Clinical trial results:
TOFFEE Trial
Toxicity OF Fluoropyrimidines: A comparative study of the cardiotoxicity of capEcitabine and tEysuno

Summary

EudraCT number	2012-005282-12
Trial protocol	GB
Global end of trial date	08 October 2020

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information

Trial identification

Sponsor protocol code	V 7.0, 10 May 2020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01845337
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD (University of Edinburgh and NHS Lothian)
Sponsor organisation address	47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Annya Smyth, University of Edinburgh, +44 01312423325, Annya.Smyth@ed.ac.uk
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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	08 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 October 2020
Global end of trial reached?	Yes
Global end of trial date	08 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of capecitabine and teysuno on cardiovascular parameters (continuous ECG recording, high sensitivity troponin and BNP) to determine whether there is a difference in the cardiotoxicity of teysuno compared to the current standard of care cancer medicine, capecitabine.

Protection of trial subjects:

All patients were aged >18 and had capacity to understand the information and make an informed decision. After detailed discussion, all patients were provided with written patient information and given time for questions before signing consent. Given opportunity to withdraw at any time. Provided with contact details for trials team.

Background therapy:

Supportive medicines such as anti-emetics and anti-diarrhoeals that are provided as standard along with chemotherapy treatment.

Evidence for comparator:

Fluoropyrimidines (FPs) are widely used chemotherapy agents for the management of patients with colorectal, breast, upper gastrointestinal, head and neck cancers. Capecitabine is an oral prodrug of 5-fluorouracil (5FU) which is used extensively in the UK and Europe but is associated with clinically overt cardiotoxicity in up to 9% of patients. Teysuno is an alternative oral fluoropyrimidine, used widely in Asia, with a marketing authorisation in Europe for use in combination with cisplatin for the treatment of gastric cancer. Teysuno is not described as having cardiotoxicity, but studies have never been performed.

Actual start date of recruitment	02 June 2014
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: 59
Worldwide total number of subjects	59
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)	27
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients starting chemotherapy with either Capecitabine or CapOx were recruited from South East Scotland between June 2014 and March 2020.

Pre-assignment

Screening details:

The trial was discussed with patients at their oncology clinic appointment and they were provided with verbal and written information. They were invited to attend a trials clinic some days thereafter. If not interested then patients proceeded to chemotherapy without participating in the trial and their rights were not affected. At least 50% of pati

Period 1

Period 1 title	Consented to treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The patient and treating oncology team knew which treatment the patient had been randomised to. The study was blinded to the trial team and to the cardiovascular research team analysing the endpoints of the study. All cardiovascular endpoint data was analysed/investigated in batches, identified only by trial number, by technicians and the cardiovascular research team, often at a time significantly removed from the patient's participation in the study. The cardiovascular research team was blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine

Arm description:

Capecitabine or Capecitabine + oxaliplatin (CapOx)

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	L01BC06
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1250mg/m2 BD for 14 days out of 21 days (or capecitabine 1000mg/m2 BD for 14 days every 21 days for patients aged >70 or with eGFR 30-50ml/min).

Capecitabine 1000mg/m2 BD for 14 days out of 21 days (or capecitabine 750mg/m2 BD for 14 days every 21 days for patients aged >70 or with eGFR 30-50ml/min) with Oxaliplatin 130mg/m2 IV Day 1 every 21 days

Arm title	Teysuno (also known as S-1)

Arm description:

Teysuno is a combination of (i) the 5-FU pro-drug, tegafur, (ii) a dihydropyrimidine dehydrogenase (DPD) inhibitor, gimeracil, and (iii) a phosphorylation inhibitor, oteracil.

Arm type	Experimental
Investigational medicinal product name	Tegafur / Gimeracil / Oteracil tablets
Investigational medicinal product code	L01BC53
Other name	S-1 or Teysuno
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Teysuno 30 mg/m2 twice daily, for 14 days every 21 days (or 25mg/m2 for patients aged >70 or with eGFR 30-50)

Teysuno 25mg/m2 twice daily, for 14 days every 21 days with Oxaliplatin 130mg/m2 IV Day 1 every 21 days

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The cardiovascular research team who performed the primary and secondary endpoint analyses were blinded to treatment allocation. The clinical study team responsible for day to day care were unblinded.

Number of subjects in period 1	Capecitabine	Teysuno (also known as S-1)
Started	30	29
Completed	28	28
Not completed	2	1
Clinical deterioration before starting	1	-
Infection and Covid pandemic before starting	1	-
family bereavement before starting	-	1

Period 2

Period 2 title	Started treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The patient and treating oncology team knew which treatment the patient had been randomised to. The study was blinded to the trial team and to the cardiovascular research team analysing the endpoints of the study. All cardiovascular endpoint data was analysed/investigated in batches, identified only by trial number, by technicians and the cardiovascular research team, often at a time significantly removed from the patient's participation in the study. The cardiovascular research team was blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Capecitabine

Arm description:

Randomised to capecitabine containing treatment and took at least one tablet

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	L01BC06
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 1250mg/m2 BD for 14 days out of 21 days (or capecitabine 1000mg/m2 BD for 14 days

every 21 days for patients aged >70 or with eGFR 30-50ml/min).

Capecitabine 1000mg/m2 BD for 14 days out of 21 days (or capecitabine 750mg/m2 BD for 14 days every 21 days for patients aged >70 or with eGFR 30-50ml/min) with Oxaliplatin 130mg/m2 IV Day 1 every 21 days

Arm title	Teysuno S-1

Arm description:

Randomised to receive Teysuno S-1 containing chemo and took at least one tablet

Arm type	Experimental
Investigational medicinal product name	Tegafur / Gimeracil / Oteracil tablets
Investigational medicinal product code	L01BC53
Other name	S-1 or Teysuno
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Teysuno 30 mg/m2 twice daily, for 14 days every 21 days (or 25mg/m2 for patients aged >70 or with eGFR 30-50)

Teysuno 25mg/m2 twice daily, for 14 days every 21 days with Oxaliplatin 130mg/m2 IV Day 1 every 21 days

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The cardiovascular research team who performed the primary and secondary endpoint analyses were blinded to treatment allocation. The clinical study team responsible for day to day care were unblinded.

Number of subjects in period 2	Capecitabine	Teysuno S-1
Started	28	28
Completed	28	27
Not completed	0	1
family bereavement before starting	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Consented to treatment
Reporting group description:	
59 patients consented to treatment, and were randomised and are therefore the baseline group	

Reporting group values	Consented to treatment	Total	
Number of subjects	59	59	
Age categorical			
All patients randomised			
Units: Subjects			
Adults (18-64 years)	27	27	
From 65-84 years	32	32	
Age continuous			
Arithmetic mean and range of ages for both groups of patients			
Units: years			
arithmetic mean	64		
full range (min-max)	39 to 83	-	
Gender categorical			
Gender of all patients consented and randomised			
Units: Subjects			
female capecitabine	8	8	
female teysuno S1	11	11	
male capecitabine	22	22	
male teysuno S1	18	18	
Baseline CTCA			
CT coronary angiography done at baseline for as many patients as possible			
Units: Subjects			
capecitabine	30	30	
teysuno S1	29	29	

Subject analysis sets	
Subject analysis set title	Capecitabine on treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who were randomised to Cap or CapOx, and started some oral chemotherapy	
Subject analysis set title	Teysuno on treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who were randomised to Teysuno or TeyOx, and who started some oral chemotherapy	

Reporting group values	Capecitabine on treatment	Teysuno on treatment	
Number of subjects	28	28	
Age categorical			
All patients randomised			
Units: Subjects			

Adults (18-64 years)	14	10	
From 65-84 years	14	18	

Age continuous			
Arithmetic mean and range of ages for both groups of patients			
Units: years			
arithmetic mean	63	66	
full range (min-max)	42 to 83	39 to 82	
Gender categorical			
Gender of all patients consented and randomised			
Units: Subjects			
female capecitabine	8	0	
female teysuno S1	0	10	
male capecitabine	20	0	
male teysuno S1	0	18	
Baseline CTCA			
CT coronary angiography done at baseline for as many patients as possible			
Units: Subjects			
capecitabine	26	0	
teysuno S1	0	27	

End points

End points reporting groups

Reporting group title	Capecitabine
Reporting group description:	
Capecitabine or Capecitabine + oxaliplatin (CapOx)	
Reporting group title	Teysuno (also known as S-1)
Reporting group description:	
Teysuno is a combination of (i) the 5-FU pro-drug, tegafur, (ii) a dihydropyrimidine dehydrogenase (DPD) inhibitor, gimeracil, and (iii) a phosphorylation inhibitor, oteracil.	
Reporting group title	Capecitabine
Reporting group description:	
Randomised to capecitabine containing treatment and took at least one tablet	
Reporting group title	Teysuno S-1
Reporting group description:	
Randomised to receive Teysuno S-1 containing chemo and took at least one tablet	
Subject analysis set title	Capecitabine on treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who were randomised to Cap or CapOx, and started some oral chemotherapy	
Subject analysis set title	Teysuno on treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients who were randomised to Teysuno or TeyOx, and who started some oral chemotherapy	

Primary: Duration of ST change baseline to max (100uV)

End point title	Duration of ST change baseline to max (100uV)
End point description:	
The primary endpoint of the study is the difference in the duration of ST deviation pre-treatment and during treatment	
End point type	Primary
End point timeframe:	
Baseline before treatment Mean duration of ST change during 3 days of continuous ECG monitoring	

End point values	Capecitabine	Teysuno (also known as S-1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[1]	27[2]		
Units: hours				
geometric mean (standard deviation)	1.08 (± 6.10)	1.35 (± 5.34)		

Notes:

[1] - capecitabine patients with >1 day 24 hour ECG recordings

[2] - teysuno S1 patients with >1 day 24 hour ECG recordings

Statistical analyses

Statistical analysis title	Comparison between cap and S1
Comparison groups	Capecitabine v Teysuno (also known as S-1)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Notes:

[3] - difference between the two groups

Secondary: Ischaemic burden baseline to max (100 uv threshold)

End point title	Ischaemic burden baseline to max (100 uv threshold)

End point description:

Before treatment and during treatment with means of 24 hour continuous ECG recordings

End point type	Secondary

End point timeframe:

Baseline and on treatment

End point values	Capecitabine	Teysuno (also known as S-1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[4]	27[5]		
Units: mV				
arithmetic mean (standard deviation)	20131 (± 55495)	1591 (± 20188)		

Notes:

[4] - > 1 24 hour ECG recording
cap treated

[5] - > 1 24 hour ECG recording
S1 treated

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

a non-parametric equivalent to the two-sample t-test since the data is not Normally distributed.

Comparison groups	Capecitabine v Teysuno (also known as S-1)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.05 [7]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Notes:

[6] - comparing treatment groups for change in ischaemic burden (baseline to max at 100uV)

[7] - p=0.0479 which is statistically significant

Secondary: Ischaemic burden Baseline to max (200 uv threshold)

End point title	Ischaemic burden Baseline to max (200 uv threshold)

End point description:

Compare ischaemic burden in both treatment groups from baseline test to max ischaemic burden for each group

End point type	Secondary

End point timeframe:

Before and during ECG monitoring

End point values	Capecitabine	Teysuno (also known as S-1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[8]	27[9]		
Units: mV				
arithmetic mean (standard deviation)	18045 (± 51604)	-1360 (± 12145)		

Notes:

[8] - capecitabine for whom > 1 24 ECG available

[9] - S1 teysuno for whom > 1 24 ECG available

Statistical analyses

Statistical analysis title	Comparison between cap and S1 IB baseline max 200

Statistical analysis description:

Baseline for each group to max IB for each group. Comparison between treatment groups

Comparison groups	Capecitabine v Teysuno (also known as S-1)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	≤ 0.05 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - comparison

[11] - p=0.0532 not statistically significant

Secondary: Ischaemic Burden Baseline to mean of all on treatment ECG days (100 uv threshold)

End point title	Ischaemic Burden Baseline to mean of all on treatment ECG days (100 uv threshold)

End point description:

Mean daily IB baseline to max for both cap and S1 treated patients for whom >1 x 24 ECG recording available

End point type	Secondary

End point timeframe:

Baseline and up to 3 days monitoring on treatment

End point values	Capecitabine	Teysuno (also known as S-1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[12]	27[13]		
Units: mv				
arithmetic mean (standard deviation)	20569 (± 56128)	1072 (± 22123)		

Notes:

[12] - cap patients

[13] - teysuno patients for whom >1 x 24 ECG recording

Statistical analyses

Statistical analysis title	Comparison of mean daily IB baseline to max at 100

Statistical analysis description:

Comparison between mean daily IB from baseline to max values for patients treated with capecitabine or teysuno , for whom >1 x 24 ECG recording available, at the 100uV threshold for detection

Comparison groups	Capecitabine v Teysuno (also known as S-1)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	≤ 0.05 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - comparison to look for differences

[15] - p=0.0442 which is statistically significant

Secondary: Ischaemic burden baseline to mean of all on treatment ECG days (200 uv threshold)

End point title	Ischaemic burden baseline to mean of all on treatment ECG days (200 uv threshold)

End point description:

comparison between cap and S1 groups, when measured at 200uV threshold and using the mean daily IB from baseline to max

End point type	Secondary

End point timeframe:

baseline and during 1-3 days of continuous ECG monitoring

End point values	Capecitabine	Teysuno (also known as S-1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[16]	27[17]		
Units: mv				
arithmetic mean (standard deviation)	18413 (± 52665)	-1410 (± 12283)		

Notes:

[16] - cap treated patients for whom > 1 x 24 ECG recording available

[17] - S1 treated patients for whom > 1 x 24 ECG recording available

Statistical analyses

Statistical analysis title	Comparison cap and S1 mean daily IB 200uV b

Statistical analysis description:

Comparison between cap and S1 treated groups, when ECGs analysed at 200uV threshold, looking at mean daily ischaemic burden measuring it from baseline to maximum over 3 days

Comparison groups	Capecitabine v Teysuno (also known as S-1)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	≤ 0.05 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - comparison to evaluate differences

[19] - P= 0.0532 which is not statistically significant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First cycle of each treatment (21 days)
Ongoing collection of SAEs for teysuno treated patients only, beyond C1, as part of safety monitoring for an off label drug. This could falsely elevate the number of SAEs when compared to capecitabine

Adverse event reporting additional description:

Both capecitabine and S1 are cytotoxic drugs with expected and anticipated adverse effects, according to the SPC. AEs were recorded.
Cycles are 3 weekly
AEs and SAEs were evaluated for cycle 1 only for both groups
SAEs were evaluated for teysuno S1 for all cycles, including beyond cycle 1 trial period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Teysuno S1

Reporting group description:

Patients treated with teysuno either as single agent or in combination with oxaliplatin. Only AEs of Grade 2,3 or 4 are included.
All AEs and SAEs collected for teysuno patients, even beyond C1

Reporting group title	Capecitabine

Reporting group description:

Patients treated with capecitabine, either as a single agent or in combination with oxaliplatin during the first cycle of treatment (the trial period)
Only AEs of grade 2,3 or 4 are counted

Serious adverse events	Teysuno S1	Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 28 (32.14%)	6 / 28 (21.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Paroxysmal arrhythmia	Additional description: AF		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain - cardiac	Additional description: Diagnosis of cardiac cause not definitively made		
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Subacute (SABO)		
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract disorder	Additional description: Catheter related infection		

subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
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: 1 %

Non-serious adverse events	Teysuno S1	Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 28 (14.29%)	4 / 28 (14.29%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 28 (14.29%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	4 / 28 (14.29%)	
occurrences (all)	2	4	
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 28 (3.57%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2015	Included patients with CUP, modified cap dose if reduced eGFR as per SPC, statement that venous plethysmography and Badimon chamber are optional substudies, platelet aggregation studies removed, unblinding section updated, new patient information booklet.
19 February 2016	Added the option of slight alteration to timing of CTCA
15 June 2018	Description of co-enrolment strategy, new RSI for capecitabine, description of details of trial steering group and data monitoring committee, added the option of reducing doses in frail/elderly in keeping with standard practice, updated the RSI for capecitabine and teysuno and added a GDPR statement and GDPR patient information.
22 May 2020	Update to SPC and RSI for capecitabine, removal of vascular substudy and tPA and PAI-1 and update to statistical analysis plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial temporarily stopped recruiting during the Covid-19 pandemic and later that year, when it was clear the impact of the pandemic continued, a decision was made to stop recruitment into the trial and close the study, without fully recruiting.

Notes: