Clinical trial results:
A multicentre prospective randomised open-label blinded end-point controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent cardiac toxicity in breast cancer and lymphoma patients receiving anthracycline adjuvant therapy

Summary

EudraCT number	2017-000896-99
Trial protocol	GB
Global end of trial date	04 April 2022

Results information

Result version number	v1 (current)
This version publication date	29 October 2023
First version publication date	29 October 2023

Trial information

Trial identification

Sponsor protocol code	AC16148

Additional study identifiers

ISRCTN number	ISRCTN24439460
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ACCORD
Sponsor organisation address	QMRI, 47 Little France Crescent, Edinburgh, United Kingdom, EH16 4TJ
Public contact	Dr Fiach O'Mahoney, ACCORD, Dr Peter Henriksen, NHS Lothian, +44 131 2429418 , fiach.o'mahony@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	31 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2022
Global end of trial reached?	Yes
Global end of trial date	04 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether known treatments for heart failure can prevent or reduce myocardial injury and the development of left ventricular systolic dysfunction.

Protection of trial subjects:

Participants were treated within a standard clinical setting by their NHS clinical care team.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2017
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: 175
Worldwide total number of subjects	175
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)	142
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Cardiac CARE opened for patient recruitment across 9 UK centres. Between 04Oct17 and 30Jun21, 424 patients were approached across 7 of the 9 centres open for recruitment. 191 patients approached were consented. 16 patients from this group were subsequently excluded owing to exclusion criteria. 57 of the remaining 175 patients were randomised.

Pre-assignment

Screening details:

Patients aged ≥18 years commencing anthracycline for adjuvant or neo-adjuvant treatment of breast cancer or non-Hodgkin lymphoma were invited to participate in the study. Patient eligibility was verified by a clinical trial physician after written informed consent was obtained.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomised IMP

Arm description: -

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

Dosage and administration details:

Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study.

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

Dosage and administration details:

Carvedilol will be started at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study

Arm title	Randomised Standard Care

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Non randomised

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Randomised IMP	Randomised Standard Care	Non randomised
Started	29	28	118
Completed	29	28	117
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Period 2	
Period 2 title	2 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomised IMP

Arm description: -

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

Dosage and administration details:

Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study.

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

Dosage and administration details:

Carvedilol will be started at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study

Arm title	Randomised Standard Care

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Non randomised

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Randomised IMP	Randomised Standard Care	Non randomised
Started	29	28	117
Completed	28	28	111
Not completed	1	0	6
Deceased	-	-	1
Consent withdrawn by subject	1	-	5

Period 3	
Period 3 title	6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Randomised IMP

Arm description: -

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

Dosage and administration details:

Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study.

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

Dosage and administration details:

Carvedilol will be started at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d. First dose will be started as soon as possible after randomisation and will continue until completion/withdrawal from the study

Arm title	Randomised Standard Care

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Non randomised

Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Randomised IMP	Randomised Standard Care	Non randomised
Started	28	28	111
Completed	28	28	106
Not completed	0	0	5
Deceased	-	-	1
Consent withdrawn by subject	-	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Randomised IMP
Reporting group description: -	
Reporting group title	Randomised Standard Care
Reporting group description: -	
Reporting group title	Non randomised
Reporting group description: -	

Reporting group values	Randomised IMP	Randomised Standard Care	Non randomised
Number of subjects	29	28	118
Age categorical Units: Subjects			
Adults (18-64 years)	21	21	100
From 65-84 years	8	7	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.0	53.5	52.1
standard deviation	± 14.1	± 13.3	± 11.0
Gender categorical Units: Subjects			
Female	23	22	107
Male	6	6	11
Disease Type Units: Subjects			
Breast Cancer	17	15	93
Non-Hodgkins Lymphoma	12	13	25
Smoking Units: Subjects			
Currently	2	5	12
Ex (<1 year)	2	0	9
Ex (>1 year)	5	5	29
Never	20	18	68
Pregnancy test			
Only recorded for female patients			
Units: Subjects			
Yes	11	12	51
No	12	10	56
Not Applicable	6	6	11
Reason no pregnancy test			
Only recorded for female patients who did not have a pregnancy test			
Units: Subjects			
Post-menopause	11	9	48
Post-sterilisation	1	1	5
Not Applicable	17	18	65
Diabettes			

Units: Subjects			
No history	29	28	114
Insulin dependent	0	0	3
Tablet controlled	0	0	1
Diet controlled	0	0	0
History of hypertension			
Units: Subjects			
Yes	2	4	10
No	27	24	108
History of coronary artery disease			
Units: Subjects			
Yes	0	2	3
No	29	26	115
History of heart failure			
Units: Subjects			
Yes	0	1	1
No	29	27	117
History of kidney disease			
Units: Subjects			
Yes	0	2	5
No	29	26	113
Planned anthracycline cycles			
Units: Subjects			
4 cycles	2	7	48
6 cycles	14	14	35
3 cycles	13	7	35
Radiotherapy received			
Units: Subjects			
Yes	16	15	79
No	12	13	32
Missing	1	0	7
Which breast			
Only recorded for patient who received radiotherapy.			
Units: Subjects			
Left	7	5	36
Right	6	8	35
Both	0	0	3
Not in breast	3	2	5
Not Applicable	13	13	39
Radiotherapy target			
Only recorded for patient who received radiotherapy 'Not in breast'.			
Units: Subjects			
Chest/mediastinum	2	1	1
Outside chest/mediastinum region	1	1	4
Not Applicable	26	26	113
Taken any concomitant medications			
Number of patients taking any concomitant medication, patients counted only once, but they could have been taking any number of medications.			
Units: Subjects			
Yes	16	21	61
No	13	7	57

Taken any prohibited Concomitant medications			
Number of patients taking any concomitant medication, patients counted only once, but they could have been taking any number of medications			
Units: Subjects			
Yes	0	0	0
No	29	28	118
Covariate Age Band Units: Subjects			
≥65	8	7	18
<65	21	21	100
Covariate Baseline LVEF Band Units: Subjects			
≥60	25	27	115
<60	4	1	3
Covariate Planned Cumulative Dose epirubicin Band Units: Subjects			
=300 mg/m²	14	7	37
>300 mg/m²	15	21	81
Height Units: cm			
arithmetic mean	166.5	167.2	165.4
standard deviation	± 8.1	± 8.4	± 7.9
Weight Units: kg			
arithmetic mean	70.73	82.51	76.63
standard deviation	± 14.99	± 16.74	± 16.51
Planned epirubicin dose			
Planned Cumulative Dose of epirubicin (or epirubicin equivalent).			
Units: mg/m²			
arithmetic mean	469.0	479.3	424.4
standard deviation	± 229.8	± 192.1	± 179.7

Reporting group values	Total		
Number of subjects	175		
Age categorical Units: Subjects			
Adults (18-64 years)	142		
From 65-84 years	33		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	152		
Male	23		
Disease Type Units: Subjects			
Breast Cancer	125		

Non-Hodgkins Lymphoma	50		
Smoking Units: Subjects			
Currently	19		
Ex (<1 year)	11		
Ex (>1 year)	39		
Never	106		
Pregnancy test			
Only recorded for female patients			
Units: Subjects			
Yes	74		
No	78		
Not Applicable	23		
Reason no pregnancy test			
Only recorded for female patients who did not have a pregnancy test			
Units: Subjects			
Post-menopause	68		
Post-sterilisation	7		
Not Applicable	100		
Diabettes Units: Subjects			
No history	171		
Insulin dependent	3		
Tablet controlled	1		
Diet controlled	0		
History of hypertension Units: Subjects			
Yes	16		
No	159		
History of coronary artery disease Units: Subjects			
Yes	5		
No	170		
History of heart failure Units: Subjects			
Yes	2		
No	173		
History of kidney disease Units: Subjects			
Yes	7		
No	168		
Planned anthracycline cycles Units: Subjects			
4 cycles	57		
6 cycles	63		
3 cycles	55		
Radiotherapy received Units: Subjects			
Yes	110		
No	57		
Missing	8		

Which breast			
Only recorded for patient who received radiotherapy.			
Units: Subjects			
Left	48		
Right	49		
Both	3		
Not in breast	10		
Not Applicable	65		
Radiotherapy target			
Only recorded for patient who received radiotherapy 'Not in breast'.			
Units: Subjects			
Chest/mediastinum	4		
Outside chest/mediastinum region	6		
Not Applicable	165		
Taken any concomitant medications			
Number of patients taking any concomitant medication, patients counted only once, but they could have been taking any number of medications.			
Units: Subjects			
Yes	98		
No	77		
Taken any prohibited Concomitant medications			
Number of patients taking any concomitant medication, patients counted only once, but they could have been taking any number of medications			
Units: Subjects			
Yes	0		
No	175		
Covariate Age Band			
Units: Subjects			
≥65	33		
<65	142		
Covariate Baseline LVEF Band			
Units: Subjects			
≥60	167		
<60	8		
Covariate Planned Cumulative Dose epirubicin Band			
Units: Subjects			
=300 mg/m²	58		
>300 mg/m²	117		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
Planned epirubicin dose			
Planned Cumulative Dose of epirubicin (or epirubicin equivalent).			
Units: mg/m²			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups	
Reporting group title	Randomised IMP
Reporting group description: -	
Reporting group title	Randomised Standard Care
Reporting group description: -	
Reporting group title	Non randomised
Reporting group description: -	
Reporting group title	Randomised IMP
Reporting group description: -	
Reporting group title	Randomised Standard Care
Reporting group description: -	
Reporting group title	Non randomised
Reporting group description: -	
Reporting group title	Randomised IMP
Reporting group description: -	
Reporting group title	Randomised Standard Care
Reporting group description: -	
Reporting group title	Non randomised
Reporting group description: -	

Primary: 1.1 Change on LVEF	
End point title	1.1 Change on LVEF
End point description:	
The primary outcome is the change in LVEF on cardiac MRI scan conducted 6 months after final anthracycline dose compared to baseline cardiac MRI scan conducted before anthracycline therapy starts. Change calculated as LVEF at 6 months minus LVEF at baseline. Both values should be present. Summary statistics are presented in end point "1.1 LVEF".	
End point type	Primary
End point timeframe:	
Change on LVEF on cardiac MRI scan (baseline to 6 months).	

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	97	
Units: %				
arithmetic mean (standard deviation)	-4.19 (± 7.4)	-4.33 (± 4.40)	-2.87 (± 6.12)	

Statistical analyses

Statistical analysis title	LVEF change-Efficacy-Adjusted-PRIMARY

Statistical analysis description:

PRIMARY: Adjusted Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy

Comparison groups	Randomised Standard Care v Randomised IMP
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.817 [2]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.373
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.593
upper limit	2.846

Notes:

[1] - Change calculated as LVEF at 6 months minus LVEF at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².
[2] - Significance level set at p<0.05.

Statistical analysis title	LVEF change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy - Sensitivity

Comparison groups	Randomised Standard Care v Randomised IMP
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.9272 [4]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	3.386

Notes:

[3] - Change calculated as LVEF at 6 months minus LVEF at baseline. Both values should be present. Outcome analysed using an non adjusted linear regression model.
[4] - Significance level set at p<0.05.

Statistical analysis title	LVEF change-Exploratory-Adjusted

Statistical analysis description:

Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Non randomised v Randomised Standard Care

Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.288 [6]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.708
upper limit	1.112

Notes:

[5] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[6] - Significant level set at p<0.05.

Statistical analysis title	LVEF change-Exploratory-Non Adjusted

Statistical analysis description:

Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Non randomised v Randomised Standard Care
Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	non-inferiority[7]
P-value	= 0.2467 [8]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.4667
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.963
upper limit	1.028

Notes:

[7] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour

[8] - Significance level set at p<0.05.

Secondary: 1.2 Left ventricular ejection fraction (LVEF)

End point title	1.2 Left ventricular ejection fraction (LVEF)

End point description:

These are the observed LVEF at the designated time point.

End point type	Secondary

End point timeframe:

First baseline MRI performed 21 Nov 2017 and final follow up MRI performed 01 Apr 2022.
The time between baseline and follow up MRI varied between 179 - 463 days.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	118	27
Units: %				
arithmetic mean (standard deviation)	69.38 (± 7.45)	69.07 (± 6.11)	69.33 (± 5.71)	65.74 (± 6.64)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	97		
Units: %				
arithmetic mean (standard deviation)	64.93 (± 5.90)	66.40 (± 6.29)		

Statistical analyses

Statistical analysis title	Change LVEF -Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in LVEF between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.917 [10]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.452
upper limit	4.28

Notes:

[9] - The mean of the within-person changes in LVEF between patients' pre and post-anthracycline MRI scans for the non randomised patients.
[10] - Outcome analysed using a paired t-test with a two One-Sided Tests (TOST) approach. Parameter shown normal or near-normal behavior.
95% CI Assessment: -2.0 < 1.63 , 4.10 > 2.0 Not equivalent

Secondary: 1.3 Ventricular Dysfunction at 6 months

End point title	1.3 Ventricular Dysfunction at 6 months

End point description:

Ventricular Dysfunction defined as a 10% points fall on LVEF from baseline to 6 months following final dose of anthracycline and a LVEF at 6 months below 50%.

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose. All available

data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: Patients				
Yes	0	0	0	
No	27	27	97	
Missing	1	1	14	

Statistical analyses

No statistical analyses for this end point

Secondary: 1.4 LVEF Fall below 40% at 6 months

End point title	1.4 LVEF Fall below 40% at 6 months

End point description:

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted 6 months after final anthracycline dose. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: Patients				
Yes	0	0	0	
No	27	27	97	
Missing	1	1	14	

Statistical analyses

No statistical analyses for this end point

Secondary: 1.5 LVEF Fall below 50% at 6 months

End point title	1.5 LVEF Fall below 50% at 6 months

End point description:

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted 6 months after final anthracycline dose. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: Patients				
Yes	0	0	0	
No	27	27	97	
Missing	1	1	14	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.1 Global Longitudinal myocardial Strain (GLS)

End point title	2.1 Global Longitudinal myocardial Strain (GLS)

End point description:

These are the observed GLS at the designated time point.

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	117	27
Units: -%				
arithmetic mean (standard deviation)	-16.71 (± 2.73)	16.09 (± 2.63)	-17.09 (± 1.91)	-16.21 (± 2.32)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	94		
Units: -%				
arithmetic mean (standard deviation)	-14.91 (± 1.96)	-16.69 (± 1.77)		

Statistical analyses

Statistical analysis title	Change GLS-Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on GLS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in GLS between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.026 [12]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.902
upper limit	-0.058

Notes:

[11] - The mean of the within-person changes in GLS between patients' pre and post-anthracycline MRI scans for the non randomised patients.
[12] - Outcome analysed using a paired t-test. Parameter shown normal or near-normal behaviour. Significance level set at $p<0.05$.

Secondary: 2.2 Change on GLS

End point title	2.2 Change on GLS

End point description:

Change in GLS on cardiac MRI scan conducted 6 months after final anthracycline dose compared to baseline cardiac MRI scan conducted before anthracycline therapy starts

End point type	Secondary

End point timeframe:

Change on GLS on cardiac MRI scan (baseline to 6 months).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	93	
Units: -%				
arithmetic mean (standard deviation)	0.58 (± 2.61)	1.19 (± 2.20)	0.48 (± 2.05)	

Statistical analyses

Statistical analysis title	GLS change-Efficacy-Adjusted

Statistical analysis description:

Adjusted Change on GLS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone – Efficacy

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.5923 [14]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.371
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.753
upper limit	1.012

Notes:

[13] - Change calculated as GLS at 6 months minus GLS at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².
[14] - Significance level set at p<0.05.

Statistical analysis title	GLS change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on GLS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy - Sensitivity.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.355 [16]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.613
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.932
upper limit	0.705

Notes:

[15] - Change calculated as GLS at 6 months minus GLS at baseline. Both values should be present. Outcome analysed using an Non-adjusted linear regression model.
[16] - Significance level set at p<0.05.

Statistical analysis title	GLS change-Exploratory-Adjusted

Statistical analysis description:

Change on GLS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[17]
P-value	= 0.0978 [18]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.749
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	1.639

Notes:

[17] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[18] - Significant level set at p<0.05.

Statistical analysis title	GLS change-Exploratory-Non-Adjusted

Statistical analysis description:

Change on GLS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	120
Analysis specification	Post-hoc
Analysis type	non-inferiority[19]
P-value	= 0.121 [20]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	1.614

Notes:

[19] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour.

[20] - Significance level set at p<0.05.

Secondary: 2.3 GLS relative fall >15%

End point title	2.3 GLS relative fall >15%

End point description:

Calculated as [(6 month value – baseline value)/baseline value]*100. GLS was measured at the Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose.

End point type	Secondary

End point timeframe:

>15% (relative) fall in GLS at 6 month post-anthracycline cMRI. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: Patients				
Yes	4	1	6	
No	23	26	87	
Missing	1	1	18	

Statistical analyses

No statistical analyses for this end point

Secondary: 2.4 GLS percent change

End point title	2.4 GLS percent change
End point description:	
Calculated as [(6 month value – baseline value)/baseline value]*100.	
End point type	Secondary
End point timeframe:	
Percentage Change on GLS on cardiac MRI scan (baseline to 6 months).	

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	93	
Units: %				
arithmetic mean (standard deviation)	-1.84 (± 16.64)	-5.93 (± 14.70)	-2.06 (± 11.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: 3.1 Global Circumferential myocardial Strain (GCS)

End point title	3.1 Global Circumferential myocardial Strain (GCS)
End point description:	
These are the observed GCS at the designated time point.	
End point type	Secondary
End point timeframe:	
Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose	

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	117	27
Units: %				
arithmetic mean (standard deviation)	-18.87 (± 3.43)	-18.03 (± 3.06)	-19.56 (± 2.30)	-18.83 (± 2.85)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	94		
Units: %				
arithmetic mean (standard deviation)	-17.73 (± 2.37)	-19.07 (± 2.25)		

Statistical analyses

Statistical analysis title	Change GCS -Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on GCS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in LVEF between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	non-inferiority[21]
P-value	= 0.006 [22]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.639
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.091
upper limit	-0.187

Notes:

[21] - The mean of the within-person changes in LVEF between patients' pre and post-anthracycline MRI scans for the non randomised patients.

[22] - Outcome analysed using a paired t-test. Parameter shown normal or near-normal behaviour. Significance level set at $p<0.05$.

Secondary: 3.2 Change on GCS

End point title	3.2 Change on GCS

End point description:

Change calculated as GCS at 6 months minus GCS at baseline.

End point type	Secondary

End point timeframe:

Change on GLS on cardiac MRI scan (baseline to 6 months).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	93	
Units: %				
arithmetic mean (standard deviation)	0.01 (± 3.69)	0.28 (± 2.41)	0.64 (± 2.19)	

Statistical analyses

Statistical analysis title	GCS change-Efficacy-Adjusted

Statistical analysis description:

Adjusted Change on GCS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone – Efficacy.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[23]
P-value	= 0.842 [24]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	1.807

Notes:

[23] - Change calculated as GCS at 6 months minus GCS at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[24] - Significance level set at p<0.05.

Statistical analysis title	GCS change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on GCS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy – Sensitivity

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
P-value	= 0.749 [26]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.273

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.975
upper limit	1.429

Notes:

[25] - Change calculated as GCS at 6 months minus GCS at baseline. Both values should be present. Outcome analysed using an Non-adjusted linear regression model.
[26] - Significance level set at p<0.05.

Statistical analysis title	GCS change-Exploratory-Adjusted

Statistical analysis description:

Change on GCS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Non randomised v Randomised Standard Care
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority[27]
P-value	= 0.443 [28]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.324
upper limit	0.583

Notes:

[27] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².
[28] - Significant level set at p<0.05.

Statistical analysis title	GCS change-Exploratory-Non-Adjusted

Statistical analysis description:

Change on GCS on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	120
Analysis specification	Post-hoc
Analysis type	non-inferiority[29]
P-value	= 0.47 [30]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.355
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.326
upper limit	0.616

Notes:

[29] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour.
[30] - Significance level set at p<0.05.

Secondary: 3.3 GCS relative fall >15%

End point title	3.3 GCS relative fall >15%

End point description:

15% (relative) fall in GCS at 6 month post-anthracycline cMRI.

End point type	Secondary

End point timeframe:

Change on GLS on cardiac MRI scan (baseline to 6 months). All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: Patients				
Yes	7	3	3	
No	20	24	90	
Missing	1	1	21	

Statistical analyses

No statistical analyses for this end point

Secondary: 3.4 GCS percent change

End point title	3.4 GCS percent change

End point description:

Calculated as [(6 month value – baseline value)/baseline value]*100.

End point type	Secondary

End point timeframe:

Percentage Change on GLS on cardiac MRI scan (baseline to 6 months).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	93	
Units: %				
arithmetic mean (standard deviation)	2.69 (± 20.97)	0.03 (± 15.66)	-1.81 (± 18.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: 4.1 Left Ventricular Mass (LVM)

End point title	4.1 Left Ventricular Mass (LVM)

End point description:

These are the observed LVM at the designated time point.

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	118	27
Units: g/m²				
arithmetic mean (standard deviation)	47.59 (± 12.08)	49.54 (± 8.20)	46.25 (± 8.43)	51.37 (± 11.24)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	97		
Units: g/m²				
arithmetic mean (standard deviation)	49.70 (± 7.36)	48.25 (± 7.96)		

Statistical analyses

Statistical analysis title	Change LVM-Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on LVEF on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in LVM between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	non-inferiority[31]
P-value	< 0.001 [32]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.103

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.283
upper limit	0.923

Notes:

[31] - The mean of the within-person changes in LVM between patients' pre and post-anthracycline MRI scans for the non randomised patients.
[32] - Outcome analysed using a paired t-test. Parameter shown normal or near-normal behaviour. Significance level set at $p<0.05$.

Secondary: 4.2 Change on LVM

End point title	4.2 Change on LVM
End point description:	
Change calculated as LVM at 6 months minus LVM at baseline.	
End point type	Secondary
End point timeframe:	
Change on LVM on cardiac MRI scan (baseline to 6 months)	

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	97	
Units: g/m²				
arithmetic mean (standard deviation)	3.19 (± 10.88)	0.00 (± 8.25)	2.10 (± 5.86)	

Statistical analyses

Statistical analysis title	LVM change-Efficacy-Adjusted
Statistical analysis description:	
Adjusted Change on LVM on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone – Efficacy	
Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[33]
P-value	= 0.184 [34]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	3.787
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.861
upper limit	9.435

Notes:

[33] - Change calculated as LVM at 6 months minus LVM at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[34] - Significance level set at p<0.05.

Statistical analysis title	LVM change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on LVM on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy – Sensitivity.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[35]
P-value	= 0.231 [36]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	3.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.086
upper limit	8.456

Notes:

[35] - Change calculated as LVM at 6 months minus LVM at baseline. Both values should be present. Outcome analysed using a Non-adjusted linear regression model

[36] - Significance level set at p<0.05

Statistical analysis title	LVM change-Exploratory-Adjusted

Statistical analysis description:

Change on LVM on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	non-inferiority[37]
P-value	= 0.213 [38]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.456
upper limit	1.006

Notes:

[37] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[38] - Significant level set at p<0.05.

Statistical analysis title	LVM change-Exploratory-Non-Adjusted

Statistical analysis description:

Change on LVM on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	non-inferiority[39]
P-value	= 0.136 [40]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.877
upper limit	0.671

Notes:

[39] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour.
[40] - Significance level set at p<0.05.

Secondary: 5.1 Left Ventricular Volume (LVV)

End point title	5.1 Left Ventricular Volume (LVV)

End point description:

These are the observed LVV at the designated time point.

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	118	27
Units: ml/m²				
arithmetic mean (standard deviation)	63.41 (± 15.36)	63.93 (± 9.88)	62.52 (± 11.09)	69.41 (± 13.85)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	97		
Units: ml/m²				
arithmetic mean (standard deviation)	64.11 (± 11.48)	63.62 (± 10.85)		

Statistical analyses

Statistical analysis title	Change LVV-Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on LVV on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in LVV between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	non-inferiority[41]
P-value	= 0.256 [42]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.162
upper limit	0.852

Notes:

[41] - The mean of the within-person changes in LVV between patients' pre and post-anthracycline MRI scans for the non randomised patients.
[42] - Outcome analysed using a paired t-test. Parameter shown normal or near-normal behaviour. Significance level set at $p<0.05$

Secondary: 5.2 Change on LVV

End point title	5.2 Change on LVV

End point description:

Change calculated as LVV at 6 months minus LVV at baseline.

End point type	Secondary

End point timeframe:

Change on LVV on cardiac MRI scan (baseline to 6 months).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	97	
Units: ml/m²				
arithmetic mean (standard deviation)	5.63 (± 8.91)	0.22 (± 9.80)	1.15 (± 9.96)	

Statistical analyses

Statistical analysis title	LVV change-Efficacy-Adjusted

Statistical analysis description:

Adjusted Change on LVV on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone – Efficacy

Comparison groups	Randomised IMP v Randomised Standard Care

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[43]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	6.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.591
upper limit	11.438

Notes:

[43] - Change calculated as LVV at 6 months minus LVV at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

Statistical analysis title	LVV change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on LVV on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy – Sensitivity

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[44]
P-value	= 0.039 [45]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	5.407
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.293
upper limit	10.522

Notes:

[44] - Change calculated as LVV at 6 months minus LVV at baseline. Both values should be present. Outcome analysed using a Non-adjusted linear regression model

[45] - Significance level set at p<0.05.

Statistical analysis title	LVV change-Exploratory-Adjusted

Statistical analysis description:

Change on LVV on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	non-inferiority[46]
P-value	= 0.708 [47]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.022
upper limit	3.423

Notes:

[46] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

[47] - Significant level set at p<0.05.

Statistical analysis title	LVV change-Exploratory-Non-Adjusted

Statistical analysis description:

Change on LVV on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	124
Analysis specification	Post-hoc
Analysis type	non-inferiority[48]
P-value	= 0.667 [49]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.932
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.208
upper limit	3.343

Notes:

[48] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour.

[49] - Significance level set at p<0.05.

Secondary: 6.1 Left Ventricular Area (LAA)

End point title	6.1 Left Ventricular Area (LAA)

End point description:

These are the observed LAA at the designated time point.

End point type	Secondary

End point timeframe:

Cardiac MRI scan conducted at baseline and at 6 months after final anthracycline dose.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	28	118	27
Units: cm²/m²				
arithmetic mean (standard deviation)	11.93 (± 2.48)	11.36 (± 2.39)	11.57 (± 2.61)	11.93 (± 1.82)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	91		
Units: cm^2/m^2				
arithmetic mean (standard deviation)	10.85 (± 2.03)	11.70 (± 2.50)		

Statistical analyses

Statistical analysis title	Change LAA -Non Randomised-Cardiotoxicity-NonAdju

Statistical analysis description:

Change on LAA on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity. Analysis of the mean of the within-person changes in LAA between patients' pre and post-anthracycline MRI scans for the non randomised patients.

Comparison groups	Non randomised v Non randomised
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	non-inferiority[50]
P-value	= 0.3185 [51]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.852
upper limit	0.28

Notes:

[50] - The mean of the within-person changes in LAA between patients' pre and post-anthracycline MRI scans for the non randomised patients.

[51] - Outcome analysed using a paired t-test. Parameter shown normal or near-normal behaviour. Significance level set at $p<0.05$.

Secondary: 6.2 Change on LAA

End point title	6.2 Change on LAA

End point description:

Change calculated as LAA at 6 months minus LAA at baseline.

End point type	Secondary

End point timeframe:

Change on LAA on cardiac MRI scan (baseline to 6 months).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	91	
Units: cm^2/m^2				
arithmetic mean (standard deviation)	-0.04 (± 2.43)	-0.52 (± 2.15)	0.29 (± 2.72)	

Statistical analyses

Statistical analysis title	LAA change-Efficacy-Adjusted

Statistical analysis description:

Adjusted Change on LAA on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone – Efficacy

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[52]
P-value	= 0.646 [53]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.305
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.021
upper limit	1.631

Notes:

[52] - Change calculated as LAA at 6 months minus LAA at baseline. Both values should be present. Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m^2 or >300 mg/m^2.

[53] - Significance level set at $p<0.05$.

Statistical analysis title	LAA change-Efficacy-Non-Adjusted-Sensitivity

Statistical analysis description:

Non-Adjusted Change on LAA on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy – Sensitivity.

Comparison groups	Randomised Standard Care v Randomised IMP
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[54]
P-value	= 0.444 [55]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.481
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.771
upper limit	1.734

Notes:

[54] - Change calculated as LAA at 6 months minus LAA at baseline. Both values should be present. Outcome analysed using a Non-adjusted linear regression model.
[55] - Significance level set at p<0.05.

Statistical analysis title	LAA change-Exploratory-Adjusted

Statistical analysis description:

Change on LAA on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority[56]
P-value	= 0.126 [57]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.856
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.956
upper limit	0.243

Notes:

[56] - Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².
[57] - Significant level set at p<0.05.

Statistical analysis title	LAA change-Exploratory-Non-Adjusted

Statistical analysis description:

Change on LAA on cardiac MRI scan (baseline to 6 months) - Statistical analysis - Low-risk vs High-risk - Exploratory. Estimated mean represents the Non-adjusted mean for the studied parameter by allocated intervention (non-randomised vs standard care alone).

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	118
Analysis specification	Post-hoc
Analysis type	non-inferiority[58]
P-value	= 0.161 [59]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.804
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.934
upper limit	0.325

Notes:

[58] - Sensitivity analysis: Outcome analysed using a non-adjusted linear regression model. Parameter shown normal or near-normal behaviour.
[59] - Significance level set at p<0.05.

Secondary: 7.1 Hs-cTnI

End point title	7.1 Hs-cTnI

End point description:

Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

Hs-cTnI (high sensitivity cardiac troponin I) assay at Cycle 1 (Baseline) and at 2 months. If the Hs-cTnI value at 2 months was missing, the value taken closest in time prior to this was used, until a non-missing value was found up to Cycle 2.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	28	111	28
Units: ng/L				
arithmetic mean (standard deviation)	2.09 (± 1.73)	4.89 (± 10.92)	1.17 (± 1.02)	27.39 (± 24.31)

End point values	Randomised Standard Care	Non randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	114		
Units: ng/L				
arithmetic mean (standard deviation)	36.25 (± 31.78)	17.36 (± 14.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7.2 Change in Hs-cTnI

End point title	7.2 Change in Hs-cTnI

End point description:

Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

Change between Hs-cTnI (high sensitivity cardiac troponin I) at baseline (cycle 1) and at 2 months. If the Hs-cTnI value at 2 months was missing, the value taken closest in time prior to this was used, until a non-missing value was found up to Cycle 2.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	28	109	
Units: ng/L				
arithmetic mean (standard deviation)	26.48 (± 24.41)	31.36 (± 32.47)	16.33 (± 14.90)	

Statistical analyses

Statistical analysis title	Change on Hs-cTnI - Efficacy - Adjusted

Statistical analysis description:

Change on Hs-cTnI (high sensitivity cardiac troponin I) (baseline to 2 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[60]
P-value	= 0.8464 [61]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.551
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.556
upper limit	14.454

Notes:

[60] - Change calculated as Hs-cTnI at baseline (cycle 1) minus Hs-cTnI at 2 months. Both values should be present. If the value at 2 months was missing, the value taken closest in time prior to this was used. Analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m². Parameter shown normal or near-normal behaviour.

[61] - Significance level set at p<0.05.

Statistical analysis title	Change on Hs-cTnI - Efficacy - Sensitivity - NonAd

Statistical analysis description:

Change on Hs-cTnI (high sensitivity cardiac troponin I) (baseline to 2 months) - Statistical analysis - Standard care plus IMP vs Standard care alone - Efficacy - Sensitivity

Comparison groups	Randomised Standard Care v Randomised IMP
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	non-inferiority[62]
P-value	= 0.538 [63]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-4.876
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.658
upper limit	10.906

Notes:

[62] - Change calculated as Hs-cTnI at baseline (cycle 1) minus Hs-cTnI at 2 months. Both values should be present. If the value at 2 months was missing, the value taken closest in time prior to this was used. Analysed using a non adjusted linear regression model. Parameter shown normal or near-normal behaviour.
[63] - Significance level set at p<0.05.

Statistical analysis title	Change on Hs-cTnI - Exploratory - adjusted

Statistical analysis description:

Change on Hs-cTnI (high sensitivity cardiac troponin I) (baseline to 2 months) - Statistical analysis - Low-risk vs High-risk - Exploratory

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[64]
P-value	< 0.001 [65]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	14.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.182
upper limit	22.414

Notes:

[64] - Change calculated as Hs-cTnI at baseline (cycle 1) minus Hs-cTnI at 2 months. Both values should be present. If the value at 2 months was missing, the value taken closest in time prior to this was used. Analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years , LVEF at baseline ≥60% or <60% and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m². Parameter shown normal or near-normal behaviour.
[65] - Significance level set at p<0.05.

Statistical analysis title	Change on Hs-cTnI - Exploratory - Non adjusted

Statistical analysis description:

Change on Hs-cTnI (high sensitivity cardiac troponin I) (baseline to 2 months) - Statistical analysis - Low-risk vs High-risk - Exploratory

Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	137
Analysis specification	Post-hoc
Analysis type	non-inferiority[66]
P-value	< 0.001 [67]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	15.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.774
upper limit	23.289

Notes:

[66] - Change calculated as Hs-cTnI at baseline (cycle 1) minus Hs-cTnI at 2 months. Both values should be present. If the value at 2 months was missing, the value taken closest in time prior to this was used. Analysed using an adjusted linear regression model.
[67] - Significance level set at p<0.05.

Secondary: 7.3.1 Hs-cTnI AUC - 3 Cycles

End point title	7.3.1 Hs-cTnI AUC - 3 Cycles

End point description:

For patients with 3 Planned cycles of Anthracycline. Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

Area under the curve (AUC) Calculated using the trapezium rule. AUC can only be calculated if there are more than four troponin values in the profile and one of the values has to be at baseline (i.e. cycle 1).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	7	32	
Units: (ng/L)*days				
arithmetic mean (standard deviation)	1588 (± 520)	3109 (± 4927)	1225 (± 893)	

Statistical analyses

Statistical analysis title	Hs-cTnI AUC 3 Cycles - Specificity

Statistical analysis description:

Hs-cTnI AUC 3 Cycles - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity

Comparison groups	Non randomised v Randomised Standard Care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	non-inferiority[68]
P-value	= 0.37 [69]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.1414
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.143

Notes:

[68] - Outcome analysed using an independent samples t-test, Unequal variances. Parameter has been log transformed and it shown normal or near-normal behaviour. The estimated mean difference represents the natural log mean difference of the AUC.
[69] - Significance level set at p<0.05.

Secondary: 7.3.2 Hs-cTnI AUC - 4 Cycles

End point title	7.3.2 Hs-cTnI AUC - 4 Cycles

End point description:

For patients with 3 Planned cycles of Anthracycline. Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

Area under the curve (AUC) Calculated using the trapezium rule. AUC can only be calculated if there are more than four troponin values in the profile and one of the values has to be at baseline (i.e. cycle 1).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	7	46	
Units: (ng/L)*days				
arithmetic mean (standard deviation)	1420 (± 98)	3174 (± 1580)	1605 (± 1150)	

Statistical analyses

Statistical analysis title	Hs-cTnI AUC 4 Cycles - Specificity

Statistical analysis description:

Hs-cTnI AUC 4 Cycles - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity

Comparison groups	Non randomised v Randomised Standard Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	non-inferiority[70]
P-value	= 0.008 [71]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.828
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.438
upper limit	-0.218

Notes:

[70] - Outcome analysed using an independent samples t-test, equal variances. Parameter has been log transformed and it shown normal or near-normal behaviour. The estimated mean difference represents the natural log mean difference of the AUC.

[71] - Significance level set at p<0.05.

Secondary: 7.3.3 Hs-cTnI AUC - 6 Cycles

End point title	7.3.3 Hs-cTnI AUC - 6 Cycles

End point description:

For patients with 3 Planned cycles of Anthracycline. Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

Area under the curve (AUC) Calculated using the trapezium rule. AUC can only be calculated if there are more than four troponin values in the profile and one of the values has to be at baseline (i.e. cycle 1).

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	14	32	
Units: (ng/L)*days				
arithmetic mean (standard deviation)	6590 (± 3528)	6052 (± 4188)	2516 (± 1559)	

Statistical analyses

Statistical analysis title	Hs-cTnI AUC 6 Cycles - Specificity
Statistical analysis description:	
Hs-cTnI AUC 6 Cycles - Statistical analysis - Specificity of hs-cTnI assay for cardiotoxicity	
Comparison groups	Randomised Standard Care v Non randomised
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	non-inferiority[72]
P-value	= 0.003 [73]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.787
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.305
upper limit	-0.27

Notes:

[72] - Outcome analysed using an independent samples t-test, equal variances. Parameter has been log transformed and it shown normal or near-normal behaviour. The estimated mean difference represents the natural log mean difference of the AUC.

[73] - Significance level set at $p<0.05$.

Secondary: 7.4 Chronic myocardial injury (MI) at 2 months or after

End point title	7.4 Chronic myocardial injury (MI) at 2 months or after
End point description:	
Defined as a persistent elevations of Hs-cTnI above the gender-specific 99th centile at 2 month follow up. If the 2-month follow up sample was not available then Hs-cTnI elevation above this threshold at any point beyond this was counted. Note 1: Gender specific thresholds (99% upper reference limit) for the Abbott ARCHITECHT assay are <16 ng/L (female) and <34 ng/L (male). Note 2: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.	
End point type	Secondary
End point timeframe:	
at 2 months or after randomisation. All available data used.	

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	117	
Units: Patients				
yes	10	15	34	
no	18	10	72	
missing	1	3	11	

Statistical analyses

No statistical analyses for this end point

Secondary: 7.5 Risk of severe and early on-treatment cardiotoxixity

End point title	7.5 Risk of severe and early on-treatment cardiotoxixity

End point description:

Defined as any hs-cTnI measurement of >80 ng/L during or after treatment (from cycle 1 to 6 months follow up). Note: When Hs-cTnI (high sensitivity cardiac troponin I) values were given as '<x ng/L', it was assumed that they were equal to x/2 ng/L.

End point type	Secondary

End point timeframe:

From cycle 1 to 6 months follow up. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	3	5	0	
no	26	23	116	
missing	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: 8.1 Death and cardiovascular death since consent

End point title	8.1 Death and cardiovascular death since consent

End point description:

At last observed point in the study for each patient, calculated from consent.

End point type	Secondary

End point timeframe:

Since consent. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
Alive	29	28	116	
Dead - Cardiovascular	0	0	0	
Dead - Other reason	20	0	2	

Statistical analyses

Statistical analysis title	Any Death

Statistical analysis description:

Note: There are not enough patients with events to perform any adjusted or unadjusted survival analysis

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 9999999 [74]
Method	Logrank

Notes:

[74] - Log-rang P-value : Not estimable

Secondary: 8.2 Any new diagnosis of heart failure

End point title	8.2 Any new diagnosis of heart failure

End point description:

End point type	Secondary

End point timeframe:

Counted from date of consent to date of last available observation for each patient. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	0	1	0	
no	29	27	118	

Statistical analyses

Statistical analysis title	New diagnosis of heart failure (HF) since consent
Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority[75]
P-value	= 9999999 [76]
Method	Logrank

Notes:

[75] - There are not enough patients with events to perform any adjusted or unadjusted survival analysis
[76] - Log-rank P-value : Not estimable

Secondary: 9.1 Pulse

End point title	9.1 Pulse

End point description:

Baseline measured before any dose of anthracycline is given (Cycle 1).

End point type	Secondary

End point timeframe:

Pulse at baseline, 2 months and 6 months

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	114	23
Units: bpm				
arithmetic mean (standard deviation)	77.43 (± 11.63)	81.82 (± 13.23)	78.59 (± 11.02)	80.13 (± 11.57)

End point values	Randomised Standard Care	Non randomised	Randomised IMP	Randomised Standard Care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	92	25	21
Units: bpm				
arithmetic mean (standard deviation)	83.80 (± 13.68)	85.11 (± 12.75)	73.56 (± 9.20)	84.76 (± 12.62)

End point values	Non randomised			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: bpm				
arithmetic mean (standard deviation)	77.22 (± 12.61)			

Statistical analyses

Statistical analysis title	Pulse at 6 months - Post Hoc - Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m²

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	non-inferiority[77]
P-value	= 0.003 [78]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-10.755
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.627
upper limit	-3.882

Notes:

[77] - Parameter shown normal or near-normal behaviour.

[78] - Significance level set at p<0.05

Statistical analysis title	Pulse at 6 months - Post Hoc - Non Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	46
Analysis specification	Post-hoc
Analysis type	non-inferiority[79]
P-value	= 0.001 [80]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-11.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.698
upper limit	-4.705

Notes:

[79] - Parameter shown normal or near-normal behaviour.

[80] - Significance level set at p<0.05

Secondary: 9.2 Systolic Blood Pressure

End point title	9.2 Systolic Blood Pressure

End point description:

Baseline was measured before any dose of anthracycline is given (Cycle 1).

End point type	Secondary

End point timeframe:

Systolic Blood Pressure at baseline, 2 months and 6 months

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	114	24
Units: mmHg				
arithmetic mean (standard deviation)	130.79 (± 16.57)	132.43 (± 18.42)	128.24 (± 16.34)	119.75 (± 21.65)

End point values	Randomised Standard Care	Non randomised	Randomised IMP	Randomised Standard Care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	92	25	22
Units: mmHg				
arithmetic mean (standard deviation)	131.92 (± 16.86)	123.21 (± 14.28)	117.92 (± 16.71)	127.68 (± 14.70)

End point values	Non randomised			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: mmHg				
arithmetic mean (standard deviation)	124.80 (± 14.71)			

Statistical analyses

Statistical analysis title	SBP at 6 months - Post Hoc - Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

Comparison groups	Randomised IMP v Randomised Standard Care

Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	non-inferiority[81]
P-value	= 0.121 [82]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-7.387
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.817
upper limit	2.043

Notes:

[81] - Parameter shown normal or near-normal behaviour.

[82] - Significance level set at p<0.05.

Statistical analysis title	SBP at 6 months - Post Hoc - Non Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m².

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	non-inferiority[83]
P-value	= 0.064 [84]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-8.762
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.066
upper limit	0.542

Notes:

[83] - Parameter shown normal or near-normal behaviour.

[84] - Significance level set at p<0.05.

Secondary: 9.3 Diastolic Blood Pressure

End point title	9.3 Diastolic Blood Pressure

End point description:

Baseline was measured before any dose of anthracycline is given (Cycle 1).

End point type	Secondary

End point timeframe:

Diastolic Blood Pressure at baseline, 2 months and 6 months

End point values	Randomised IMP	Randomised Standard Care	Non randomised	Randomised IMP
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	28	114	24
Units: mmHg				
arithmetic mean (standard deviation)	79.71 (± 12.43)	79.79 (± 11.27)	78.15 (± 9.69)	68.38 (± 11.22)

End point values	Randomised Standard Care	Non randomised	Randomised IMP	Randomised Standard Care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	92	25	22
Units: mmHg				
arithmetic mean (standard deviation)	81.0 (± 9.07)	76.37 (± 8.37)	72.60 (± 11.09)	79.32 (± 9.19)

End point values	Non randomised			
Subject group type	Reporting group			
Number of subjects analysed	86			
Units: mmHg				
arithmetic mean (standard deviation)	78.12 (± 10.02)			

Statistical analyses

Statistical analysis title	DBP at 6 months - Post Hoc - Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model. Covariates: age at consent ≥65 or <65 years, LVEF at baseline ≥60% or <60%, and planned cumulative epirubicin equivalent dose as =300 mg/m² or >300 mg/m²

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	non-inferiority[85]
P-value	= 0.055 [86]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-6.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.498
upper limit	0.152

Notes:

[85] - Parameter shown normal or near-normal behaviour.

[86] - Significance level set at p<0.05.

Statistical analysis title	DBP at 6 months - Post Hoc - Non Adjusted

Statistical analysis description:

Outcome analysed using an adjusted linear regression model.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	47
Analysis specification	Post-hoc
Analysis type	non-inferiority[87]
P-value	= 0.03 [88]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-6.718
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.752
upper limit	0.684

Notes:

[87] - Parameter shown normal or near-normal behaviour.

[88] - Significance level set at p<0.05.

Secondary: 9.4 Hypotension at 2 months

End point title	9.4 Hypotension at 2 months

End point description:

Hypotension is present if a systolic blood pressure strictly below(<) 90 mmHg occurred. If the value at 2 months is missing, the value taken closest in time prior to this was used until a non-missing value was found up to Cycle 2. Statistical analysis was planned but not feasible for this outcome.

End point type	Secondary

End point timeframe:

at 2 months. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	117	
Units: patients				
yes	0	0	0	
no	29	28	113	
missing	0	0	5	

Statistical analyses

No statistical analyses for this end point

Secondary: 9.5 Bradycardia at 2 months

End point title	9.5 Bradycardia at 2 months

End point description:

Bradycardia is present if a heart rate of fewer than 50 beats per minute (bpm) at 2 months occurred. If the value at 2 months is missing, the value taken closest in time prior to this was used until a non-missing value was found up to Cycle 2. Statistical analysis was planned but not feasible for this outcome.

End point type	Secondary

End point timeframe:

at 2 months. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	28	117	
Units: patients				
yes	0	0	0	
no	29	28	113	
missing	0	0	5	

Statistical analyses

No statistical analyses for this end point

Secondary: 10.1 Any hyperkalaemia

End point title	10.1 Any hyperkalaemia

End point description:

Hyperkalemia is an elevated level of potassium (K+) in the blood, (K+≥ 5.0 mmol/L).

End point type	Secondary

End point timeframe:

Measured at any point after randomisation. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	6	5	12	
no	23	23	104	
missing	0	0	2	

Statistical analyses

Statistical analysis title	Incidence of hyperkalaemia - Adjusted

Statistical analysis description:

Outcome analysed using logistic regression. The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone and the covariates were the binary fixed effects: age at consent ≥65 or <65 years, planned cumulative epirubicin equivalent dose 300 mg/m² or >300 mg/m² and baseline LVEF ≥60% or <60%.

Comparison groups	Randomised Standard Care v Randomised IMP
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.539 [89]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.378
upper limit	6.446

Notes:

[89] - Significance level set at p<0.05.

Statistical analysis title	Incidence of hyperkalaemia - Non Adjusted

Statistical analysis description:

Outcome analysed using logistic regression. The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.539 [90]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.321
upper limit	4.492

Notes:

[90] - Significance level set at p<0.05.

Secondary: 10.2 Any worsening renal function

End point title	10.2 Any worsening renal function

End point description:

Worsening renal function: Decrease in eGFR of > 25% from baseline or an increase in creatinine of > 30% from baseline. Baseline was measured before any dose of anthracycline is given (Cycle 1). Change calculated as (value at timepoint - value at baseline)/(value at baseline).

End point type	Secondary

End point timeframe:

Measured at any point after baseline. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	2	2	3	
no	27	26	110	
missing	0	0	5	

Statistical analyses

Statistical analysis title	Incidence of worsening renal function - Adjusted

Statistical analysis description:

The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone and the covariates were the binary fixed effects: age at consent ≥65 or <65 years, planned cumulative epirubicin equivalent dose 300 mg/m² or >300 mg/m² and baseline LVEF ≥60% or <60%.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority[91]
P-value	= 0.918 [92]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.135
upper limit	9.265

Notes:

[91] - Outcome analysed using logistic regression

[92] - Significance level set at p<0.05.

Statistical analysis title	Incidence of worsening renal function-NonAdjusted

Statistical analysis description:

The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority[93]
P-value	= 0.971 [94]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.963

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.126
upper limit	7.35

Notes:

[93] - Outcome analysed using logistic regression

[94] - Significance level set at p<0.05.

Secondary: 10.3 Any acute kidney injury

End point title	10.3 Any acute kidney injury

End point description:

Acute kidney injury: An eGFR drop to <45 ml/min/1.73m². Where eGRF = estimated glomerular filtration rate. Statistical analysis was planned but it is not feasible for this outcome

End point type	Secondary

End point timeframe:

Measured at any point after randomisation. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	0	0	0	
no	29	28	116	
missing	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: 10.4 Any fatigue

End point title	10.4 Any fatigue

End point description:

Fatigue grade ≥ 2 by Common terminology criteria for adverse events (CTCAE) classification.

End point type	Secondary

End point timeframe:

Measured at any point after randomisation. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	1	7	14	
no	28	21	102	
missing	0	0	2	

Statistical analyses

Statistical analysis title	Incidence of Fatigue - Adjusted

Statistical analysis description:

Outcome analysed using logistic regression. The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone and the covariates were the binary fixed effects: age at consent ≥65 or <65 years, planned cumulative epirubicin equivalent dose 300 mg/m² or >300 mg/m² and baseline LVEF ≥60% or <60%.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority[95]
P-value	= 0.057 [96]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	1.065

Notes:

[95] - Outcome analysed using logistic regression

[96] - Significance level set at p<0.05.

Statistical analysis title	Incidence of Fatigue - Non Adjusted

Statistical analysis description:

Outcome analysed using logistic regression. The main studied effect is: Standard care plus candesartan and carvedilol vs standard care alone.

Comparison groups	Randomised IMP v Randomised Standard Care
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	non-inferiority[97]
P-value	= 0.0437 [98]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.107

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.939

Notes:

[97] - Outcome analysed using logistic regression

[98] - Significance level set at p<0.05.

Secondary: 10.5 New diagnosis of atrial fibrillation

End point title	10.5 New diagnosis of atrial fibrillation

End point description:

Statistical analysis was planned but it is not feasible for this outcome.

End point type	Secondary

End point timeframe:

Measured at any point after randomisation. All available data used.

End point values	Randomised IMP	Randomised Standard Care	Non randomised	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	28	111	
Units: patients				
yes	0	0	0	
no	29	28	116	
missing	0	0	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From consent to last study visit for each participant	
Adverse event reporting additional description:	
The sites will only record symptoms of interest that could be considered an AR to the study intervention.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	Received intervention
Reporting group description:	
Participants who received at least one dose of Carvedilol or Candesartan	
Reporting group title	Not received Intervention
Reporting group description:	
Participants who did not receive any Carvedilol or Candesartan	

Serious adverse events	Received intervention	Not received Intervention	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 28 (21.43%)	17 / 147 (11.56%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Liver function test abnormal	Additional description: blood and lymphatic system disorders - deranged LFTs		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture	Additional description: 1 participant had T12 fracture 1 participant had a hip fracture		

subjects affected / exposed	0 / 28 (0.00%)	2 / 147 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose	Additional description: Deliberate overdose		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis	Additional description: Right internal jugular vein thrombosis		
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Thrombosis	Additional description: Right atrial thrombosis		
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness and syncope		
subjects affected / exposed	3 / 28 (10.71%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain	Additional description: 1 participant had Atypical chest pain 1 participant had pleuritic chest pain		
subjects affected / exposed	1 / 28 (3.57%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Worsening left leg rash and pyrexial		

subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Proptosis	Additional description: right eye proptosis		
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea (not meeting criteria for new or worsening heart failure)		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction	Additional description: Lower airway obstruction		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (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			
Pain in extremity	Additional description: Admitted to hospital wit sudden onset of leg pain		

subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 147 (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: 0 %

Non-serious adverse events	Received intervention	Not received Intervention	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 28 (60.71%)	7 / 147 (4.76%)	
Vascular disorders			
Mass	Additional description: Right atrial mass		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Hypotension	Additional description: 1 participant Hypotension secondary to neutropenic sepsis 1 participant hypotension grade 2		
subjects affected / exposed	1 / 28 (3.57%)	1 / 147 (0.68%)	
occurrences (all)	1	1	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness	Additional description: Dizziness and syncope		
subjects affected / exposed	16 / 28 (57.14%)	3 / 147 (2.04%)	
occurrences (all)	18	3	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea (not meeting criteria for new or worsening heart failure)		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash on hand at infusion site		
subjects affected / exposed	0 / 28 (0.00%)	1 / 147 (0.68%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2017	Protocol v2.0 was the initial approved protocol. SA01 - notified REC that co-enrolment with Add-Aspirin study would be permitted. Did various corrections, clarifications and defined visit windows in the protocol and updated to v3.0 The REC requested to include website details in the protocol and it was updated to v4.0
31 January 2018	SA02 Updated protocol inclusion criteria to allow recruitment of participants scheduled to receive 300 mg/m2 epirubicin dose, and 3 cycles of chemo. Updated co-enrolment section in protocol to clarify how co-enrolment would be recorded, and protocol version updated to v5.0
14 March 2018	SA03 Updated protocol inclusion criteria to include enrolment of non-Hodgkin Lymphoma patients scheduled for CHOP or R-CHOP. Update to randomisation minimisation section and protocol updated to v6.0
18 June 2018	SA05 Various sections in protocol updated including - can withdraw patients who didn't receive full anthracycline dose, clarify CHOP regimes permitted, expand to allow randomisation at any of cycles 2-6 if the cTnI threshold is reached, and clarification about SAE recording and reporting. Protocol updated to v7.0
27 May 2019	SA07 - Updated protocol to clarify timing of treatment allocation after randomisation and that IMP dose changes can be done at clinician discretion. Protocol updated to v8.0
04 September 2019	SA08 - updated protocol to permit IMP to be provided by post, and that cTnI could also be done using the Alinity assay. The protocol was updated to v9.0 Recruitment was temporarily halted due to the global pandemic.
14 June 2021	SA09 Update to the wording of secondary endpoints and they were split into groupings. Protocol updated to v10.0. A minor amendment followed to correct typos and the protocol was updated to v11.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

16 March 2020	Covid19 pandemic: the sponsor put a temporary halt to recruitment on 17 March 2020. Participants already enrolled continued their study visits as these coincided with cancer treatment. From 06 Jul 2020 the temporary halt was lifted. Sites were required to complete a risk assessment and following sponsor approval they were permitted to restart recruitment. Recruitment restarted, albeit at a slower rate.	06 July 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29217634

http://www.ncbi.nlm.nih.gov/pubmed/35766037