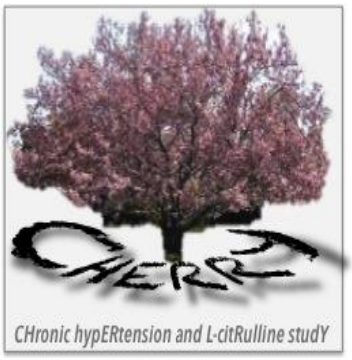

CHERRY Trial

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

EudraCT No. 2015-005792-25

Final Analysis Report V3.0

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
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Date	20/09/2019		
Protocol Version and Date	V4.0 23/10/2017		

Change Control

Updated version no.	Shell section changed	Description of change	Date changed	Initials
V2.0	Post-Hoc analysis 1 – pregnancy outcomes	Added section for pregnancy outcomes as post-hoc analyses	04/04/2019	AB
V3.0	Section 6.6.6	Added the analysis of the lab data (ADMA)	21/08/2019	AB
V3.0	Section 6.6.6	Added the analysis of the lab data (Arginine)	20/09/2019	AB
V3.0	Section 6.2.3	Added details of serious breaches of GCP	21/08/2019	AB

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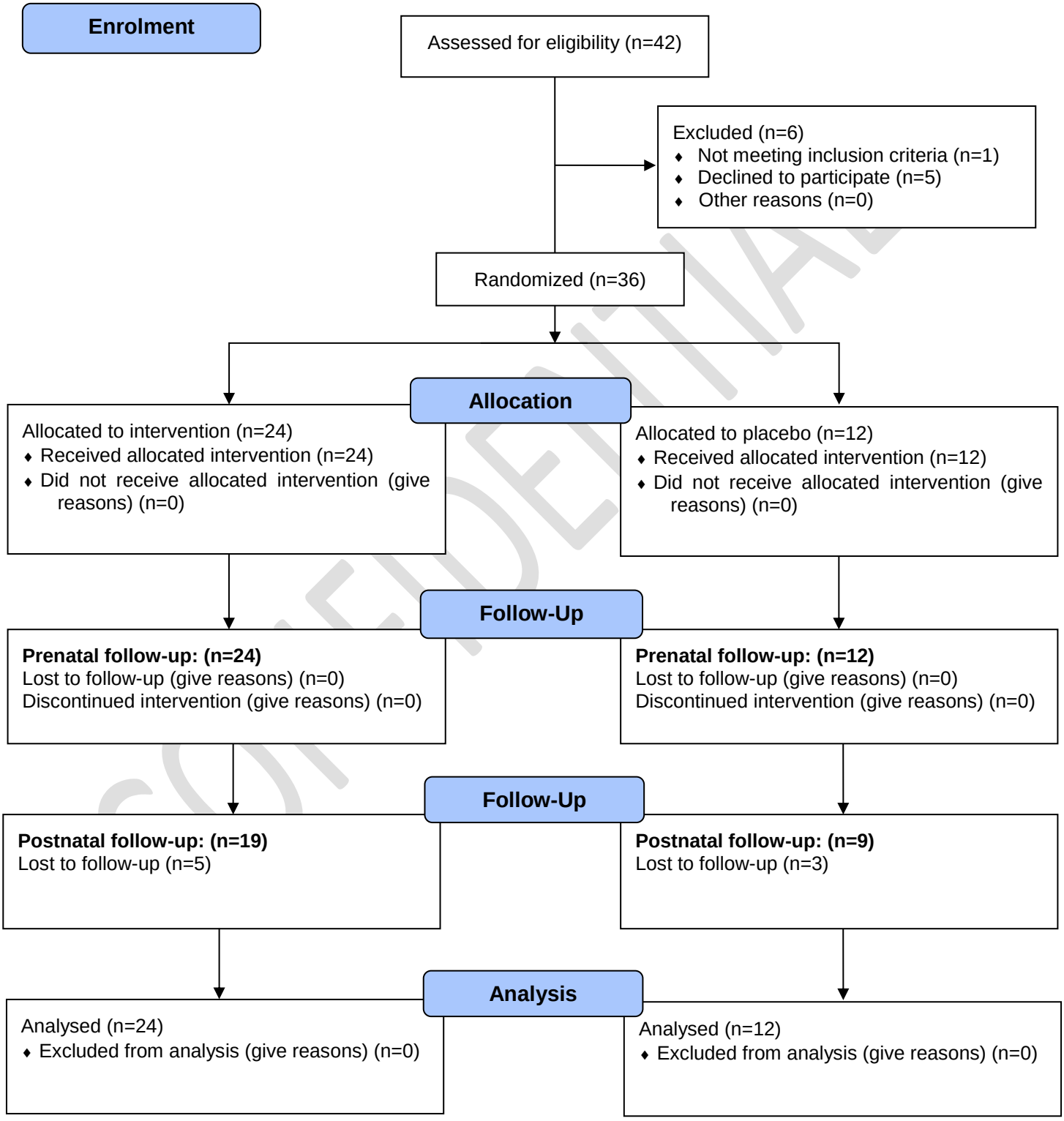

4. Randomisation

4.1 Randomisation checks

Table 4.1-1 Out of sequence or missing randomisation numbers

Randomisation number out of sequence/ missing	Description of issue	Explanation
CH0002	Randomisation number missing	See below*
CH0003	Randomisation number missing	See below*

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\00_01-EXTRACT allocations.sas

****Note:*** There was a problem with the system when randomisation numbers CH0002 and CH0003 were skipped, which meant the second patient randomised was assigned randomisation number CH0004 instead of CH0002. However, they did receive the second allocation from the allocation schedule. The incident was investigated by the information systems team and they concluded that the incident was an isolated incident and there was no cause for concern. The randomising statistician confirmed that there was no impact to treatment allocation distribution and the allocation schedule has not been affected.

5. Recruitment and screening

5.1 Screening summary

Table 5.1-1 Summary of screening logs

Centre Code	Hospital	Number screened [i]	Number eligible (% of [i]) [ii]	Number ineligible (% of [i]) [iii]	Number eligible and consenting (% of [ii]) [iv]	Number eligible but not consenting (% of [ii]) [v]	Number not randomised (eligible and consented) (% of [iv]) [vi]	Number randomised (% of [iv]) [vii]
0035	St. Mary's	42	41 (97.6%)	1 (2.4%)	36 (87.8%)	5 (12.2%)	0 (0.00%)	36 (100%)
0053[A]	St. Thomas's	NA	NA	NA	NA	NA	NA	NA
Total		**42**	**41 (97.6%)**	**1 (2.4%)**	**36 (87.8%)**	**5 (12.2%)**	**0 (0.00%)**	**36 (100%)**

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\01-Sreening and recruitment.SAS

[A] ***Note:*** Due to contractual delays site never opened to recruitment.

Table 5.1-2 Reasons screen patients were ineligible

Reasons For ineligibility	N (% of [iii])
1C: Diastolic BP < 89 mmHg (average of two clinical readings) or BP < 79 mmHg (if taking antihypertensive medication) or PWV < 9ms/ before 16 weeks	1 (100%)

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Table 5.1-3 Reasons eligible patients declined consent

Reasons For declining consent	N (% of [v])

2C: Does not wish to be randomly assigned treatment	2 (40.0%)
2B: Does not wish to take part in research	3 (60.0%)

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5.2 Randomisation Summary

Table 5.2-1 Randomisation Summary

Centre Code	Hospital	Date of site opening	Date of Site closed	First randomisation	Last randomisation	Number recruited (randomised and consented) L-citrulline	Number recruited (randomised and consented) Placebo
0035	St. Mary's Hospital	01-Jul-17	31-Jan-18	04-Jul-17	29-Jan-18	24	12
0053	St. Thomas's Hospital	NA	NA	NA	NA	NA	NA
					Total	**24**	**12**

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\01-Sreening and recruitment.SAS

6. Tables

6.1 Baseline characteristics

6.1.1 Demographic details

Table 6.1-1 Baseline demographic and disease details for continuous variables
SD=standard deviation, LQ=lower quartile, UQ=upper quartile

Variable	Treatment	N	N missing	Mean	SD	Median	LQ	UQ	Min	Max
Age (Years)	Overall	36	0	33.91	4.15	34.17	31.48	36.67	24.43	42.97
	L-citrulline	24	0	33.73	4.09	33.84	31.05	35.56	26.42	42.97
	placebo	12	0	34.26	4.42	35.97	32.72	37.7	24.43	38.26
BMI (KG/m^2)	Overall	36	0	31.87	8.46	29.48	26.8	34.41	16.36	51.9
	L-citrulline	24	0	31.13	7.59	28.98	27.96	32.99	20.81	51.9
	placebo	12	0	33.36	10.16	31.47	25.32	42.15	16.36	50.19
Diastolic BP (mmHg)	Overall	36	0	89.13	9.24	89.83	82.5	95.17	73	116.33
	L-citrulline	24	0	86.96	8.08	85.83	81.67	93	73	102.33
	placebo	12	0	93.47	10.21	93	86.67	99.17	77.33	116.33
Gestational Age (days)	Overall	36	0	94.53	7.26	94	89.5	99	84	110
	L-citrulline	24	0	94.08	8.14	91	87.5	98.5	84	110
	placebo	12	0	95.42	5.25	95	93.5	99.5	84	102
Systolic BP (mmHg)	Overall	36	0	133.63	13.21	132	122.5	140	113.33	158.33
	L-citrulline	24	0	131.4	11.65	130.67	122.5	135.83	115.67	156.67
	placebo	12	0	138.08	15.47	138.67	124.5	152.5	113.33	158.33
Years since diagnosis (Years)	Overall	36	0	5.94	5.33	3.82	1.22	10.23	0.02	20.04
	L-citrulline	24	0	5.88	5.25	3.35	0.98	10.23	0.02	15.83
	placebo	12	0	6.06	5.73	4.71	1.46	9.71	0.94	20.04

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Table 6.1-2 Baseline demographic and disease details for categorical baseline variables

Variable	Demographic	L-citrulline	Placebo	Overall
Age (Categorical), n(%)	**N**	**24**	**12**	**36**
	Adult	24 (100%)	12 (100%)	36 (100%)
Antihypertensive treatment last 12 months, n(%)	**N**	**24**	**12**	**36**
	No	9 (37.5%)	6 (50.0%)	15 (41.7%)
	Yes	15 (62.5%)	6 (50.0%)	21 (58.3%)
Cardiac disease, n(%)	**N**	**24**	**12**	**36**
	No	23 (95.8%)	12 (100%)	35 (97.2%)
	Data unobtainable	1 (4.2%)	0 (0.0%)	1 (2.8%)
Diagnosis, n(%)	**N**	**24**	**12**	**36**
	Primary	19 (79.2%)	11 (91.7%)	30 (83.3%)
	Secondary	4 (16.7%)	1 (8.3%)	5 (13.9%)
	Data unobtainable	1 (4.2%)	0 (0.0%)	1 (2.8%)
Ethnicity, n(%)	**N**	**24**	**12**	**36**
	Black African	6 (25.0%)	2 (16.7%)	8 (22.2%)
	Black Caribbean	1 (4.2%)	2 (16.7%)	3 (8.3%)
	East/Central Asian	2 (8.3%)	0 (0.0%)	2 (5.6%)
	Other	1 (4.2%)	0 (0.0%)	1 (2.8%)
	South Asian	2 (8.3%)	0 (0.0%)	2 (5.6%)
	White	12 (50.0%)	8 (66.7%)	20 (55.6%)
Number of past viable pregnancies, n(%)	**N**	**24**	**12**	**36**
	0	6 (25.0%)	0 (0.0%)	6 (16.7%)
	1	8 (33.3%)	8 (66.7%)	16 (44.4%)
	2	3 (12.5%)	1 (8.3%)	4 (11.1%)
	3	6 (25.0%)	1 (8.3%)	7 (19.4%)
	5	1 (4.2%)	1 (8.3%)	2 (5.6%)
	7	0 (0.0%)	1 (8.3%)	1 (2.8%)
Presence of Proteinuria (No/Yes), n(%)	**N**	**24**	**12**	**36**
	No	22 (91.7%)	12 (100%)	34 (94.4%)
	Yes	2 (8.3%)	0 (0.0%)	2 (5.6%)

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\02-Baseline.SAS

6.2 Study population

6.2.1 Data sets analysed

Table 6.2-1 Data sets analysed

Population	L-citrulline	Placebo	Total
Screened	42 (total)	42 (total)	42 (total)
Randomised	24	12	36
Intention-to-treat	24 (100%)	12(100%)	36 (100%)
Per-protocol	NA	NA	NA
Safety	24 (100%)	12(100%)	36 (100%)

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6.2.2 Protocol deviations

Table 6.2-2 Protocol deviations

Protocol deviations: n patients (%)	L-citrulline	Placebo	Total
N	**24**	**12**	**36**
Any protocol deviation	23 (95.8%)	11 (91.7%)	34 (94.4%)
At least one major:	**23 (95.8%)**	**11 (91.7%)**	**34 (94.4%)**
PD07 – treatment compliance	23 (95.8%)	11 (91.7%)	34 (94.4%)
At least one minor:	**8 (33.3%)**	**3 (25.0%)**	**11 (30.6%)**
Minor PD01 – visit 2 outside of visit window	2 (8.3%)	0	2 (5.6%)
Minor PD02 – visit 3 outside of visit window	7 (29.2%)	3 (25.0%)	10 (27.8%)

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\01-00-PDs and trt complaince.sas

Table 6.2-3 Withdrawals from treatment

Allocation	Assessment no.	Assessment date	Reason	Date of Last Dose
L-citrulline	2	02-Oct-17	Vomiting due to medication	18-Sep-17
placebo	2	30-Oct-17	Nausea	15-Oct-17
placebo	2	20-Nov-17	dislikes taste	06-Nov-17

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

6.2.3 Serious Breaches of GCP

There was one serious breach of GCP during CHERRY. The details are outlined below.

6.2.3.1 Serious Breach 1

For full details of the serious breach see pSB002 (06/02/2019) below is an outline:

The data for a secondary outcome (change in maternal plasma ADMA Arginine ratio) were expected to be sent to the CTRC team following the laboratory analysis of the data at the end of the study. The expected data were Plasma ADMA and Arginine concentrations.

CTRC's acting Head of Statistics raised an issue when discussing the lab data with the CTRC Trial Statistician regarding the traceability and accountability of the data, as these data had been sent in an unprotected workbook which had been assembled from several sources and without CHERRY participant identification numbers.

The impact of the breach is on the scientific value of the study and the credibility of the results. The integrity of the results of secondary endpoints cannot be assured because the data were deemed unusable: there were no clear processes as to how the data were constructed and the data could not be retraced.

Follow-up:
Following the serious breach, the laboratory analysis of the samples was conducted again and the raw data were provided to the CTRC with agreement from study sponsor and the Trial Steering Committee. This was subsequently analysed as part of the trial results with the approval of sponsor.

6.3 Compliance with treatment

The discrepancy between the volume of study drug remaining in the bottles returned at follow-up visits was to be estimated and assessed against the number of missed doses reported by the participants at the visits. This was to estimate compliance with treatment, however bottles were not always returned and as such accurate estimates of the volume returned were not generally available.

Also, there was no threshold set for the number of missed doses to be considered non-compliant so the following is a summary of the number of missed doses in each arm. Any patient who has missed a dose will be considered to have a protocol deviation for treatment compliance (34/36).

The percentage of missed doses was calculated to aid the interpretation of the number of missed doses, the denominator is the number of expected doses. For each patient the expected number of doses was estimated as the number of days between baseline and the week 8 visit multiplied by 2 (number of required doses per day). This will take into account patients whose visit 3 was later or earlier than the specified 8 weeks.

Table 6.3-1 Compliance with treatment

Summary	Treatment	N	N missing	Mean	S.D	Median	LQ	UQ	Min	Max
Number of missed Doses	**Overall**	**36**	**0**	**10.9**	**12.1**	**6**	**2**	**16.5**	**0**	**56**
	L-citrulline	24	0	9.4	8.5	7	2.5	14	0	31
	placebo	12	0	13.8	17.3	4.5	2	27	0	56
Percentage of missed Doses	**Overall**	**36**	**0**	**8.9**	**9.9**	**4.8**	**1.9**	**14.3**	**0**	**46.7**
	L-citrulline	24	0	7.7	6.6	5.9	2.4	11.6	0	22.1
	placebo	12	0	11.5	14.6	3.1	1.8	23.3	0	46.7

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6.4 Unblinding

Unblinding was not required for any patients during the study.

6.5 Safety data

6.5.1 Adverse events

6.5.1.1 Adverse events

In total there were 4 adverse events (AEs) from 4 (11.1%) patients from the 36 randomised patients in the study.
There were 2 AEs reported from 2 (8.3%) patients from the 24 patients in the L-citrulline arm of the study.
There were 2 AEs reported from 2 (16.7%) patients from the 12 patients in the placebo arm of the study.

Table 6.5-1 Adverse events line listings

Allocation	Description	Severity	Relationship	SAE	Outcome
L-citrulline	Vomiting due to medication	Mild	Yes	No	Discontinued trial treatment. Consents to follow-up.
placebo	Discontinued trial treatement [*sic*] as feeling nauseous	Mild	Yes	No	Discontinued trial treatment. Consent gained for study follow-up.
placebo	Congenital abnormality	Mild	No	Yes	Fetal ventriculomegaly diagnosed on fetal MRI at 33 weeks gestation. Baby delivered 30/05/2018, well at birth, will have neonatal follow-up.
L-citrulline	Nausea/vomiting began to increase after taking treatment	Mild	Yes	No	Missed 4 doses of treatment when could not tolerate.

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\07-Safety analysis.sas

6.5.1.2 Adverse events by severity

See Table 6.5-1 Adverse events line listings for details of severity, in summary 4 AEs were recorded from 4 patients, all of which were reported as mild.

6.5.2 Serious adverse events

In total there was 1 SAE reported from 1 (2.8%) patient of the 36 randomised patients.
There were 0 SAEs reported from 0 patients from the 24 patients in the L-citrulline arm of the study.
There was 1 SAE reported from 1 (8.3%) patient from the 12 patients in the placebo arm of the study.

Table 6.5-2 Serious adverse events line listing

Allocation	MedDra details		Description of event	PI assessment		CI assessment		Outcome	status
	System organ class	Preferred term		Severity	Causality	Expectedness	Causality		
placebo	Pregnancy, puerperium and perinatal conditions	Foetal disorder	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.	Mild	Unrelated	Unexpected	Unrelated	Resolved with sequelae	Completed trial

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\07-Safety analysis.sas

6.6 Efficacy data

6.6.1 Primary efficacy assessment

6.6.1.1 Primary efficacy assessment – Reduction in Diastolic Blood Pressure

Differences in diastolic blood pressure (dBP) were calculated by subtracting the baseline dBP measurement from the week 8 dBP measurements. Therefore a negative value indicates a decrease from baseline to follow up.

Table 6.6-1 Change in diastolic BP pressure (mmHg)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
dBP differences	L-citrulline	24	0	-1.82	9.56	-1.5	-8	1	-21.33	18.67	(-5.86,2.22)
dBP differences	placebo	12	0	-5	12.21	-4.67	-12.33	1.83	-25	14.67	(-12.76,2.76)
dBP standardised differences	L-citrulline	24	0	-0.03	0.16	-0.02	-0.13	0.02	-0.33	0.32	(-0.1,0.03)
dBP standardised differences	placebo	12	0	-0.08	0.2	-0.07	-0.18	0.03	-0.45	0.26	(-0.21,0.05)

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Figure 6.6-1 Distribution of mean difference in dBP (week 8 - baseline) in L-Citrulline arm

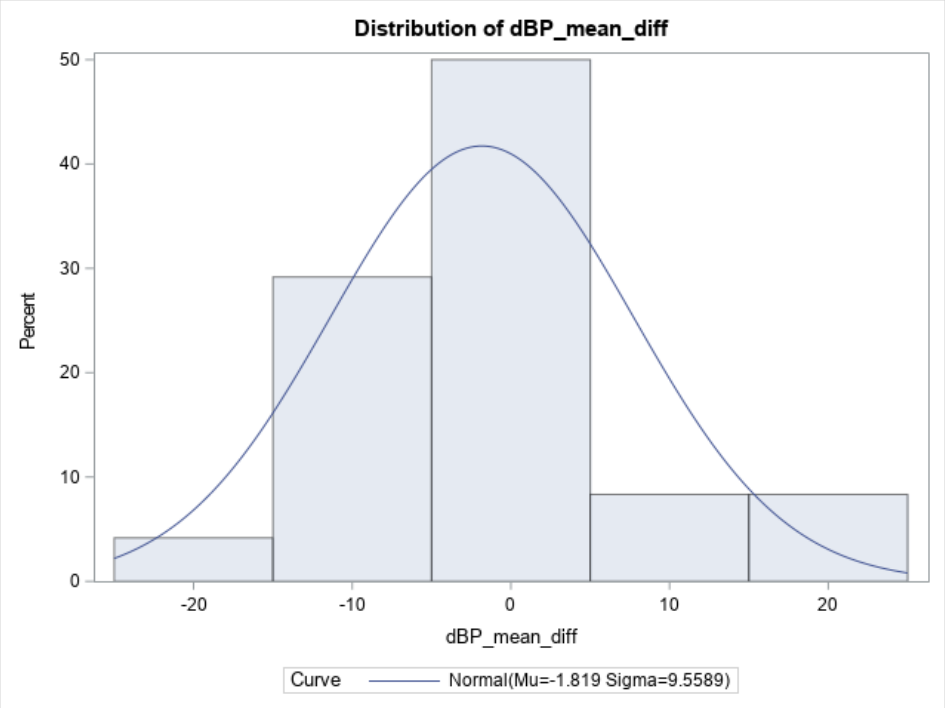

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Figure 6.6-2 Distribution of standardised mean difference in dBP (week 8 – baseline standardised by number of days between visits) in L-Citrulline arm

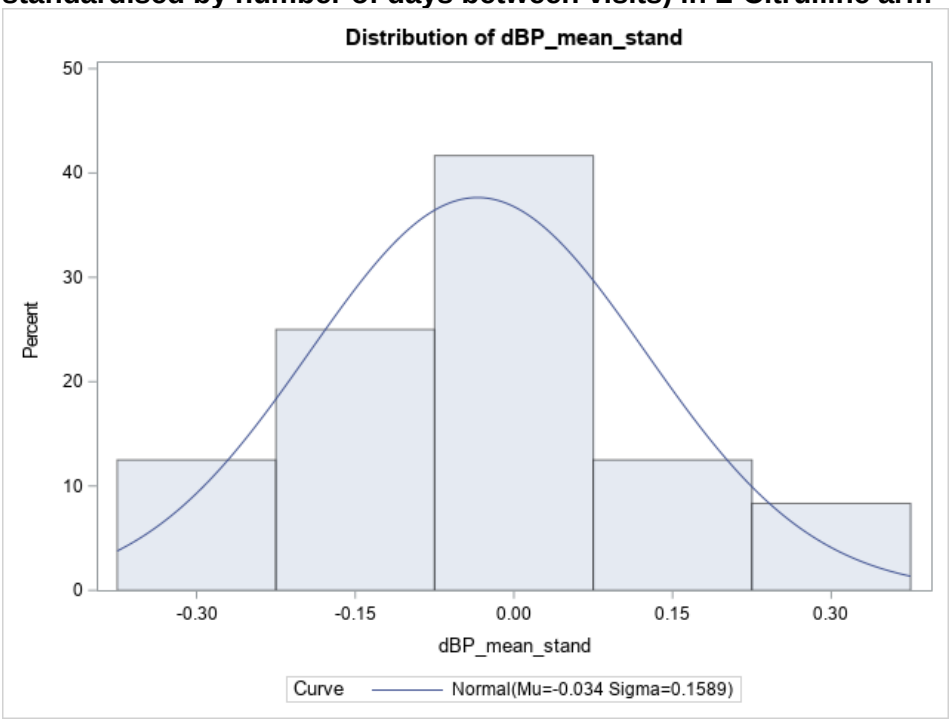

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Figure 6.6-3 Distribution of mean difference in dBP (week 8 - baseline) in placebo arm

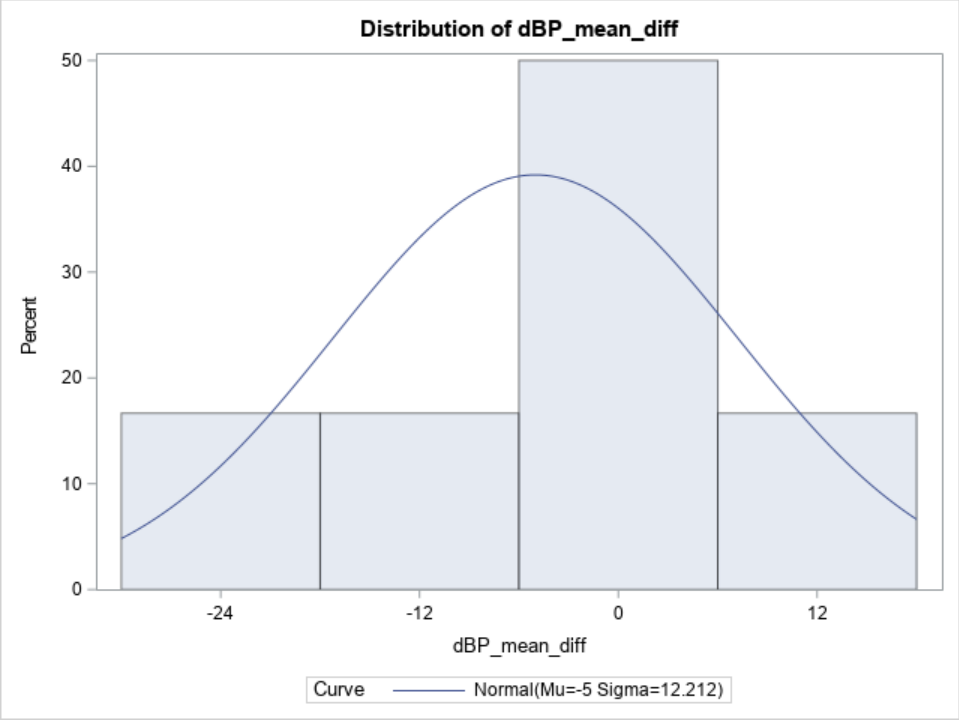

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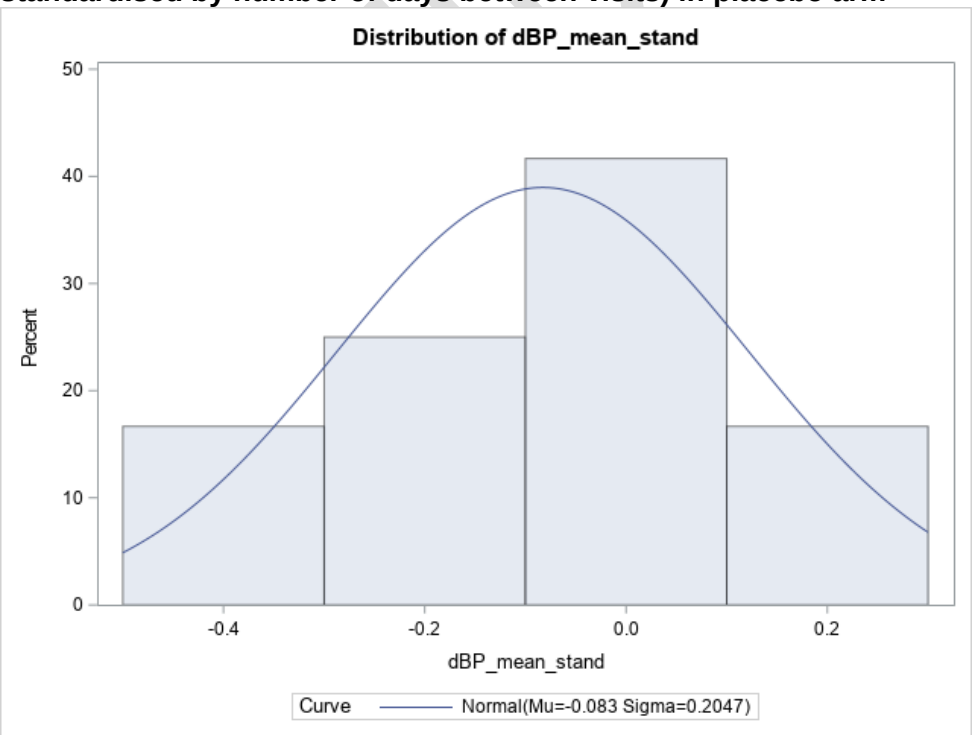
Figure 6.6-4 Distribution of standardised mean difference in dBP (week 8 – baseline standardised by number of days between visits) in placebo arm



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6.6.1.2 Primary efficacy assessment – sensitivity analysis 1

The Diastolic BP measure was based on the average of 3 clinical readings at each visit. If any of the 3 readings were missing for particular patients, it was planned that these patients would not be included in the primary efficacy assessment, and a sensitivity analysis would be carried out including all patients, using an average of their available measurements at each visit.

N/A – all patient had 3 readings at both baseline and week 8 visits; therefore, no patients were excluded from the main analysis and no sensitivity analyses were conducted.

6.6.1.3 Primary process assessment 1 – recruitment rates

In total 42 patients were screened, of which 41 were eligible and 36 were recruited. This gives the percentage of randomised patients from all eligible patients of 87.8%, with corresponding confidence interval of (73.8, 95.9) using the Clopper-Pearson exact method.

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6.6.1.1 Primary process assessment 2 – acceptability of intervention

In total 32 (88.9%) patients completed question from 36 patients randomised in the trial.

Table 6.6-2 Acceptability of intervention questionnaires

Question	Answer	L-citrulline	Placebo	Overall
Q1: Was taking your allocated treatment, n(%)	**N**	**22**	**10**	**32**
	a) Easy	18 (81.8%)	8 (80.0%)	26 (81.3%)
	b) Neither difficult or easy	2 (9.1%)	2 (20.0%)	4 (12.5%)
	c) Difficult	2 (9.1%)	0 (0.0%)	2 (6.3%)
Q2: How would you describe the taste of the treatment you were given, n(%)	**N**	**22**	**10**	**32**
	a) Delicious	1 (4.5%)	0 (0.0%)	1 (3.1%)
	b) Pleasant	12 (54.5%)	4 (40.0%)	16 (50.0%)
	c) Unpleasant	8 (36.4%)	6 (60.0%)	14 (43.8%)
	d) Awful	1 (4.5%)	0 (0.0%)	1 (3.1%)
Q3L How often did you miss a dose of your medication, n(%)	**N**	**22**	**10**	**32**
	a) Every day	0 (0.0%)	1 (10.0%)	1 (3.1%)
	b) Once/twice per week	8 (36.4%)	2 (20.0%)	10 (31.3%)
	c) Once/twice per month	4 (18.2%)	2 (20.0%)	6 (18.8%)
	d) Hardly ever	10 (45.5%)	5 (50.0%)	15 (46.9%)

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6.6.2 Secondary efficacy endpoint 1 – Ambulatory BP monitor

Difference in Ambulatory blood measure monitor (AMBP) measurements were calculated by subtracting the baseline AMBP measurement from the week 8 AMBP measurements. Therefore, a negative value indicates a decrease from baseline to follow up.

6.6.2.1 AMBP – Systolic BP

Table 6.6-3 Change in AMBP systolic BP pressure (mmHg)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
day time sBP differences	L-citrulline	20	4	-0.35	7.18	0	-6	6.5	-14	9	(-3.71,3.01)
day time sBP differences	placebo	9	3	-2.78	6.82	-4	-8	2	-10	10	(-8.02,2.46)
day time sBP standardised differences	L-citrulline	20	4	-0.003	0.12	0	-0.11	0.12	-0.24	0.15	(-0.06,0.05)
day time sBP standardised differences	placebo	9	3	-0.04	0.12	-0.07	-0.14	0.03	-0.18	0.18	(-0.14,0.05)
night time sBP differences	L-citrulline	17	7	0.18	8.92	0	-3	5	-15	18	(-4.41,4.77)
night time sBP differences	placebo	7	5	3.29	8.6	1	-5	10	-6	17	(-4.66,11.24)
night time sBP standardised differences	L-citrulline	17	7	0.01	0.16	0	-0.05	0.09	-0.25	0.32	(-0.07,0.09)
night time sBP standardised differences	placebo	7	5	0.06	0.15	0.02	-0.07	0.18	-0.1	0.3	(-0.07,0.2)

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6.6.2.2 AMBP – Diastolic BP

Table 6.6-4 Change in diastolic BP pressure (mmHg)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
day time dBP differences	L-citrulline	20	4	-2.05	7.25	-2.5	-7	1	-14	18	(-5.44,1.34)
day time dBP differences	placebo	9	3	-3.11	5.97	-2	-6	1	-14	5	(-7.7,1.48)
day time dBP standardised differences	L-citrulline	20	4	-0.03	0.13	-0.04	-0.11	0.02	-0.24	0.32	(-0.09,0.03)
day time dBP standardised differences	placebo	9	3	-0.05	0.1	-0.03	-0.09	0.02	-0.23	0.09	(-0.13,0.03)
night time dBP differences	L-citrulline	17	7	0.41	7.67	0	-5	4	-15	18	(-3.53,4.35)
night time dBP differences	placebo	7	5	2	5.63	2	-3	7	-7	9	(-3.2,7.2)
night time dBP standardised differences	L-citrulline	17	7	0.01	0.13	0	-0.07	0.06	-0.23	0.32	(-0.06,0.08)
night time dBP standardised differences	placebo	7	5	0.04	0.09	0.03	-0.05	0.13	-0.1	0.16	(-0.05,0.13)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

6.6.3 Secondary efficacy endpoint 2 – Cardiovascular compliance measurements

Difference in cardiovascular compliance measurements were calculated by subtracting the baseline measurement from the week 8 measurement. Therefore, a negative value indicates a decrease from baseline to follow up.

Table 6.6-5 Change in central blood pressure (mmHg)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
Central BP differences	L-citrulline	14	10	-4.86	19.42	-7.45	-15	6.8	-44.5	29.4	(-16.07,6.35)
Central BP differences	placebo	8	4	-6.28	29.03	0.2	-20	12.95	-63.8	27.3	(-30.54,17.99)
Central BP standardised differences	L-citrulline	14	10	-0.08	0.32	-0.12	-0.23	0.12	-0.75	0.52	(-0.26,0.11)
Central BP standardised differences	placebo	8	4	-0.1	0.5	0.004	-0.3	0.21	-1.14	0.49	(-0.52,0.32)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

Table 6.6-6 Change in pulse wave velocity (m/s)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
PWV differences	L-citrulline	14	10	-0.36	0.94	-0.3	-1.1	0.1	-1.8	1.6	(-0.9,0.18)
PWV differences	placebo	8	4	0.04	1.51	-0.45	-0.85	0.55	-1.5	3.3	(-1.22,1.3)
PWV standardised differences	L-citrulline	14	10	-0.01	0.02	-0.005	-0.02	0.002	-0.03	0.03	(-0.02,0.003)
PWV standardised differences	placebo	8	4	0.0006	0.03	-0.01	-0.01	0.01	-0.03	0.06	(-0.02,0.02)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

Table 6.6-7 Change in normalised augmentation index aortic values (%)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
Normalised Augmentation index Aortic differences	L-citrulline	14	10	-4.95	10.14	-4.03	-14.33	5.32	-22.55	7.22	(-10.8,0.91)
Normalised Augmentation index Aortic differences	placebo	8	4	-1.73	41.82	-1.02	-18.85	14.85	-75.55	71.75	(-36.69,33.23)
Normalised Augmentation index Aortic differences standardised differences	L-citrulline	14	10	-0.08	0.17	-0.06	-0.22	0.09	-0.4	0.13	(-0.18,0.02)
Normalised Augmentation index Aortic differences standardised differences	placebo	8	4	-0.01	0.74	-0.02	-0.32	0.24	-1.26	1.35	(-0.63,0.61)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

6.6.4 Secondary efficacy endpoint 3 – Change in vascular compliance

Difference in vascular compliance measurements were calculated by subtracting the baseline measurement from the week 8 measurement. Therefore, a negative value indicates a decrease from baseline to follow up.

Table 6.6-8 Change in cardiac output (L/minute)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
Cardiac Output differences	L-citrulline	23	1	-0.54	1.75	-0.4	-1.9	0.5	-4	4.1	(-1.3,0.21)
Cardiac Output differences	placebo	12	0	-1.18	1.22	-1.1	-2.1	-0.35	-3.3	0.7	(-1.96,-0.41)
Cardiac Output standardised differences	L-citrulline	23	1	-0.01	0.03	-0.01	-0.03	0.01	-0.07	0.06	(-0.02,0.003)
Cardiac Output standardised differences	placebo	12	0	-0.02	0.02	-0.02	-0.04	-0.01	-0.06	0.01	(-0.03,-0.01)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

Table 6.6-9 Change in cardiac index (L/minute/m^2)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
CI differences	L-citrulline	23	1	-0.28	0.88	-0.2	-0.9	0.2	-1.8	1.9	(-0.66,0.1)
CI differences	placebo	12	0	-0.57	0.63	-0.45	-1.15	-0.15	-1.5	0.4	(-0.97,-0.17)
CI standardised differences	L-citrulline	23	1	-0.01	0.01	-0.004	-0.02	0.004	-0.03	0.03	(-0.01,0.001)
CI standardised differences	placebo	12	0	-0.01	0.01	-0.01	-0.02	-0.002	-0.03	0.01	(-0.02,-0.003)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

Table 6.6-10 Change in stroke volume index (ml/m^2)

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
SVI differences	L-citrulline	23	1	-4.43	10.69	-2	-15	2	-24	22	(-9.06,0.19)
SVI differences	placebo	11	1	-7.82	8.3	-7	-13	0	-20	5	(-13.4,-2.24)
SVI standardised differences	L-citrulline	23	1	-0.08	0.17	-0.04	-0.23	0.04	-0.36	0.31	(-0.15,-0.002)
SVI standardised differences	placebo	11	1	-0.13	0.14	-0.13	-0.22	0	-0.34	0.09	(-0.22,-0.04)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

Table 6.6-11 Change in total peripheral resistance index (mmHg mL^{-1}min^{-1}kg^{-1})

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
TRPI differences	L-citrulline	23	1	140.35	1508.87	132	-638	1216	-4832	2128	(-512.13,792.83)
TRPI differences	placebo	12	0	574.92	963.77	588.5	-5	1242	-1034	2377	(-37.43,1187.27)
TRPI standardised differences	L-citrulline	23	1	2.89	23.58	1.71	-10.91	21.12	-69.03	38	(-7.31,13.09)
TRPI standardised differences	placebo	12	0	9.25	16.61	8.99	-0.13	20.27	-18.46	39.62	(-1.31,19.8)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\03-PO and CV.sas

6.6.5 Secondary efficacy endpoint 4 – Change in uteroplacental measurements

The difference in uteroplacental measurements were calculated by subtracting the baseline measurement from the week 8 measurement. Therefore, a negative value indicates a decrease from baseline to follow up.

Table 6.6-12 Change in Uterine artery resistance index

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
RI differences	L-citrulline	23	1	-0.1	0.11	-0.11	-0.2	-0.04	-0.27	0.15	(-0.15,-0.05)
RI differences	placebo	12	0	-0.08	0.09	-0.08	-0.13	-0.05	-0.24	0.12	(-0.13,-0.03)
RI standardised differences	L-citrulline	23	1	-0.002	0.002	-0.002	-0.003	-0.0005	-0.005	0.003	(-0.003,-0.0008)
RI standardised differences	placebo	12	0	-0.001	0.002	-0.001	-0.002	-0.0009	-0.004	0.002	(-0.002,-0.0004)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\05-01-Continuous SO.sas

Table 6.6-13 Change in pulsatility index

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
PI differences	L-citrulline	23	1	-0.43	0.43	-0.43	-0.73	-0.23	-1.12	0.66	(-0.61,-0.25)
PI differences	placebo	12	0	-0.37	0.34	-0.28	-0.58	-0.19	-1.17	0.21	(-0.59,-0.15)
PI standardised differences	L-citrulline	23	1	-0.01	0.01	-0.01	-0.01	-0.003	-0.02	0.01	(-0.01,-0.004)
PI standardised differences	placebo	12	0	-0.01	0.01	-0.004	-0.01	-0.003	-0.02	0.004	(-0.01,-0002)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\05-01-Continuous SO.sas

Table 6.6-14 Presence of bilateral Notchings

Allocation	Notchings present		Change from Visit 1 to visit 3
	Visit 1	Visit 3	n (n / number with notching at visit 1 %)
L-citrulline, n (%)	10 (41.7%)	5 (20.8%)	5 (50%)
Placebo, n (%)	2 (16.7%)	0 (0%)	2 (100%)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\05-02-Other SO.sas

6.6.6 Secondary efficacy endpoint 5 – Change plasma ADMA and arginine

The difference in plasma ADMA and arginine concentrations were calculated by subtracting the baseline measurement from the week 8 measurement. Therefore, a negative value indicates a decrease from baseline to follow up.

Table 6.6-15 Change in plasma ADMA

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
plasma ADMA differences	L-citrulline	19	5	0.01	0.05	0.02	-0.02	0.04	-0.11	0.11	(-0.01,0.03)
plasma ADMA differences	placebo	8	4	-0.01	0.05	0.003	-0.03	0.02	-0.11	0.03	(-0.05,0.02)
plasma ADMA standardised differences	L-citrulline	19	5	0.0002	0.0008	0.0003	-0.0003	0.0006	-0.002	0.002	(-0.0002,0.0006)
plasma ADMA standardised differences	placebo	8	4	-0.0002	0.0008	0.00006	-0.0005	0.0002	-0.002	0.005	(-0.0009,0.0004)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis v3.0\SAS Programmes\09-Lab Analysis.sas

Table 6.6-16 Change in Arginine concentrations

Endpoint	allocation	N	N missing	Mean	Std. Dev.	median	LQ	UQ	Minimum	Maximum	95% CI for mean
Arginine differences	L-citrulline	21	3	6.86	36.34	-3	-8	17	-50	112	(-9.69,23.40)
Arginine differences	placebo	11	1	-2.55	13.34	-5	-12	8	-29	18	(-11.51,6.42)
Arginine standardised differences	L-citrulline	21	3	0.14	0.62	-0.05	-0.14	0.28	-0.65	2	(-0.15,0.42)
Arginine standardised differences	placebo	11	1	-0.04	0.23	-0.08	-0.19	0.11	-0.52	0.32	(-0.2,0.11)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis v3.0\SAS Programmes\09-Lab Analysis.sas

6.6.7 Secondary efficacy endpoint 6 – Change in antihypertensive therapy

In the Table 6.6-17 Change in antihypertensive medication "No" indicates the patients was not taking the con-med and "Yes" indicates they were taking the con-med. A patient who is "Yes" and baseline and "No" at week 8 indicates a reduction in con-meds.

16 (66.7%) of 24 patients had con-meds at baseline in the L-citrulline arm.
6 (50%) of 12 patients had con-meds at baseline in the placebo arm.

Table 6.6-17 Change in antihypertensive medication

		L-citrulline: n(%) N=24		Placebo: n (%) N=12	
		Week 8		Week 8	
Con-meds	**Baseline**	No	Yes	No	Yes
	No [A]	8 (100%)	-	6 (100%)	-
	Yes [B]	3 (18.8%)	13 (81.3%)	-	6 (100%)

SAS file: SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\05-02-Other SO.sas

[A] ***Note:*** Percentages calculated from the number of patients within this treatment group who were **not** taking con-meds at baseline.
[B] ***Note:*** Percentages calculated from the number of patients within this treatment group who were taking con-meds at baseline.

6.7 Additional analyses 1

6.7.1 Exploratory regression analysis

Table 6.7-1 Exploratory regression analysis

Dependent Variable	Parameter	Estimate	Standard Error	t Value	Pr > |t|	Lower CL	Upper CL
Visit 3 Diastolic BP	Intercept	43.74	24.13	1.81	0.0792	-5.4	92.89
	Visit 1 Diastolic BP	0.41	0.18	2.26	0.0311	0.04	0.78
	Allocation L-citrulline	-0.64	3.5	-0.18	0.857	-7.77	6.5
	Allocation placebo	0					
	N Days*	0.1	0.24	0.42	0.6744	-0.39	0.59
Visit 3 Central BP	Intercept	103.07	51.42	2	0.0603	-4.97	211.11
	Visit 1 Central BP	0.41	0.19	2.16	0.0448	0.01	0.81
	Allocation L-citrulline	1.69	8.81	0.19	0.8498	-16.82	20.21
	Allocation placebo	0					
	N Days*	-0.48	0.75	-0.63	0.5337	-2.06	1.1
Visit 3 Pulse Wave velocity	Intercept	-4.4	4.07	-1.08	0.2936	-12.94	4.14
	Visit 1 Pulse Wave velocity	1.18	0.27	4.33	0.0004	0.61	1.75
	Allocation L-citrulline	-0.42	0.54	-0.78	0.4429	-1.56	0.71
	Allocation placebo	0					
	N Days*	0.05	0.05	1.09	0.2909	-0.05	0.16
Visit 3 Normalised AIO	Intercept	40.3	62.67	0.64	0.5282	-91.35	171.96
	Normalised AIO	0.95	0.49	1.96	0.0653	-0.07	1.98
	Allocation L-citrulline	-1.88	12.18	-0.15	0.8788	-27.46	23.7
	Allocation placebo	0					
	N Days*	-0.69	1.09	-0.63	0.5337	-2.98	1.6
Visit 3 Cardiac Output	Intercept	0.88	1.84	0.48	0.6363	-2.88	4.63
	Visit 1 Cardiac Output	0.3	0.11	2.84	0.0079	0.09	0.52
	Allocation L-citrulline	0.06	0.38	0.16	0.8731	-0.72	0.84
	Allocation placebo	0					
	N Days*	0.03	0.03	1.23	0.2289	-0.02	0.09

Dependent Variable	Parameter	Estimate	Standard Error	t Value	Pr > |t|	Lower CL	Upper CL
Visit 3 Cardiac Index	Intercept	0.95	0.9	1.06	0.2963	-0.88	2.79
	Visit 1 Cardiac Index	0.17	0.12	1.5	0.1438	-0.06	0.41
	Allocation L-citrulline	0.03	0.18	0.15	0.8808	-0.34	0.4
	Allocation placebo	0					
	N Days*	0.02	0.01	1.19	0.2436	-0.01	0.04
Visit 3 Stroke Volume Index	Intercept	9.68	11.11	0.87	0.3907	-13.02	32.37
	Visit 1 Stroke Volume Index	0.14	0.12	1.13	0.2692	-0.11	0.39
	Allocation L-citrulline	1.93	2.36	0.82	0.4211	-2.9	6.75
	Allocation placebo	0					
	N Days*	0.18	0.18	1.05	0.3035	-0.17	0.54
Visit 3 TRPI	Intercept	3755.58	1327.76	2.83	0.0081	1047.6	6463.56
	Visit 1 TRPI	0.2	0.11	1.87	0.0704	-0.02	0.42
	Allocation L-citrulline	-135.64	295.43	-0.46	0.6493	-738.18	466.89
	Allocation placebo	0					
	N Days*	-11.56	21.32	-0.54	0.5917	-55.04	31.93
Visit 3 AMBP day systolic BP	Intercept	8.13	20.7	0.39	0.6977	-34.5	50.76
	Visit 1 AMBP day systolic BP	1.06	0.11	9.86	0	0.84	1.28
	Allocation L-citrulline	2.71	2.87	0.94	0.354	-3.2	8.63
	Allocation placebo	0					
	N Days*	-0.31	0.24	-1.29	0.2092	-0.8	0.18
Visit 3 AMBP night systolic BP	Intercept	32.19	24.57	1.31	0.2051	-19.07	83.45
	Visit 1 AMBP night systolic BP	0.98	0.11	8.64	0	0.74	1.21
	Allocation L-citrulline	-3.33	3.98	-0.84	0.4128	-11.62	4.97
	Allocation placebo	0					
	N Days*	-0.44	0.31	-1.43	0.1672	-1.08	0.2
Visit 3 AMBP day diastolic BP	Intercept	26.55	19.15	1.39	0.178	-12.9	66
	Visit 1 AMBP day diastolic BP	0.79	0.17	4.72	0.0001	0.44	1.13
	Allocation L-citrulline	-0.08	2.89	-0.03	0.9779	-6.04	5.88

Dependent Variable	Parameter	Estimate	Standard Error	t Value	Pr > |t|	Lower CL	Upper CL
	Allocation placebo	0					
	N Days*	-0.19	0.23	-0.84	0.4104	-0.67	0.28
Visit 3 AMBP night diastolic BP	Intercept	46.58	18.24	2.55	0.0189	8.53	84.64
	Visit 1 AMBP night diastolic BP	0.76	0.16	4.64	0.0002	0.42	1.11
	Allocation L-citrulline	-2.52	3	-0.84	0.4103	-8.78	3.74
	Allocation placebo	0					
	N Days*	-0.46	0.23	-2.02	0.0566	-0.93	0.01
Visit 3 artery resistance index	Intercept	0.28	0.17	1.69	0.1018	-0.06	0.63
	Visit 1 artery resistance index	0.38	0.15	2.61	0.0138	0.08	0.68
	Allocation L-citrulline	0.01	0.03	0.34	0.7345	-0.05	0.08
	Allocation placebo	0					
	N Days*	0	0	0.2	0.8414	0	0.01
Visit 3 Pulsatility index	Intercept	0.33	0.52	0.64	0.5245	-0.73	1.4
	Visit 1 Pulsatility index	0.44	0.11	3.87	0.0005	0.21	0.67
	Allocation L-citrulline	-0.02	0.11	-0.16	0.8704	-0.24	0.21
	Allocation placebo	0					
	N Days*	0	0.01	0.15	0.8847	-0.02	0.02

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis\SAS Programmes\06-Additional analysis.sas

Note: N days represents the number of days between visit 1 (baseline) and visit 3 (week 8).

6.8 Post-Hoc Analysis

6.8.1 Post-Hoc analysis 1 – pregnancy outcomes

Table 6.8-1 Pregnancy outcomes

Pregnancy Outcome		L-Citrulline n(%)	Placebo n(%)	Overall n (%)
New born Data	Live born			
	Yes	24 (100%)	12 (100%)	36 (100%)
	No	0	0	0
	Gender			
	Female	14 (58.3%)	5 (41.7%)	19 (52.8%)
	Male	10 (41.7%)	7 (58.3%)	17 (47.2%)
	Gestational age (Days)			
	Mean (standard deviation)	264.0 (12.2)	259.8 (12.1)	262.6 (12.2)
	Birthweight (grams)			
	Mean (standard deviation)	2846.8 (622.1)	3123.6 (707.8)	2939.1 (655.2)
Delivery Medication	Magnesium Sulphate required			
	Yes	1 (4.2%)	0	1 (2.8%)
	Steroids required			
	Yes	5 (20.8%)	2 (16.7%)	7 (19.4%)
Pregnancy Summary, Complications - Summary of Diagnoses	Preeclampsia			
	Yes	5 (20.8%)	3 (25.0%)	8 (22.2%)
	Chronic Hypertension			
	Yes	24 (100%)	12 (100%)	36 (100%)
	SGA by Population Centile			

Pregnancy Outcome		L-Citrulline n(%)	Placebo n(%)	Overall n (%)
	(less than 10th sex adjusted local centiles) Yes	7 (29.2%)	3 (25.0%)	10 (27.8%)
	FGR Yes	7 (29.2%)	3 (25.0%)	10 (27.8%)
	Pregestational diabetes Yes	3 (12.5%)	3 (25.0%)	6 (16.7%)
	Gestational diabetes Yes	4 (16.7%)	0	4 (11.1%)
	Perinatal Outcome Alive	24 (100%)	12 (100%)	36 (100%)
Final Maternal and Perinatal Outcome	Perinatal Survival Yes	24 (100%)	12 (100%)	36 (100%)

SAS file: T:\CHERRY\Statistical Analysis\Main Analysis\Final analysis v2.0\SAS Programmes\08-Pregnancy Outcomes.sas

7. Plots and graphs

Plot number	Title	Section number of data to be included	Population	x-axis/y-axis
Figure 6.6-1 Distribution of mean difference in dBP (week 8 - baseline) in L-Citrulline arm	Primary efficacy assessment distribution (L-Citrulline arm)	Table 6.6-1 Change in diastolic BP pressure (mmHg)	ITT	Difference between baseline and week 8 diastolic BP (mmHg) / relative frequency (percent)

Plot number	Title	Section number of data to be included	Population	x-axis/y-axis
Figure 6.6-2 Distribution of standardised mean difference in dBP (week 8 – baseline standardised by number of days between visits) in L-Citrulline arm	Primary efficacy assessment distribution (L-Citrulline arm)	Table 6.6-1 Change in diastolic BP pressure (mmHg)	ITT	Standardised difference between baseline and week 8 diastolic BP (mmHg) / relative frequency (percent)
Figure 6.6-3 Distribution of mean difference in dBP (week 8 - baseline) in placebo arm	Primary efficacy assessment distribution (placebo arm)	Table 6.6-1 Change in diastolic BP pressure (mmHg)	ITT	Difference between baseline and week 8 diastolic BP (mmHg) / relative frequency (percent)
Figure 6.6-4 Distribution of standardised mean difference in dBP (week 8 – baseline standardised by number of days between visits) in placebo arm	Primary efficacy assessment distribution (placebo arm)	Table 6.6-1 Change in diastolic BP pressure (mmHg)	ITT	Standardised difference between baseline and week 8 diastolic BP (mmHg) / relative frequency (percent)

Appendix 1: Mapping report contents to SAP

This report has been created following the CHERRY Statistical Analysis Plan V2.0 (dated 27/02/2019).

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Section/subsection of SAP	Item within report	Additional details (if required)
Section 12: Disposition of participants	Figure 3.1-1 CONSORT flow diagram Table 5.1-1 Summary of screening logs	

Section/subsection of SAP	Item within report	Additional details (if required)
	Table 5.1-2 Reasons screen patients were ineligible Table 5.1-3 Reasons eligible patients declined consent Table 5.2-1 Randomisation Summary	
Section 12.2: Post randomisation discontinuations	Table 6.2-3 Withdrawals from treatment	
Section 12.2: Protocol deviations	Table 6.2-2 Protocol deviations	
Section 14: Unblinding	Page 13	
Section 15.1: Data Sets Analysed	Table 6.2-1 Data sets analysed	
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