Clinical trial results:
Investigating Aspirin and Ticagrelor for the prevention of tumour cell-induced platelet aggregation

Summary

EudraCT number	2014-004049-29
Trial protocol	GB
Global end of trial date	29 January 2020

Results information

Result version number	v1 (current)
This version publication date	14 October 2020
First version publication date	14 October 2020
Summary attachment (see zip file)	Published manuscript (TICONC.full.pdf)

Trial information

Trial identification

Sponsor protocol code	0456

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2014-004049-29

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Academic Department, Leicester General Hospital, Leicester, United Kingdom, LE5 4PW
Public contact	Dr D Adlam, University of Leicester, da134@le.ac.uk
Scientific contact	Dr D Adlam, University of Leicester, da134@le.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	29 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2020
Global end of trial reached?	Yes
Global end of trial date	29 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does Ticagrelor effect platelets in ways that are likely to reduce the spread of cancer in the blood of people taking Ticagrelor (i.e. in vivo), and does Ticagrelor seem to have more effect than Aspirin.

Protection of trial subjects:

Patients and healthy volunteers recruited to the cross-over study were assessed by a study clinician at screening, on commencement of treatment 1 (day 1) and a 2 week intervals until the end of the study (day 54-60). Adverse events were reviewed at each visit. Patients received a telephone follow-up 30-days following the final dose of study drug to check on any additional potentially relevant adverse events. All adverse event information was reviewed by the independent Data and Safety Monitoring Committee.

Patients and healthy volunteers recruited to the blood sampling study did not require follow-up.

Background therapy:

Patients were excluded from the cross-over study if, at the time of screening, they were taking antiplatelet therapy, anticoagulation, non-steroidal anti-inflammatory drugs, tamoxifen, cytotoxic chemotherapy, more than 3 lines of chemotherapy or were using strong CYP3A4 inhibitors. Patients were also excluded if they had a history of group, gastrointestinal bleeding or peptic ulceration in the last year.

All other prescribed medications were permissible in recruited patients.

Evidence for comparator:

A range of established methods of the assessment of platelet function were used for comparison including:
- Platelet spontaneous aggregation
- Platelet aggregation in response to agonists
- Expression of platelet activation markers on platelets and extracellular vesicles
- Quantity of circulating free DNA

The affects of drug treatment were then assessed.

Actual start date of recruitment	02 February 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: 113
Worldwide total number of subjects	113
EEA total number of subjects	113

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)	74
From 65 to 84 years	37
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

All patients and healthy volunteers were recruited from patients attending the University Hospitals Leicester and Healthy Volunteers responding to open advertisement and attending the University of Leicester.
Patients and healthy volunteers were recruited between November 2015 and July 2018.

Pre-assignment

Screening details:

For phase 1 (blood sampling without drug treatment) 62 cancer patients and 17 healthy volunteers. 4 cancer patients were excluded. 1 failed inclusion criteria, 2 declined, 1 unable to bleed.
Phase 2 (cross-over) Healthy 24 consented, 1 failed screening (past cancer), 1 withdrew. 22 entered.
Cancer 18 consented 2 failed screening bloods

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:

This study was not designed to assess clinical endpoints but was an exploratory study to investigate in vitro effects. this study was open label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 2 Cross-over treatment study

Arm description:

Note Phase 1 patients were not drug treated and therefore are not include here.

Phase 2. Study patients and healthy volunteers were randomly assigned to one of 2 cross-over designs:
1. Ticagrelor 2weeks, washout 2 weeks, aspirin 2 weeks, dual aspirin and ticagrelor 2 weeks
2. Aspirin 2 weeks, washout 2 weeks, ticagrelor 2 weeks, dual aspirin and ticagrelor 2 weesk

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:

Ticagrelor 180mg loading dose then 90mg twice daily for duration of therapy as per cross-over design above.

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

Dosage and administration details:

Aspirin 300mg loading dose then 75 mg daily for duration of treatment in accordance with cross-over design above.

