0.9 to 14.0)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1. All non-serious adverse reactions will be recorded at 6-month follow-up
2. Any serious adverse events will be recorded throughout the duration of the trial until 4 weeks after trial therapy is stopped

Assessment type	Systematic

Dictionary used

Dictionary name	Study protocol
Dictionary version	5.0

Reporting groups

Reporting group title	Aspirin
Reporting group description: -	
Reporting group title	Ticagrelor
Reporting group description: -	
Reporting group title	DAPT
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Aspirin	Ticagrelor	DAPT
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)	5 / 29 (17.24%)	5 / 29 (17.24%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall/Head injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
atrial fibrillation with fast ventricular response			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stable angina			

subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Perforation of sigmoid colon			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper GI bleed			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Exacerbation of Bronchiectasis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exacerbation of COPD			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	2 / 29 (6.90%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of COPD			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left lower lobe collapse	Additional description: breathlessness		
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia and pleurisy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right sided pneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected lung malignancy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bilateral ankle fractures			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fracture neck and left femur			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 31 (19.35%)		
number of deaths (all causes)	1		

number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall/Head injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
atrial fibrillation with fast ventricular response			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stable angina			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Perforation of sigmoid colon			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper GI bleed			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Exacerbation of Bronchiectasis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Exacerbation of COPD				
subjects affected / exposed	4 / 31 (12.90%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of COPD				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left lower lobe collapse	Additional description: breathlessness			
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia and pleurisy				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right sided pneumonia				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Suspected lung malignancy				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary tract infection				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue				

disorders			
Bilateral ankle fractures			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
fracture neck and left femur			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Aspirin	Ticagrelor	DAPT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 31 (54.84%)	18 / 29 (62.07%)	21 / 29 (72.41%)
Injury, poisoning and procedural complications			
Fall - Rotator Cuff Injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 29 (3.45%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Exacerbation of COPD			
subjects affected / exposed	14 / 31 (45.16%)	13 / 29 (44.83%)	5 / 29 (17.24%)
occurrences (all)	19	24	6
Exacerbation of Bronchiectasis			

subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Worsening breathlessness			
subjects affected / exposed	1 / 31 (3.23%)	5 / 29 (17.24%)	4 / 29 (13.79%)
occurrences (all)	1	5	4
Skin and subcutaneous tissue disorders			
Bruising			
subjects affected / exposed	0 / 31 (0.00%)	4 / 29 (13.79%)	4 / 29 (13.79%)
occurrences (all)	0	4	6
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	0 / 29 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 31 (45.16%)		
Injury, poisoning and procedural complications			
Fall - Rotator Cuff Injury			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Exacerbation of COPD subjects affected / exposed occurrences (all)	11 / 31 (35.48%) 16		
Exacerbation of Bronchiectasis subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 2		
Worsening breathlessness subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Skin and subcutaneous tissue disorders Bruising subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Infections and infestations Cellulitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2015	A change to the recruitment strategy, allowing PICs to help identify potentially eligible patients for study participation, along with minor amendments to the protocol and updated investigators brochure.
23 June 2016	This amendment concerned changes to the protocol, PIS and ICF in relation to broadening the eligibility criteria. This resulted in the randomisation of all eligible patients to receive treatment with the IMP and / or placebo regardless of their QRISK2 scores, removing the observational arm of the study. In addition as a result of the removal of the observational arm, the recruitment target was reduced from 240 to 120 patients.
17 November 2016	Removal of the QRISK2 score as a stratifying variable. Achange to the method of how SAEs will be reported to the funder. Extension of the originally planned end date from 01/12/2017 to 20/12/2018.
02 October 2017	This amendment was submitted in order to discontinue the 12 month follow-up, make administrative changes to the protocol, change the safety reporting, and inform of staffing changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported