Clinical trial results:
A Randomised Controlled Trial Investigating the Pharmacodynamic Effect of Ticagrelor Monotherapy on Platelet Reactivity in Patients with Coronary Artery Disease: The TEMPLATE Study

Summary

EudraCT number	2013-002734-20
Trial protocol	GB
Global end of trial date	21 October 2020

Results information

Result version number	v1 (current)
This version publication date	18 February 2021
First version publication date	18 February 2021

Trial information

Trial identification

Sponsor protocol code	CS/2014/4525

Additional study identifiers

ISRCTN number	ISRCTN84335288
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Research & Innovation, University Hospitals Bristol NHS Foundation Trust
Sponsor organisation address	Education & Research Centre, Level 3, Upper Maudlin Street, Bristol, United Kingdom, BS2 8AE
Public contact	Andrew Mumford, University of Bristol, 44 0117 342 3152, andrew.mumford@bristol.ac.uk
Scientific contact	Andrew Mumford, University of Bristol, 44 0117 342 3152, andrew.mumford@bristol.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	22 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2018
Global end of trial reached?	Yes
Global end of trial date	21 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall study aim is to determine whether aspirin is required to achieve full platelet inhibition in patients with coronary artery disease who are also receiving ticagrelor. We will investigate this by comparing the pharmacodynamic effects of aspirin + ticagrelor (ASP + TIC) and ticagrelor alone (TIC) on platelets from patients allocated at random to the intervention.

Protection of trial subjects:

Trial participants were closely followed up to identify any adverse reactions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 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: 110
Worldwide total number of subjects	110
EEA total number of subjects	0

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)	45
From 65 to 84 years	60

85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	110
Number of subjects completed	

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	ASP + TIC

Arm description:

Loading dose of 180mg ticagrelor followed by aspirin 75mg/day AND ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

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

Dosage and administration details:

aspirin 75mg/day for 4 weeks unless the patient is already on ASP+TIC

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

Dosage and administration details:

Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

Arm title	TIC alone

Arm description:

Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

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

Dosage and administration details:

Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

Number of subjects in period 1	ASP + TIC	TIC alone
Started	55	55
Completed	49	53
Not completed	6	2
Not possible to schedule visit 2	1	-
Ineligible	-	1
Patient unhappy with side effects	1	-
Can no longer attend visit schedule	-	1
Patient died	1	-
GP	1	-
Patient no longer wanted to take part	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ASP + TIC
Reporting group description:	
Loading dose of 180mg ticagrelor followed by aspirin 75mg/day AND ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC	
Reporting group title	TIC alone
Reporting group description:	
Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC	

Reporting group values	ASP + TIC	TIC alone	Total
Number of subjects	55	55	110
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 Units: years			
arithmetic mean	67.3	66.1	
standard deviation	± 10.3	± 11.8	-
Gender categorical Units: Subjects			
Female	11	11	22
Male	44	44	88
Smoking history Units: Subjects			
Yes	6	7	13
Ex-smoker >1 month	29	27	56
Never	20	21	41
Family history of heart disease Units: Subjects			
Yes	29	21	50
No	26	34	60
Hypertension requiring treatment Units: Subjects			
Yes	26	31	57
No	29	24	53
Hypercholesterolaemia Units: Subjects			

Yes	30	31	61
No	25	24	49
Diabetes Units: Subjects			
Insulin	3	4	7
Oral	5	4	9
Diet	1	0	1
None	46	47	93
Congestive heart failure Units: Subjects			
Yes	4	1	5
No	51	54	105
CVA/TIA Units: Subjects			
Yes	3	3	6
No	52	52	104
Chronic pulmonary disease Units: Subjects			
Yes	0	2	2
No	55	53	108
Asthma Units: Subjects			
Yes	6	5	11
No	49	50	99
Peripheral vascular disease Units: Subjects			
Yes	2	1	3
No	53	54	107
Hypothyroidism Units: Subjects			
Yes	3	6	9
No	52	49	101
Previous PCI Units: Subjects			
Yes	12	15	27
No	43	40	83
Previous cardiac surgery Units: Subjects			
Yes	5	4	9
No	50	51	101
Previous MI Units: Subjects			
Yes	27	30	57
No	28	25	53
Heart rhythm Units: Subjects			
Sinus	55	53	108
Block	0	1	1
Missing	0	1	1
Other medical history Units: Subjects			

Yes	42	40	82
No	13	15	28
LV function Units: Subjects			
Good (>50%)	36	38	74
Moderate (30-50%)	17	14	31
Poor (<30%)	0	1	1
Missing	2	2	4
>50% disease in left main stem Units: Subjects			
Yes	4	3	7
No	51	52	103
Coronary disease, number of vessels Units: Subjects			
Single	26	28	54
Double	21	14	35
Triple	8	13	21
Pacemaker Units: Subjects			
Yes	0	2	2
No	55	53	108
Aspirin Units: Subjects			
Yes	55	55	110
No	0	0	0
Clopidogrel Units: Subjects			
Yes	19	20	39
No	36	35	71
Ticagrelor Units: Subjects			
Yes	23	25	48
No	32	30	62
Prasugrel Units: Subjects			
Yes	13	10	23
No	42	45	87
Warfarin Units: Subjects			
Yes	0	0	0
No	55	55	110
Heparin Units: Subjects			
Yes	0	0	0
No	55	55	110
Clexane Units: Subjects			
Yes	0	0	0
No	55	55	110
Fondaparinux Units: Subjects			

Yes	0	0	0
No	55	55	110
Beta blockers Units: Subjects			
Yes	43	42	85
No	12	13	25
Calcium antagonists Units: Subjects			
Yes	11	9	20
No	44	46	90
ACE inhibitors Units: Subjects			
Yes	35	37	72
No	20	18	38
Angiotensin II blockers Units: Subjects			
Yes	6	12	18
No	49	43	92
Statins Units: Subjects			
Yes	54	51	105
No	1	4	5
Other lipid lowering agent Units: Subjects			
Yes	1	4	5
No	54	51	105
Oral nitrates Units: Subjects			
Yes	18	13	31
No	37	42	79
Nicorandil Units: Subjects			
Yes	2	1	3
No	53	54	107
Diuretics Units: Subjects			
Yes	4	9	13
No	51	46	97
Oral anti-diabetics Units: Subjects			
Yes	3	4	7
No	52	51	103
Insulin Units: Subjects			
Yes	7	6	13
No	48	49	97
Anti arrhythmic Units: Subjects			
Yes	26	24	50
No	29	31	60
PPIs			

Units: Subjects			
Yes	0	0	0
No	55	55	110
Other medications Units: Subjects			
Yes	29	40	69
No	26	15	41
Heart rate Units: rpm			
arithmetic mean	62.7	62.1	
standard deviation	± 10.1	± 10.9	-
Systolic blood pressure Units: mmHg			
arithmetic mean	135.8	140.8	
standard deviation	± 14.6	± 20.0	-
Diastolic blood pressure Units: mmHg			
arithmetic mean	76.9	78.5	
standard deviation	± 10.9	± 10.9	-
BMI Units: unitless			
arithmetic mean	27.6	27.0	
standard deviation	± 3.8	± 4.9	-

End points

End points reporting groups

Reporting group title	ASP + TIC
Reporting group description:	
Loading dose of 180mg ticagrelor followed by aspirin 75mg/day AND ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC	
Reporting group title	TIC alone
Reporting group description:	
Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC	

Primary: MA of the LTA response of PRP to TRAP-6

End point title	MA of the LTA response of PRP to TRAP-6
End point description:	
The primary outcome is defined as the maximum amplitude of the light transmission aggregation response of platelet rich plasma (PRP) to TRAP-6 expressed as a % of the absolute difference in light transmission between PRP and platelet poor plasma. This assay measures the ability of platelets to aggregate when exposed to the aggregation promoting agent TRAP-6.	
End point type	Primary
End point timeframe:	
Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.	

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: 10uM				
arithmetic mean (standard deviation)	80.9 (± 13.6)	85.5 (± 13.4)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	ASP + TIC v TIC alone
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	9.46

Secondary: MA of the LTA response of PRP to TRAP-6 5uM

End point title	MA of the LTA response of PRP to TRAP-6 5uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: uM				
arithmetic mean (standard deviation)	70.1 (± 20.3)	77.8 (± 20.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: MA of the LTA response of PRP to CRP 1ug/mL

End point title	MA of the LTA response of PRP to CRP 1ug/mL

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: mg/mL				
arithmetic mean (standard deviation)	85.6 (± 9.9)	92.5 (± 12.3)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	ASP + TIC v TIC alone
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.04
upper limit	10.9

Secondary: MA of the LTA response of PRP to CRP 0.5ug/mL

End point title	MA of the LTA response of PRP to CRP 0.5ug/mL

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	51		
Units: ug/mL				
arithmetic mean (standard deviation)	72.8 (± 15.6)	87.8 (± 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: MA of the LTA response of PRP to U46619 5uM

End point title	MA of the LTA response of PRP to U46619 5uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: uM				
arithmetic mean (standard deviation)	74.0 (± 12.4)	73.2 (± 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: MA of the LTA response of PRP to U46619 2.5uM

End point title	MA of the LTA response of PRP to U46619 2.5uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: uM				
arithmetic mean (standard deviation)	48.3 (± 16.5)	48.6 (± 20.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: MA of the LTA response of PRP to ADP 10uM

End point title	MA of the LTA response of PRP to ADP 10uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	52		
Units: uM				
arithmetic mean (standard deviation)	35.6 (± 11.6)	37.6 (± 12.5)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	ASP + TIC v TIC alone
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.709
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.89
upper limit	7.19

Secondary: MA of the LTA response of PRP to AA 1mM

End point title	MA of the LTA response of PRP to AA 1mM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2. primary analysis is comparing the treatment groups at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	52		
Units: mM				
median (inter-quartile range (Q1-Q3))	5 (3 to 8)	75 (59 to 83)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	ASP + TIC v TIC alone
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Log mean difference
Point estimate	11.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.55
upper limit	15.95

Secondary: Flow cytometry of PAC-1 after activation with TRAP-6 10uM

End point title	Flow cytometry of PAC-1 after activation with TRAP-6 10uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2, before and after activation and the change. Primary analysis is comparing the treatment groups change at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	53		
Units: uM				
median (inter-quartile range (Q1-Q3))	1285.5 (1064 to 2565)	1206 (980 to 1745)		

Statistical analyses

No statistical analyses for this end point

Secondary: Flow cytometry of PAC-1 after activation with CRP 1ug/mL

End point title	Flow cytometry of PAC-1 after activation with CRP 1ug/mL

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2, before and after activation and the change. Primary analysis is comparing the treatment groups change at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	50		
Units: ug/mL				
median (inter-quartile range (Q1-Q3))	3127.5 (2079 to 4401.5)	3055.5 (2244 to 3752)		

Statistical analyses

No statistical analyses for this end point

Secondary: Flow cytometry of CD62P after activation with TRAP-6 10uM

End point title	Flow cytometry of CD62P after activation with TRAP-6 10uM

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2, before and after activation and the change. Primary analysis is comparing the treatment groups change at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	52		
Units: uM				
median (inter-quartile range (Q1-Q3))	3011.5 (2569.5 to 5811.5)	2893 (1931 to 4957)		

Statistical analyses

No statistical analyses for this end point

Secondary: Flow cytometry of CD62P after activation with CRP 1ug/mL

End point title	Flow cytometry of CD62P after activation with CRP 1ug/mL

End point description:

End point type	Secondary

End point timeframe:

Data collected at baseline, visit 1 and visit 2, before and after activation and the change. Primary analysis is comparing the treatment groups change at visit 2.

End point values	ASP + TIC	TIC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: ug/mL				
median (inter-quartile range (Q1-Q3))	3405 (1985 to 7232.5)	3350 (2468 to 5161)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data on adverse events were collected from consent for the duration of the participant's participation in the trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	ASP + TIC

Reporting group description:

Loading dose of 180mg ticagrelor followed by aspirin 75mg/day AND ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

Reporting group title	TIC alone

Reporting group description:

Loading dose of 180mg ticagrelor followed by ticagrelor 90 mg b.d. for 4 weeks unless the patient is already on ASP+TIC

Serious adverse events	ASP + TIC	TIC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)	2 / 55 (3.64%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary revascularisation			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ASP + TIC	TIC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 55 (69.09%)	45 / 55 (81.82%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	4 / 55 (7.27%)	0 / 55 (0.00%)	
occurrences (all)	4	0	
Haemorrhage subcutaneous			
subjects affected / exposed	3 / 55 (5.45%)	2 / 55 (3.64%)	
occurrences (all)	3	2	
Haematoma			
subjects affected / exposed	20 / 55 (36.36%)	12 / 55 (21.82%)	
occurrences (all)	20	12	
Post procedural haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Wound haemorrhage			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Traumatic haemorrhage			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Haemorrhage			

subjects affected / exposed	3 / 55 (5.45%)	0 / 55 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Confusion postoperative			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 55 (3.64%)	1 / 55 (1.82%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	3 / 55 (5.45%)	4 / 55 (7.27%)	
occurrences (all)	3	4	
Paraesthesia			
subjects affected / exposed	1 / 55 (1.82%)	4 / 55 (7.27%)	
occurrences (all)	1	4	
Vertigo			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Other	Additional description: Other adverse events		
subjects affected / exposed	17 / 55 (30.91%)	24 / 55 (43.64%)	
occurrences (all)	25	32	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 55 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Abdominal pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 55 (5.45%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	5 / 55 (9.09%)	6 / 55 (10.91%)	
occurrences (all)	6	9	

Vomiting			
subjects affected / exposed	3 / 55 (5.45%)	4 / 55 (7.27%)	
occurrences (all)	3	6	
Diarrhoea			
subjects affected / exposed	4 / 55 (7.27%)	14 / 55 (25.45%)	
occurrences (all)	6	14	
Constipation			
subjects affected / exposed	0 / 55 (0.00%)	2 / 55 (3.64%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 55 (1.82%)	7 / 55 (12.73%)	
occurrences (all)	1	8	
Hepatobiliary disorders			
Liver function test abnormal			
subjects affected / exposed	1 / 55 (1.82%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 55 (1.82%)	2 / 55 (3.64%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	15 / 55 (27.27%)	18 / 55 (32.73%)	
occurrences (all)	15	18	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	3 / 55 (5.45%)	8 / 55 (14.55%)	
occurrences (all)	4	10	
Renal and urinary disorders			
Fluid retention			
subjects affected / exposed	2 / 55 (3.64%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
Blood creatinine increased			
subjects affected / exposed	1 / 55 (1.82%)	2 / 55 (3.64%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported