



Clinical trial results:

Feasibility study on the effects of L-citrulline on uteroplacental and cardiovascular function in hypertensive pregnant women.

Summary

EudraCT number	2015-005792-25
Trial protocol	GB
Global end of trial date	06 March 2019

Results information

Result version number	v1 (current)
This version publication date	18 March 2020
First version publication date	18 March 2020
Summary attachment (see zip file)	Cherry results (CHERRY Final Analysis Report v3.0 20190920.pdf)

Trial information

Trial identification

Sponsor protocol code	R04341
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Additional study identifiers

ISRCTN number	ISRCTN12695929
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC number: 16/NW/0557

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, research.sponsor@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, research.sponsor@mft.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2018
Global end of trial reached?	Yes
Global end of trial date	06 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Process outcome:

Recruitment rate (number of women eligible, recruited and completing study per month per centre)

Clinical outcome:

Reduction in diastolic blood pressure following L-citrulline supplementation compared with placebo (baseline compared 8 weeks post treatment)

Protection of trial subjects:

Trial monitoring was carried out to ensure that the rights and well-being of human participants were protected during the course of a clinical trial. A detailed risk assessment was performed for CHERRY to determine the level and type of monitoring required for specific hazards. Monitoring activities were carried out via central monitoring, this included safety and consent monitoring and site visits were conducted when required. A trial steering committee and Independent data safety & monitoring committee were convened and met regularly throughout the trial to provide independent oversight of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Randomisation start (first recruiting site opened): 04/07/2017. Randomisation end (last recruiting site closed): 31/01/2018. Recruitment planned at 2 sites in UK. Only 1 site opened.

Pre-assignment

Screening details:

42 patients screened, 41 eligible, 36 consented, 36 randomised.

Pre-assignment period milestones

Number of subjects started	42 ^[1]
Intermediate milestone: Number of subjects	Screened: 42
Intermediate milestone: Number of subjects	Eligible: 41
Intermediate milestone: Number of subjects	Consented: 36
Intermediate milestone: Number of subjects	Randomised: 36
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not provide consent: 5
Reason: Number of subjects	Ineligible: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients who started the pre-assignment period (screened = 42) is larger than the number who enrolled in the trial (randomised = 36).

Period 1

Period 1 title	Baseline & Analysis (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

L-citrulline

Arm type	Experimental
Investigational medicinal product name	L-citrulline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dietary supplements of L-Citrulline (3g)/ placebo were taken twice daily from randomisation, 14 +/-2 weeks gestational age until 22 +/-2 weeks gestational age (maximum 10 weeks).

Each 30ml of L Citrulline solution contains:

L Citrulline 3g

Orange syrup 4.5mL
Sodium methylhydroxybenzoate 24mg
Sodium propylhydroxybenzoate 6mg
Dilute hydrochloric acid 10% 0.069mL
Purified water to 30ml

Arm title	Arm B
Arm description:	
Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Dietary supplements of L-Citrulline (3g)/ placebo were taken twice daily from randomisation, 14 +/-2 weeks gestational age until 22+/-2 weeks gestational age (maximum 10 weeks).

Each 30ml of placebo solution contains:

Orange syrup 4.5mL
Sodium methylhydroxybenzoate 24mg
Sodium propylhydroxybenzoate 6mg
Dilute hydrochloric acid 10% 0.069mL
Purified water to 30ml

Number of subjects in period 1	Arm A	Arm B
Started	24	12
Completed	24	12

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description:	
L-citrulline	
Reporting group title	Arm B
Reporting group description:	
Placebo	

Reporting group values	Arm A	Arm B	Total
Number of subjects	24	12	36
Age categorical			
Age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	12	36
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	33.73	34.26	
standard deviation	± 4.09	± 4.42	-
Gender categorical			
Units: Subjects			
Female	24	12	36
Male	0	0	0
Antihypertensive medication			
Any antihypertensive medication taken if last 12 months			
Units: Subjects			
Yes	15	6	21
No	9	6	15
Cardiac disease			
Units: Subjects			
Yes	0	0	0
No	23	12	35
Data unobtainable	1	0	1
Diagnosis			
Units: Subjects			
Primary	19	11	30
Secondary	4	1	5
Data unobtainable	1	0	1

Ethnicity			
Units: Subjects			
Black African	6	2	8
Black Caribbean	1	2	3
East/ Central Asian	2	0	2
South Asian	2	0	2
White	12	8	20
Other	1	0	1
Viable pregnancies			
Number of past viable pregnancies			
Units: Subjects			
Zero	6	0	6
One	8	8	16
Two	3	1	4
Three	6	1	7
Four	0	0	0
Five	1	1	2
Six	0	0	0
Seven	0	1	1
Presence of Proteinuria			
Units: Subjects			
Yes	2	0	2
No	22	12	34
BMI			
Units: Kg/ m ²			
arithmetic mean	31.13	33.36	
standard deviation	± 7.59	± 10.16	-
Diastolic Blood pressure			
Units: mmHg			
arithmetic mean	86.96	93.47	
standard deviation	± 8.08	± 10.21	-
Gestational age			
Units: days			
arithmetic mean	94.08	95.42	
standard deviation	± 8.14	± 5.25	-
Systolic blood pressure			
Units: mmHg			
arithmetic mean	131.4	138.08	
standard deviation	± 11.65	± 15.47	-
Time since diagnosis			
Units: Years			
median	3.35	4.71	
inter-quartile range (Q1-Q3)	0.98 to 10.23	1.46 to 9.71	-

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
L-citrulline	
Reporting group title	Arm B
Reporting group description:	
Placebo	

Primary: Diastolic blood pressure

End point title	Diastolic blood pressure
End point description:	
<p>Change in diastolic BP (average of 3 readings) between randomisation (visit 1) and the 8 week clinic visit (visit 3). Within-patient change in diastolic BP from randomisation will be calculated by subtracting each patient's average diastolic BP measurement at randomisation (visit 1) from their average diastolic BP measurement at 8 weeks (visit 3). Standardised within-patient change in diastolic BP will be calculated by dividing each patient's change in diastolic BP from baseline by the number of days between visit 3 and visit 1.</p> <p>Within-patient change and standardised within-patient change from visit 1 to visit 3 of dBP was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).</p>	
End point type	Primary
End point timeframe:	
Change in diastolic BP between randomisation (visit 1) and the 8 week clinic visit (visit 3).	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: mmHg				
arithmetic mean (standard deviation)				
dBP differences	-1.82 (± 9.56)	-5 (± 12.21)		
dBP standardised differences	-0.03 (± 0.16)	-0.08 (± 0.2)		

Statistical analyses

Statistical analysis title	Exploratory regression dBP
Statistical analysis description:	
<p>Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.</p>	
Comparison groups	Arm A v Arm B

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.857
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.77
upper limit	6.5
Variability estimate	Standard error of the mean
Dispersion value	3.5

Notes:

[1] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size

Primary: Recruitment rates

End point title	Recruitment rates ^[2]
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End point description:

The primary process outcomes is overall recruitment rate, based on the screening logs. Recruitment rate = total number recruited / total eligible women entered on screening log. Recruitment rate (averaged over the entire recruitment period) was presented with 95% CI, along with the number of women eligible and recruited (see supplementary material for confidence interval).

End point type	Primary
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End point timeframe:

Screening occurred prior to randomisation.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No between group comparisons were conducted for this outcome.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[3]	12 ^[4]		
Units: persons				
Eligible	41	41		
Randomised	24	12		

Notes:

[3] - The number eligible (above) can only be provided overall for both arms (41).

[4] - The number eligible (above) can only be provided overall for both arms (41).

Statistical analyses

No statistical analyses for this end point

Primary: Acceptability of intervention

End point title	Acceptability of intervention ^[5]
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End point description:

Acceptability of the intervention was assessed based on feedback from questions 1-3 of a patient questionnaire:

Q1: The number (and percentage) of women who selected each response (i.e. who found taking the treatment easy, neither difficult/easy or difficult) will be summarised for each treatment group separately.

Q2: The number (and percentage) of women who described the taste of the treatment as delicious/pleasant (as opposed to neither unpleasant/awful) will be summarised for each treatment group separately.

Q3: The number (and percentage) of women who selected each response (i.e. missed doses every day, 1-2 times per week, 1-2 per month or hardly ever) will be summarised for each treatment group separately.

End point type	Primary
End point timeframe:	
After completion of intervention.	
Notes:	
[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: No between group comparisons were conducted for this outcome.	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[6]	10 ^[7]		
Units: persons				
Q1: Easy	18	8		
Q1: Neither difficult or easy	2	2		
Q1: Difficult	2	0		
Q2: Delicious	1	0		
Q2: Pleasant	12	4		
Q2: Unpleasant	8	6		
Q2: Awful	1	0		
Q3: Every day	0	1		
Q3: Once/ twice per week	8	2		
Q3: Once/ twice per month	4	2		
Q3: Hardly ever	10	5		

Notes:

[6] - n missing = 2

[7] - n missing = 2

Statistical analyses

No statistical analyses for this end point

Secondary: Ambulatory BP monitor

End point title	Ambulatory BP monitor
End point description:	
Within-patient change in average day and night time systolic and diastolic ABPM measurements from randomisation will be calculated by subtracting each patient's average visit 1 systolic ABPM measurement from their average visit 3 systolic ABPM measurement, for day and night time averages separately. Standardised within-patient change in average day and night time systolic and diastolic ABPM from baseline will be calculated by dividing each patient's change in average day and night time systolic ABPM by the number of days between visit 3 and visit 1, for day and night time averages separately.	
Within-patient change and standardised within-patient change from visit 1 to visit 3 of ABPM measurements was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).	
End point type	Secondary

End point timeframe:

Change in average day and night time ambulatory BP monitor (ABPM) measurements (systolic and diastolic) between randomisation (visit 1) and the 8 week clinic visit (visit 3).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20 ^[8]	9 ^[9]		
Units: mmHg				
arithmetic mean (standard deviation)				
day time sBP differences	-0.35 (± 7.18)	-2.78 (± 6.82)		
day time sBP standardised differences	-0.003 (± 0.12)	-0.04 (± 0.12)		
night time sBP differences	0.18 (± 8.92)	3.29 (± 8.6)		
night time sBP standardised differences	0.01 (± 0.16)	0.06 (± 0.15)		
day time dBP differences	-2.05 (± 7.25)	-3.11 (± 5.97)		
day time dBP standardised differences	-0.03 (± 0.13)	-0.05 (± 0.1)		
night time dBP differences	0.41 (± 7.67)	2 (± 5.63)		
night time dBP standardised differences	0.01 (± 0.13)	0.04 (± 0.09)		

Notes:

[8] - Day time: n=20, n missing= 4. Night time: n=17, n missing=7

[9] - Day time: n=9, n missing= 3. Night time: n=7, n missing=5

Statistical analyses

Statistical analysis title	Exploratory regression day time sBP (ABPM)
Statistical analysis description:	
Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	= 0.354
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	8.63
Variability estimate	Standard error of the mean
Dispersion value	2.87

Notes:

[10] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression night time sBP (ABPM)
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other ^[11]
P-value	= 0.4128
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.62
upper limit	4.97
Variability estimate	Standard error of the mean
Dispersion value	3.98

Notes:

[11] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Note: for ABPM night time exploratory regression analysis the group numbers are n=17 for L-citrulline and n=7 for placebo (overall n=24).

Statistical analysis title	Exploratory regression day time dBP (ABPM)
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	= 0.9779
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.04
upper limit	5.88
Variability estimate	Standard error of the mean
Dispersion value	2.89

Notes:

[12] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression night time dBP (ABPM)
Statistical analysis description:	
Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other ^[13]
P-value	= 0.4103
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.78
upper limit	3.74
Variability estimate	Standard error of the mean
Dispersion value	3

Notes:

[13] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Note: for ABPM night time exploratory regression analysis the group numbers are n=17 for L-citrulline and n=7 for placebo (overall n=24).

Secondary: Cardiovascular compliance

End point title	Cardiovascular compliance
End point description:	
Within-patient change in central BP, PWV and normalised augmentation index was calculated by subtracting each patient's randomisation measurements from their 8 week measurements. Standardised within-patient change in measurement from baseline was calculated by dividing each patient's change in measurement from randomisation by the number of days between visit 3 and visit 1.	
Normalised augmentation index aortic values are calculated as follows: Augmentation Index Aortic – $0.431 \times (75 - \text{Heart rate})$	
Standardised within-patient change from visit 1 to visit 3 of each vascular compliance measurement was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).	
End point type	Secondary
End point timeframe:	
Change in vascular compliance measurements (central BP, pulse wave velocity (PWV) and normalised augmentation index) measured at randomisation (visit 1) and the 8 week clinic visit (visit 3).	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14 ^[14]	8 ^[15]		
Units: (see below)				
arithmetic mean (standard deviation)				
central BP differences (mmHg)	-4.86 (± 19.42)	-6.28 (± 29.03)		
central BP standardised differences (mmHg)	-0.08 (± 0.32)	-0.1 (± 0.5)		
PWV differences (m/s)	-0.36 (± 0.94)	0.04 (± 1.51)		
PWV standardised differences (m/s)	-0.01 (± 0.02)	0.0006 (± 0.03)		
Augmentation index differences (%)	-4.95 (± 10.14)	-1.73 (± 41.82)		
Augmentation index standardised differences (%)	-0.08 (± 0.17)	-0.01 (± 0.74)		

Notes:

[14] - n missing = 10

[15] - n missing = 4

Statistical analyses

Statistical analysis title	Exploratory regression central BP
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other ^[16]
P-value	= 0.8498
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.82
upper limit	20.21
Variability estimate	Standard error of the mean
Dispersion value	8.81

Notes:

[16] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression PWV
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.4429
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	0.71
Variability estimate	Standard error of the mean
Dispersion value	0.54

Notes:

[17] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size

Statistical analysis title	Exploratory regression normalised AIO
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.8788
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.46
upper limit	23.7
Variability estimate	Standard error of the mean
Dispersion value	12.18

Notes:

[18] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Secondary: Vascular compliance

End point title	Vascular compliance
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End point description:

Within-patient change in vascular compliance measure was calculated by subtracting each patient's visit 1 vascular compliance measurement from their visit 3 vascular compliance measurement. Standardised within-patient change in vascular compliance measurements was calculated by dividing each patient's change in vascular compliance measurement by the number of days between visit 3 and visit 1.

Within-patient change and standardised within-patient change from visit 1 to visit 3 of ADMA concentration and Arginine concentrations was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).

End point type	Secondary
End point timeframe:	
Change in vascular compliance measurements (cardiac output (CO), cardiac index (CI), stroke volume index (SVI) and total peripheral resistance index (TPRI) between randomisation (visit 1) and the 8 week clinic visit (visit 3).	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[19]	12 ^[20]		
Units: (see below)				
arithmetic mean (standard deviation)				
CO (L/minute) differences	-0.54 (± 1.75)	-1.18 (± 1.22)		
CO (L/minute) standardised differences	-0.01 (± 0.03)	-0.02 (± 0.02)		
CI (L/min/m ²) differences	-0.28 (± 0.88)	-0.57 (± 0.63)		
CI (L/min/m ²) standardised differences	-0.01 (± 0.01)	-0.01 (± 0.01)		
SVI (ml/m ²) differences	-4.43 (± 10.69)	-7.82 (± 8.3)		
SVI (ml/m ²) standardised differences	-0.08 (± 0.17)	-0.13 (± 0.14)		
TPRI (mmHg ml ⁻¹ min ⁻¹ kg ⁻¹) differences	140.35 (± 1508.87)	574.92 (± 963.77)		
TPRI (mmHg ml ⁻¹ min ⁻¹ kg ⁻¹) standardised diffs	2.89 (± 23.58)	9.25 (± 16.61)		

Notes:

[19] - n missing = 1

[20] - For CO, CI and TRPI: n=12, n missing = 0

For SVI: n=11, n missing = 1

Statistical analyses

Statistical analysis title	Exploratory regression CO
Statistical analysis description:	
Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[21]
P-value	= 0.8731
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.84
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[21] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression CI
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[22]
P-value	= 0.8808
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[22] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression SVI
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[23]
P-value	= 0.4211
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	6.75
Variability estimate	Standard error of the mean
Dispersion value	2.36

Notes:

[23] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Note: for SVI exploratory regression analysis the group numbers are n=23 for L-citrulline and n=11 for

placebo (overall n=34).

Statistical analysis title	Exploratory regression TRPI
Statistical analysis description:	
Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.	
Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[24]
P-value	= 0.6493
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-135.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-738.18
upper limit	466.89
Variability estimate	Standard error of the mean
Dispersion value	295.43

Notes:

[24] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Secondary: Uteroplacental measurements (continuous)

End point title	Uteroplacental measurements (continuous)
End point description:	
Within-patient change in RI and PI was calculated by subtracting each patient's visit 1 RI or PI measurement from their visit 3 RI or PI measurement. Standardised within-patient change in RI and PI measurements was calculated by dividing each patient's change in RI or PI measurement by the number of days between visit 3 and visit 1.	
Within-patient change and standardised within-patient change from visit 1 to visit 3 of RI and PI was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).	
End point type	Secondary

End point timeframe:

Change in uteroplacental blood flow measurements (uterine artery resistance index (RI) and pulsatility index (PI)) from randomisation (visit 1) to 8 weeks (visit 3).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23 ^[25]	12 ^[26]		
Units: Ratio				
arithmetic mean (standard deviation)				
RI differences	-0.1 (± 0.11)	-0.08 (± 0.09)		
RI standardised differences	-0.002 (± 0.002)	-0.001 (± 0.002)		

PI differences	-0.43 (± 0.43)	-0.37 (± 0.34)		
PI standardised differences	-0.01 (± 0.01)	-0.01 (± 0.01)		

Notes:

[25] - n missing = 1

[26] - n missing = 0

Statistical analyses

Statistical analysis title	Exploratory regression RI
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[27]
P-value	= 0.7345
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

[27] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Statistical analysis title	Exploratory regression PI
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Statistical analysis description:

Exploratory regression analyses was conducted using ANCOVA for each continuous outcomes to directly account for the duration in days between visit 1 and visit 3 when assessing the change in outcome from visit 1 to visit 3. In particular, the visit 3 outcome was regressed against visit 1 outcome, treatment group and duration (in days) between visit 1 and visit 3.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other ^[28]
P-value	= 0.8704
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.21

Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[28] - Exploratory regression analyses. These analyses are viewed as entirely hypothesis generating, rather than confirmatory analyses, in light of the small sample size.

Secondary: Uteroplacental measurments (discrete)

End point title	Uteroplacental measurments (discrete)
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End point description:

Presence/absence of notching. Bilateral notching is defined as "L Notch" = Yes and "R Notch" = Yes, and change in bilateral notching is defined as patients with bilateral notching at visit 1 no longer having bilateral notching at visit 3.

End point type	Secondary
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End point timeframe:

Change in uteroplacental blood flow measurements (presence of bilateral notching) from randomisation (visit 1) to 8 weeks (visit 3).

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: persons				
Visit 1 notchings present	10	2		
Visit 3 notchings present	5	0		
Change in notchings	5	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma ADMA and Arginie

End point title	Plasma ADMA and Arginie
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End point description:

Within-patient change in plasma ADMA concentration and Arginine concentration was calculated by subtracting each patient's visit 1 concentrations from their visit 3 concentrations. Standardised within-patient change in concentration was calculated by dividing each patient's change in concentration by the number of days between visit 3 and visit 1.

Within-patient change and standardised within-patient change from visit 1 to visit 3 of ADMA concentration and Arginine concentrations was presented using mean and 95% confidence interval for each treatment group separately. (See supplementary material for confidence intervals).

End point type	Secondary
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End point timeframe:

Change in plasma ADMA and arginine concentrations between randomisation (visit 1) and the 8 week clinic visit (visit 3)

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21 ^[29]	11 ^[30]		
Units: µmol/L				
arithmetic mean (standard deviation)				
Plasma ADMA differences	0.01 (± 0.05)	-0.01 (± 0.05)		
Plasma ADMA standardised differences	0.0002 (± 0.0008)	-0.0002 (± 0.0008)		
Arginine differences	6.86 (± 36.34)	-2.55 (± 13.34)		
Arginine standardised differences	0.14 (± 0.62)	-0.04 (± 0.23)		

Notes:

[29] - Plasma ADMA: n=19, n missing=5

Arginine: n=21, n missing = 3

[30] - Plasma ADMA: n=8, n missing=4

Arginine: n=11, n missing = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Antihypertensive therapy

End point title	Antihypertensive therapy
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End point description:

Antihypertensive therapy (AHT) information was used to determine whether patients were taking antihypertensive therapy at visit 1 or visit 3, for at least one of "Methyldopa", "Labetalol", "Beta blocking agent" or "Calcium channel antagonist". The number of patients who are taking antihypertensive therapy at visit 1 is presented for each treatment group separately. The number of patients who are taking antihypertensive therapy at visit 3 will be presented for each treatment group separately. The number of patients who change from taking (any) antihypertensive therapy from visit 1 to visit 3 is presented for each treatment group separately

End point type	Secondary
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End point timeframe:

Change in antihypertensive therapy from visit 1 to visit 3.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[31]	12 ^[32]		
Units: persons				
Visit 1 AHT	16	6		
Visit 3 AHT	13	6		

Notes:

[31] - AHT: Visit 1 only n = 3, visit 1 & 3 n = 13 (overall n = 16)

[32] - AHT: Visit 1 only n = 0, visit 1 & 3 n = 6 (overall n = 6)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Pregnancy outcomes (continuous)

End point title	Pregnancy outcomes (continuous)
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End point description:

Post- hoc summaries for the status and outcomes after giving birth. Continuous outcomes presented with means and standard deviation. Categorical outcomes present using frequencies.

End point type	Post-hoc
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End point timeframe:

Status and outcomes of pregnancy after giving birth.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: (see below)				
arithmetic mean (standard deviation)				
Gestational age (days)	264.0 (± 12.2)	259.8 (± 12.1)		
Birthweight (grams)	2846.8 (± 622.1)	3123.6 (± 707.8)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Pregnancy outcomes (discrete)

End point title	Pregnancy outcomes (discrete)
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End point description:

Post- hoc summaries for the status and outcomes after giving birth. Continuous outcomes presented with means and standard deviation. Categorical outcomes present using frequencies.

End point type	Post-hoc
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End point timeframe:

Status and outcomes of pregnancy after giving birth.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	12		
Units: persons				
Live born: Yes	24	12		
Gender: Female	14	5		
Gender: Male	10	7		
Magnesium sulfate required: Yes	1	0		
Steroids required: Yes	5	2		
Preeclampsia: Yes	5	3		
Chronic hypertension: Yes	24	12		
SGA by population centile: Yes	7	3		
FGR: Yes	7	3		
Pregestational diabetes: Yes	3	3		
Gestational diabetes: Yes	4	0		

Perinatal outcome: Alive	24	12		
Perinatal survival: Yes	24	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

The appearance or worsening of any undesirable sign, symptom, or medical condition occurring after the study has commenced, even if not considered to be related to the study.

See uploaded results for details of non-serious adverse events.

Adverse event reporting additional description:

Medical conditions/diseases present before starting the study will only be considered as adverse events if they worsen after the start of the study. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	L-citrulline safety set
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Reporting group description:

Any participant who received at least 1 dose of L-citrulline.

Reporting group title	Placebo safety set
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Reporting group description:

Any participant who received at least one dose of placebo.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious adverse events not coded using MedDRA so these are included in the main study report which is attached.

Serious adverse events	L-citrulline safety set	Placebo safety set	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Foetal disorder	Additional description: Fetal ventriculomegaly diagnosed on fetal MRI on 8th May 2018. Participant delivered on 26th May 2018. Baby well at birth and will have neonatal follow-up.		
subjects affected / exposed	0 / 24 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	L-citrulline safety set	Placebo safety set	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 24 (0.00%)	0 / 12 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2017	Amendment 2: Submitted to meet MHRA conditions on initial approval Approved by MHRA – 19/03/2017 Approved by REC – 27/03/2017 Approved by HRA – 23/03/2017 (initial approval) IB document update -As per MHRA recommendations to clarify stability data testing. Contact card - This was omitted from the original application in error. Change to participant questionnaire - Removal of question 1
23 March 2017	Amendment 1: Inclusion of IRAS ID on patient information sheets. Approved by HRA – 23/03/2017 (initial approval) Approved by MHRA – N/A Approved by REC – N/A
03 July 2017	Amendment 3: Submitted to amend the protocol Approved by MHRA – 18/08/2017 Approved by REC – 03/07/2017 Approved by HRA - 31/08/2017 Protocol - ABPM will now be issued at study visit 1 and 3 Patient information sheets ABPM will now be issued at study visit 1 and 3 Change of PI at St Thomas' Hospital
24 August 2017	Amendment 4: Submitted to amend PISCs Approved by HRA and REC - 24/08/2017 Approved by MHRA – N/A Amendment to Patient Information sheets to clarify what scans are optional research scans and inclusion of further data protection information
17 November 2017	Amendment 5: Submitted to clarify that other sites within MFT can identify patients for CHERRY and amend the Sponsor name throughout the protocol Approved by MHRA – N/A Approved by REC – 17/11/2017 Approved by HRA – 23/11/2017

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported