Clinical trial results:
Study of the Effect of Ticagrelor and Clopidogrel on the Immune Response of Healthy Volunteers

Summary

EudraCT number	2012-005514-18
Trial protocol	GB
Global end of trial date	10 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 October 2022
First version publication date	14 October 2022
Summary attachment (see zip file)	End of Trial Report (2012-005514-18 Final Report for REC and MHRA[1].pdf)

Trial information

Trial identification

Sponsor protocol code	STH17062

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01846559
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Trust Headquarters, 8 Beech Hill Road, Sheffield, United Kingdom, S10 2SB
Public contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net
Scientific contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net

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	10 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2014
Global end of trial reached?	Yes
Global end of trial date	10 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Do the anti-clotting medications, ticagrelor and clopidogrel, also have an effect on the immune response?

Protection of trial subjects:

Careful monitoring with prompt appropriate treatment for symptoms caused by endotoxaemia e.g. nausea or pain.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 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	United Kingdom: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

44 healthy volunteers consented and screened, of which 30 proceeded to randomisation and are therefore included in this report.

Pre-assignment

Screening details:

Healthy volunteers were recruited by local advertising using approved posters and email wording. Eligibility criteria was as follows: aged between 18- 65 years, non smokers, BMI 18- 28, body weight 60-100 kg, in good health, providing informed consent, females not of child bearing potential. Screen fails did not meet the above criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	No study medication

Arm description:

No study medication

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Ticagrelor

Arm description:

Loading dose of ticagrelor 180 mg on day 1 followed by ticagrelor 90 mg BD for 6 days prior to endotoxin injection.

Arm type	Experimental
Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	274693-27-5
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

180 mg loading dose of ticagrelor on d1 followed by 90 mg BD for the following 6 days.

Arm title	Clopidogrel

Arm description:

300 mg loading dose of clopidogrel on day 1 followed by 6 days of 75 mg clopidogrel OD

Arm type	Experimental
Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	113665-84-2
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loading dose of 300 mg clopidogrel on day 1 followed by 6 days of clopidogrel 75 mg OD

Number of subjects in period 1	No study medication	Ticagrelor	Clopidogrel
Started	10	10	10
Screening	10	10	10
Randomisation	10	10	10
IMP administration	10	10	10
Completed	10	10	10

Baseline characteristics

Reporting groups	
Reporting group title	No study medication
Reporting group description:	
No study medication	
Reporting group title	Ticagrelor
Reporting group description:	
Loading dose of ticagrelor 180 mg on day 1 followed by ticagrelor 90 mg BD for 6 days prior to endotoxin injection.	
Reporting group title	Clopidogrel
Reporting group description:	
300 mg loading dose of clopidogrel on day 1 followed by 6 days of 75 mg clopidogrel OD	

Reporting group values	No study medication	Ticagrelor	Clopidogrel
Number of subjects	10	10	10
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)	10	10	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	10	10	10

Reporting group values	Total		
Number of subjects	30		
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)	30		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	0		
Male	30		

Subject analysis sets

Subject analysis set title	Randomised Participants
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised participants

Reporting group values	Randomised Participants		
Number of subjects	30		
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)	30		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	0		
Male	30		

End points

End points reporting groups

Reporting group title	No study medication
Reporting group description:	
No study medication	
Reporting group title	Ticagrelor
Reporting group description:	
Loading dose of ticagrelor 180 mg on day 1 followed by ticagrelor 90 mg BD for 6 days prior to endotoxin injection.	
Reporting group title	Clopidogrel
Reporting group description:	
300 mg loading dose of clopidogrel on day 1 followed by 6 days of 75 mg clopidogrel OD	
Subject analysis set title	Randomised Participants
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised participants	

Primary: TNF alpha

End point title	TNF alpha
End point description:	
End point type	Primary
End point timeframe:	
Measured at 2 hours post endotoxin administration.	

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/ml				
arithmetic mean (standard error)	107.7 (± 27.8)	41.9 (± 16.3)	43.0 (± 11.9)	

Statistical analyses

Statistical analysis title	Dunnetts test
Statistical analysis description:	
Multiple comparison between groups at 2 hours post endotoxin administration.	
Comparison groups	No study medication v Ticagrelor
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0001
Method	Dunnetts test
Parameter estimate	Mean difference (final values)
Point estimate	-65.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.59
upper limit	-44.02
Variability estimate	Standard error of the mean

Secondary: High sensitivity C-reactive protein

End point title	High sensitivity C-reactive protein

End point description:

End point type	Secondary

End point timeframe:

24 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: mg/L				
arithmetic mean (standard deviation)	32.7 (± 13.9)	27.6 (± 4.3)	28.3 (± 10.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Leucocyte count

End point title	Leucocyte count

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: x10^9/L				
arithmetic mean (standard deviation)	5.9 (± 1.1)	8.5 (± 3.6)	7.6 (± 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Neutrophil count

End point title	Neutrophil count

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: x10^9/L				
arithmetic mean (standard deviation)	5.2 (± 1.3)	7.6 (± 3.5)	6.7 (± 2.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet count

End point title	Platelet count

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: x10^9/L				
arithmetic mean (standard deviation)	198.6 (± 31.1)	209.4 (± 47.7)	203.5 (± 29.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Monocyte count

End point title	Monocyte count

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: x10^9/L				
arithmetic mean (standard deviation)	0.03 (± 0.01)	0.05 (± 0.03)	0.04 (± 0.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: Macrophage chemoattractant protein 1

End point title	Macrophage chemoattractant protein 1

End point description:

End point type	Secondary

End point timeframe:

4 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/mL				
arithmetic mean (standard deviation)	4934.5 (± 1938.7)	3043.2 (± 2027.8)	4023.6 (± 2775.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Granulocyte colony stimulating factor

End point title	Granulocyte colony stimulating factor

End point description:

End point type	Secondary

End point timeframe:

4 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/mL				
arithmetic mean (standard deviation)	102.1 (± 28.2)	55.6 (± 15.0)	83.8 (± 20.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Interleukin-10

End point title	Interleukin-10

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/mL				
arithmetic mean (standard deviation)	20.3 (± 20.9)	31.9 (± 44.0)	22.8 (± 10.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Interleukin-8

End point title	Interleukin-8

End point description:

End point type	Secondary

End point timeframe:

2 hours after endotoxin administration

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: pg/mL				
arithmetic mean (standard deviation)	583.7 (± 187.4)	463.2 (± 252.2)	550.3 (± 262.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Platelet monocyte aggregates

End point title	Platelet monocyte aggregates

End point description:

End point type	Secondary

End point timeframe:

6 hours after endotoxin administration, with ADP stimulation

End point values	No study medication	Ticagrelor	Clopidogrel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	10	10	
Units: MFI				
arithmetic mean (standard deviation)	5862.1 (± 2756.5)	2301.1 (± 457.2)	3002.4 (± 1851.4)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for EudraCT report: enrolment to 30 days after last administration of IMP

Adverse event reporting additional description:

Adverse events were collected as per protocol from the time of informed consent to until 30 days after last administration of the IMP, EudraCT allows for entering AEs for enrolled participants only.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	All randomised participants

Reporting group description: -

Serious adverse events	All randomised participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Fracture of tibia			
subjects affected / exposed	1 / 30 (3.33%)		
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	All randomised participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 30 (93.33%)		
Investigations			
Monocyte count decreased			
subjects affected / exposed	24 / 30 (80.00%)		
occurrences (all)	24		
Lymphocyte count low			

subjects affected / exposed	24 / 30 (80.00%)		
occurrences (all)	24		
Neutrophils increased			
subjects affected / exposed	24 / 30 (80.00%)		
occurrences (all)	24		
Hemoglobin low			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Eosinophil count decreased			
subjects affected / exposed	18 / 30 (60.00%)		
occurrences (all)	18		
Eosinophil count increased			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Neutrophil count low			
subjects affected / exposed	10 / 30 (33.33%)		
occurrences (all)	10		
White blood cell count low			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Raised bilirubin			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Platelet count low			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
ALT increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Red blood cell count low			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
T wave inversion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Cardiac disorders			

Light-headed subjects affected / exposed occurrences (all) Sinus bradycardia subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
Nervous system disorders Tingling feet/hands subjects affected / exposed occurrences (all) Restless subjects affected / exposed occurrences (all)	 1 / 30 (3.33%) 1 1 / 30 (3.33%) 1		
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Shivering subjects affected / exposed occurrences (all) Hot subjects affected / exposed occurrences (all) Cold subjects affected / exposed occurrences (all)	 9 / 30 (30.00%) 9 14 / 30 (46.67%) 14 3 / 30 (10.00%) 3 4 / 30 (13.33%) 4		
Eye disorders Photophobia subjects affected / exposed occurrences (all)	 3 / 30 (10.00%) 3		
Respiratory, thoracic and mediastinal disorders Yawn subjects affected / exposed occurrences (all)	 2 / 30 (6.67%) 2		
Musculoskeletal and connective tissue disorders			

Muscle ache subjects affected / exposed occurrences (all) Aches & pains in legs subjects affected / exposed occurrences (all)	8 / 30 (26.67%) 8 1 / 30 (3.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2013	Change of brand of clopidogrel during the trial period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26515417