Arm title	Phase 1

Arm description:

Blood sampling study. No study drug administration

Arm type	No intervention

Number of subjects in period 1	Phase 2 Cross-over treatment study	Phase 1
Started	38	75
Completed	31	74
Not completed	7	1
Physician decision	4	1
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
This refers to Phase 2 the cross-over drug study. This does not include patients in Phase 1 the blood sampling phase.	

Reporting group values	overall trial	Total	
Number of subjects	113	113	
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			
10 Breast Cancer Patients mean age 57.1 range 56-73 6 Colorectal Cancer Patients mean age 59.8 range 52-74 22 Healthy volunteers mean age 43.4 range 25-60			
Units: years			
arithmetic mean	53		
full range (min-max)	25 to 74	-	
Gender categorical Units: Subjects			
Female	68	68	
Male	45	45	

Subject analysis sets	
Subject analysis set title	Healthy Volunteers
Subject analysis set type	Full analysis
Subject analysis set description: Healthy volunteers in the cross-over study	
Subject analysis set title	Metastatic Breast Cancer patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Breast Cancer Patients included in the cross-over study	
Subject analysis set title	Metastatic Colorectal Cancer Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Colorectal Cancer Patients included in the cross-over study	
Subject analysis set title	Phase 1 (blood study)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Phase 1 patients were recruited for blood analysis only. They were not included in the drug study. There were 58 cancer patients and 17 Healthy Volunteers included in this element.

Reporting group values	Healthy Volunteers	Metastatic Breast Cancer patients	Metastatic Colorectal Cancer Patients
Number of subjects	22	10	6
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			
10 Breast Cancer Patients mean age 57.1 range 56-73 6 Colorectal Cancer Patients mean age 59.8 range 52-74 22 Healthy volunteers mean age 43.4 range 25-60			
Units: years arithmetic mean full range (min-max)	 43.4 25 to 60	 57.1 56 to 73	 59.8 52 to 74
Gender categorical Units: Subjects			
Female Male	16 6	10 0	3 3

Reporting group values	Phase 1 (blood study)		
Number of subjects	75		
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			
10 Breast Cancer Patients mean age 57.1 range 56-73 6 Colorectal Cancer Patients mean age 59.8 range 52-74 22 Healthy volunteers mean age 43.4 range 25-60			
Units: years arithmetic mean			

full range (min-max)			

Gender categorical Units: Subjects			
Female	39		
Male	36		

End points

End points reporting groups

Reporting group title	Phase 2 Cross-over treatment study

Reporting group description:

Note Phase 1 patients were not drug treated and therefore are not include here.

Phase 2. Study patients and healthy volunteers were randomly assigned to one of 2 cross-over designs:
1. Ticagrelor 2weeks, washout 2 weeks, aspirin 2 weeks, dual aspirin and ticagrelor 2 weeks
2. Aspirin 2 weeks, washout 2 weeks, ticagrelor 2 weeks, dual aspirin and ticagrelor 2 weesk

Reporting group title	Phase 1

Reporting group description:

Blood sampling study. No study drug administration

Subject analysis set title	Healthy Volunteers
Subject analysis set type	Full analysis

Subject analysis set description:

Healthy volunteers in the cross-over study

Subject analysis set title	Metastatic Breast Cancer patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Breast Cancer Patients included in the cross-over study

Subject analysis set title	Metastatic Colorectal Cancer Patients
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Colorectal Cancer Patients included in the cross-over study

Subject analysis set title	Phase 1 (blood study)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Phase 1 patients were recruited for blood analysis only. They were not included in the drug study. There were 58 cancer patients and 17 Healthy Volunteers included in this element.

Primary: Spontaneous Aggregation Comparison

End point title	Spontaneous Aggregation Comparison

End point description:

Measured on Light Transmission Aggregometry
There was a significantly higher amount of spontaneous aggregation at baseline in colorectal cancer patient's platelets (14.8±6.5%), compared to healthy donor platelets (8.11±4.6%) with a p-value of 0.007. Colorectal cancer platelets had a significantly higher amount of spontaneous aggregation at baseline compared to breast cancer platelets (p-value=0.02).

End point type	Primary

End point timeframe:

All crossover participant samples were compared at each treatment point

End point values	Healthy Volunteers	Metastatic Breast Cancer patients	Metastatic Colorectal Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	10	6	
Units: Percentage	8	9	15	

Attachments (see zip file)	SPA cross.jpg

Statistical analyses

Statistical analysis title	Spontaneous Aggregation Comparison
Comparison groups	Metastatic Breast Cancer patients v Healthy Volunteers v Metastatic Colorectal Cancer Patients
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 1-sided

Other pre-specified: Spontaneous Aggregation

End point title	Spontaneous Aggregation[1]

End point description:

Spontaneous platelet Aggregation as measured by light transmission aggregometry
The graph shows that there was a significantly increased amount of spontaneous aggregation in the cancer population (9±7.34%) when compared to healthy individuals (4±3.45%).
Compared using T-Test
Standard Deviations shown

End point type	Other pre-specified

End point timeframe:

Spontaneous platelet Aggregation measured at initial blood sampling of Phase 1

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The trial is designed to have separate data in Phase 1 of the trial (observational data and in vitro data) to Phase 2 which is interventional data

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Percentage	9			

Attachments (see zip file)	Spontaneous Aggregation Healthy vs Cancer/SpA Phase 1.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: P-Selectin Expression in Phase 1

End point title	P-Selectin Expression in Phase 1[2]

End point description:

Samples were taken from 15 cancer patients who were not on any medications known to affect platelet function or the coagulation cascade. The platelet activation was measured by flow cytometric analysis of platelet markers. The blood samples were prepared and analysed for P-selectin expression. Controls from healthy volunteers were also prepared. Aspirin, Ticagrelor monotherapies and dual therapies were added in vitro.
An unpaired T-Test showed that cancer patients had a significantly higher baseline resting expression of P-selectin compared to healthy volunteers, with a p-value of 0.04

End point type	Other pre-specified

End point timeframe:

P-selectin measured on initial samples from Phase 1 volunteers

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The trial is designed to have separate data in Phase 1 of the trial (observational data and in vitro data) to Phase 2 which is interventional data

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Percentage	9			

Attachments (see zip file)	P-Selectin in unstimulated platelets/Phase 1 P Selectin.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fibrinogen Binding in Phase 1

End point title	Fibrinogen Binding in Phase 1[3]

End point description:

Samples were taken from 13 cancer patients who were not on any medications known to affect platelet function or the coagulation cascade. The platelet activation was measured by flow cytometric analysis of platelet markers. The blood samples were prepared and analysed for Fibrinogen Binding. Controls from healthy volunteers were also prepared. Aspirin, Ticagrelor monotherapies and dual therapies were added in vitro.
There was no significant difference at rest between the amount of fibrinogen bound to cancer patient or healthy donor platelets

End point type	Other pre-specified

End point timeframe:

Fibrinogen Binding was measured on initial samples from Phase 1 volunteers

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The trial is designed to have separate data in Phase 1 of the trial (observational data and in vitro data) to Phase 2 which is interventional data

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Percentage	3			

Attachments (see zip file)	Fibrinogen Binding in unstimulated platelets/Fibrinogen Phase

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Healthy Volunteer Spontaneous Platelet Aggregation

End point title	Healthy Volunteer Spontaneous Platelet Aggregation

End point description:

Measured by Light Transmission Aggregometry. The final aggregation percentage for the healthy volunteers after each antiplatelet treatment were combined to obtain the mean final aggregation in healthy individuals taking that treatment, regardless of the order it was taken in. See graph
The mean final spontaneous aggregation at baseline was 8.1±4.2%, and there was no significant difference on two-tailed paired T-Test between this and the 9.2±3.2% aggregation after the washout period. This result shows that in the evaluation of spontaneous aggregation, the washout period was sufficient regardless of randomisation to remove the effect of the first drug given, to return the spontaneous aggregation levels to within that of the baseline level. This is important because if the was

End point type	Other pre-specified

End point timeframe:

Spontaneous aggregation of platelets from healthy donors was measured over 30 minutes

End point values	Healthy Volunteers			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage	8			

Attachments (see zip file)	Healthy Volunteer Spontaneous Aggregation /HV SPA.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annexin V Binding Healthy Volunteers

End point title	Annexin V Binding Healthy Volunteers

End point description:

Assessed at rest and in response to CRP-XL stimulation, and results were obtained via flow cytometry
There was no difference between the baseline and washout values at rest. There appeared to be a trend to reduced Annexin-V binding with dual therapy, and this supports the in vitro work that our group has

completed. In activated platelets stimulated with CRP-XL, there was a trend suggesting that with Ticagrelor and dual antiplatelet therapy there was less Annexin-V binding. However, on two-tailed paired T-tests compared to baseline, there was no significant difference.

End point type	Other pre-specified

End point timeframe:

Annexin-V binding to platelets was assessed at each treatment point

End point values	Healthy Volunteers			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage	3			

Attachments (see zip file)	Annexin V Binding in unstimulated and stimulated/Annexin HV.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: P-Selectin Expression in Healthy Volunteers

End point title	P-Selectin Expression in Healthy Volunteers

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP.
No difference between baseline and washout values. In unstimulated resting platelets, there was no statistically significant difference of platelet P-selectin expression between the treatment groups compared to the baseline. There was a significant reduction with Ticagrelor compared to baseline P-selectin expression level when platelets were stimulated by ADP. When dual antiplatelet therapy was taken, P-selectin expression was significantly reduced compared to baseline when stimulated by ADP.

End point type	Other pre-specified

End point timeframe:

P-selectin was measured as an activation marker by flow cytometry on the healthy samples at each treatment point

End point values	Healthy Volunteers			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage	15			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fibrinogen Binding in Healthy Volunteers

End point title	Fibrinogen Binding in Healthy Volunteers

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP. Fibrinogen binding appears to have a high variability at rest. There was a significant reduction in the amount of fibrinogen binding with Ticagrelor treatment compared to baseline, with a p-value of 0.008. When the platelets were activated, Ticagrelor treatment resulted in a significant reduction of fibrinogen binding at both ADP concentrations (p-values are <0.0001). Dual antiplatelet therapy showed a significant reduction in fibrinogen binding on stimulation with ADP. (p-values are <0.0001)

End point type	Other pre-specified

End point timeframe:

Fibrinogen binding was measured as an activation marker by flow cytometry on the healthy samples at each treatment point

End point values	Healthy Volunteers			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Percentage	32			

Attachments (see zip file)	Fibrinogen Binding in Healthy during treatment/Fib HV.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Spontaneous Aggregation in Breast Cancer

End point title	Spontaneous Aggregation in Breast Cancer

End point description:

Measured by Light Transmission Aggregometry. The final aggregation percentage for the patients after each antiplatelet treatment were combined to obtain the mean final aggregation in healthy individuals taking that treatment, regardless of the order it was taken in. See graph
At baseline, platelets from breast cancer patients had 8.7±3.4% final aggregation. This significantly increased after two weeks of aspirin to 12.6±4.6%, when analysed with two-tailed paired T-tests. Ticagrelor and dual therapy had no significant overall effect in changing the amount of aggregation. However, some individual patients were found to have lower levels of aggregation after these treatments.

End point type	Other pre-specified

End point timeframe:

Spontaneous aggregation of platelets from breast cancer patients was measured over 30 minutes

End point values	Metastatic Breast Cancer patients			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Percentage	9			

Attachments (see zip file)	Spontaneous Aggregation in Breast Cancer Patients/Breast

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Spontaneous Aggregation in Colorectal Cancer Patients

End point title	Spontaneous Aggregation in Colorectal Cancer Patients

End point description:

Measured by Light Transmission Aggregometry. The final aggregation percentage for the patients after each antiplatelet treatment were combined to obtain the mean final aggregation in healthy individuals taking that treatment, regardless of the order it was taken in. See graph
The baseline final aggregation was varied with a mean of 14.8±6.5%. This was significantly reduced to 7.7±6.5% with Ticagrelor.

End point type	Other pre-specified

End point timeframe:

Spontaneous aggregation of platelets from colorectal cancer patients was measured over 30 minutes

End point values	Metastatic Colorectal Cancer Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage	15			

Attachments (see zip file)	Spontaneous Aggregation in Colorectal Cancer/SPA colo.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annexin V Binding in Breast Cancer Patients

End point title	Annexin V Binding in Breast Cancer Patients

End point description:

Assessed at rest and in response to CRP-XL stimulation, and results were obtained via flow cytometry
No significant difference in the amount of Annexin-V binding found in unstimulated, resting platelets from breast cancer patients, when they are treated with different antiplatelets. When the platelets were activated with CRP-XL, there was no significant difference between baseline levels of Annexin-V binding compared to treated platelets. At washout, aspirin, Ticagrelor and dual therapy treatments, there was a significantly increased amount of Annexin-V binding when platelets were stimulated

End point type	Other pre-specified

End point timeframe:

Annexin-V binding to platelets was assessed at each treatment point

End point values	Metastatic Breast Cancer patients			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Percentage	3			

Attachments (see zip file)	Annexin V Binding in Breast Cancer/Annexin Breast.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annexin V Binding Colorectal Cancer

End point title	Annexin V Binding Colorectal Cancer

End point description:

Assessed at rest and in response to CRP-XL stimulation, and results were obtained via flow cytometry There was no significant difference in Annexin-V binding to platelets from colorectal cancer patients treated with antiplatelets when compared to baseline, and when the platelets were stimulated no effect of the treatment was seen. At baseline, washout, aspirin, and Ticagrelor treatments, there was a significantly increased amount of Annexin-V binding when platelets were stimulated with CRP-XL compared to unstimulated resting platelets.

End point type	Other pre-specified

End point timeframe:

Annexin-V binding to platelets was assessed at each treatment point

End point values	Metastatic Colorectal Cancer Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage	3			

Attachments (see zip file)	Annexin V Binding in Colorectal Cancer/Annexin Colo.png

Statistical analyses

No statistical analyses for this end point

Other pre-specified: P-Selectin Expression in Breast Cancer Patients

End point title	P-Selectin Expression in Breast Cancer Patients

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP.
P-selectin expression in resting, unstimulated breast cancer platelets did not significantly alter with antiplatelet treatment, and there was no statistically significant difference between all the treatment groups at baseline. When platelets from breast cancer patients were stimulated, Ticagrelor significantly reduced the expression of P-selectin (p-values 0.0011 and <0.0001). Dual therapy also reduced the expression of P-selectin significantly (p-values 0.0029 and <0.0001).

End point type	Other pre-specified

End point timeframe:

P-selectin was measured as an activation marker by flow cytometry on cancer patient samples at each treatment point

End point values	Metastatic Breast Cancer patients			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Percentage	18			

Attachments (see zip file)	P-Selectin Expression in Breast Cancer /P Sel Breast.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: P-Selectin Expression in Colorectal Patients

End point title	P-Selectin Expression in Colorectal Patients

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP.
No statistically significant difference between all the treatment groups at baseline when unstimulated resting platelets were examined. There was a significant reduction in the expression of P-selectin with Ticagrelor and dual therapy when platelets were stimulated with ADP.

End point type	Other pre-specified

End point timeframe:

P-selectin was measured as an activation marker by flow cytometry on cancer patient samples at each treatment point

End point values	Metastatic Colorectal Cancer Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage	21			

Attachments (see zip file)	P-Selectin Expression in Colorectal Cancer/P Sel Colo.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fibrinogen Binding in Breast Cancer Patients

End point title	Fibrinogen Binding in Breast Cancer Patients

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP.
There were high levels of fibrinogen binding found at baseline in unstimulated and resting platelets (49.5±24.7%), and there was no significant change in this level at the washout. Ticagrelor had a significant effect on paired T-test to reduce the resting unstimulated baseline fibrinogen binding to 26.7±15.6% (p-value 0.04). Dual therapy also significantly reduced fibrinogen binding to 31.4±19.5% from baseline (p-value 0.009).

End point type	Other pre-specified

End point timeframe:

Fibrinogen binding was measured as an activation marker by flow cytometry on the patient samples at each treatment point

End point values	Metastatic Breast Cancer patients			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: Percentage	50			

Attachments (see zip file)	Fibrinogen Binding in Breast Cancer/fib breast.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fibrinogen Binding in Colorectal Cancer

End point title	Fibrinogen Binding in Colorectal Cancer

End point description:

Measured by flow cytometry at rest and on activation with two different concentrations of ADP.
There was a significant reduction in fibrinogen binding with Ticagrelor when platelets were stimulated with ADP 1x10-5M and 1x10-6M, and with dual therapy upon stimulation with the higher concentration of ADP.

End point type	Other pre-specified

End point timeframe:

Fibrinogen binding was measured as an activation marker by flow cytometry on the patient samples at each treatment point

End point values	Metastatic Colorectal Cancer Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Percentage	38			

Attachments (see zip file)	Fibrinogen Binding in Colorectal Cancer/Fib colo.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Annexin Binding Comparison

End point title	Annexin Binding Comparison

End point description:

Measure on flow cytometry
When the cancer populations were compared to the healthy volunteers there was no significant difference in the amount of Annexin-V binding on resting, unstimulated platelets. When the platelets were activated, there was a significantly lower amount of Annexin-V binding in breast cancer platelets at baseline, washout and with Ticagrelor treatment compared to platelets from healthy donors. There was no significant difference in the amount of Annexin-V binding in colorectal cancer platelets

End point type	Other pre-specified

End point timeframe:

All crossover participant samples were compared at each treatment point

End point values	Healthy Volunteers	Metastatic Breast Cancer patients	Metastatic Colorectal Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	10	6	
Units: Percentage	3	3	4	

Attachments (see zip file)	Annexin in all populations unstimulated/Ann Cross.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: P-Selectin Comparison

End point title	P-Selectin Comparison

End point description:

Measured on flow cytometry
When resting, unstimulated platelets from healthy donors were compared to breast cancer platelets using unpaired T-Tests there was no significant difference in the amount of P-selectin expression. There was a significantly higher amount of P-selectin expression in colorectal cancer platelets compared to platelets from healthy donors at baseline. After dual therapy, the amount of P-selectin expression in breast cancer platelets was higher than platelets from healthy donors.

End point type	Other pre-specified

End point timeframe:

All crossover participant samples were compared at each treatment point

End point values	Healthy Volunteers	Metastatic Breast Cancer patients	Metastatic Colorectal Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	10	6	
Units: Percentage	13	18	21	

Attachments (see zip file)	P Selectin in all populations (Unstimulated)/P Sel Cross.jpg

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Fibrinogen Binding Comparison

End point title	Fibrinogen Binding Comparison

End point description:

Measured by flow cytometry
At baseline, breast cancer platelets that were resting and unstimulated had a significantly higher amount of fibrinogen bound, compared to platelets from healthy donors. Colorectal cancer patients had higher amounts of fibrinogen binding after aspirin treatment compared to platelets from healthy donors at rest. There were no significant differences in fibrinogen binding between platelets from healthy donors or cancer platelets with antiplatelet treatments upon ADP stimulation

End point type	Other pre-specified

End point timeframe:

All crossover participant samples were compared at each treatment point

End point values	Healthy Volunteers	Metastatic Breast Cancer patients	Metastatic Colorectal Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18	10	6	
Units: Percentage	30	50	38	

Attachments (see zip file)	Fibrinogen Binding all populations (Unstimulated)/fib cross.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From recruitment to 30 days post final administered dose of study drug for phase 2 cross-over study patients only.

Adverse event reporting additional description:

Adverse events were reviewed at in person by the study physician at 2-week intervals from first administered dose to completion of the cross-over study plus at a phone call made 30-days after the final dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Phase 2 Cross-over treatment study

Reporting group description:

Note Phase 1 patients were not drug treated and therefore are not include here.

Phase 2. Study patients and healthy volunteers were randomly assigned to one of 2 cross-over designs:
1. Ticagrelor 2weeks, washout 2 weeks, aspirin 2 weeks, dual aspirin and ticagrelor 2 weeks
2. Aspirin 2 weeks, washout 2 weeks, ticagrelor 2 weeks, dual aspirin and ticagrelor 2 weesk

Reporting group title	Phase 1

Reporting group description:

Blood sampling study. No study drug administration

Serious adverse events	Phase 2 Cross-over treatment study	Phase 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	0 / 74 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
hydronephrosis	Additional description: Patient found on a routine cancer staging scan to have hydronephrosis due to cancer progression. Not related to study medication.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria	Additional description: This occurred during dual treatment with Ticagrelor and Aspirin and stopped immediately following cessation of study drugs with no sequelae.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Elective hip replacement	Additional description: Occurred at the end of the follow-up period and had no relationship to the study		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Phase 2 Cross-over treatment study	Phase 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 38 (65.79%)	0 / 74 (0.00%)	
Cardiac disorders			
Palpitations	Additional description: Patient reported episode of palpitations - not recorded on ECG		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Bruising	Additional description: 19 Occurrences of bruising of the skin		
subjects affected / exposed	11 / 38 (28.95%)	0 / 74 (0.00%)	
occurrences (all)	19	0	
Bleeding	Additional description: Non major bleeding occurences reported		
subjects affected / exposed	5 / 38 (13.16%)	0 / 74 (0.00%)	
occurrences (all)	6	0	
Ear and labyrinth disorders			
Dizziness	Additional description: Episodes of intermittent dizziness described		
subjects affected / exposed	2 / 38 (5.26%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Minor abdominal discomfort described		
subjects affected / exposed	2 / 38 (5.26%)	0 / 74 (0.00%)	
occurrences (all)	2	0	
Reflux	Additional description: Non severe reflux		
subjects affected / exposed	4 / 38 (10.53%)	0 / 74 (0.00%)	
occurrences (all)	5	0	
Dry mouth	Additional description: One episode of dry mouth reported		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Nausea	Additional description: One episode of nausea reported		

subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 38 (10.53%)	0 / 74 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Itchy Skin	Additional description: Episode of itchy skin on the back, no rash		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Low mood	Additional description: Patient reported an episode of low mood and feeling 'jittery'		
subjects affected / exposed	1 / 38 (2.63%)	0 / 74 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2016	Addition of a healthy volunteer non interventional cohort to the study to allow comparison to the non-interventional cancer population in Phase 1. Addition of new posters and leaflets for all groups to advertise the study for the interventional phases 2 and 3.
30 October 2017	Personnel and contact detail changes made The '2 hour post dose' blood test made an optional test. There have been numerous protocol deviations made when participants can not commit the time to have this blood test. This will not affect the scientific value, safety or integrity of the study. Additional recruitment strategy changes have been outlined in the protocol, with the sending out of leaflets to suitable Oncology patients. To reflect this, a covering invitation letter has been created and 2 leaflets summarising the study have been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported