Clinical trial results:
A phase III randomised study of folic acid supplementation in the management of menopausal symptoms in cancer survivors and healthy postmenopausal women

Summary

EudraCT number	2013-004246-41
Trial protocol	GB
Global end of trial date	30 July 2020

Results information

Result version number	v1 (current)
This version publication date	25 December 2020
First version publication date	25 December 2020

Trial information

Trial identification

Sponsor protocol code	RG_13-198

Additional study identifiers

ISRCTN number	ISRCTN98158824
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRCTU Reference No: MX3009

Notes:

Sponsors

Sponsor organisation name	Sandwell and West Birmingham Hospitals NHS Trust
Sponsor organisation address	Dudley Road, Birmingham , United Kingdom, B18 7QH
Public contact	Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net
Scientific contact	Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net
Sponsor organisation name	University of Birmingham
Sponsor organisation address	Vincent Drive, Birmingham , United Kingdom, B15 2TT
Public contact	Sean Jennings, University of Birmingham, +44 01214158011, researchgovernance@contacts.bham.ac.uk
Scientific contact	Sean Jennings, University of Birmingham, +44 01214158011, researchgovernance@contacts.bham.ac.uk

Notes:

Paediatric regulatory details

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

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2020
Global end of trial reached?	Yes
Global end of trial date	30 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to assess the efficacy of folic acid supplementation in terms of relief of the frequency and severity of vasomotor symptoms as compared to placebo

Protection of trial subjects:

The trial was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996.

The trial was conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and GCP. This trial was carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol was submitted to and approved by the REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site was required to obtain local Research and Development (R&D) approval. Sites were not be permitted to enrol patients until written confirmation of R&D approval was received by the FOAM Trial Office.

It was the responsibility of the Principal Investigator to ensure that all subsequent amendments gained the necessary local approval. The individual clinicians' had the responsibility to take immediate action if they thought necessary to protect the health and interest of individual patients.

Background therapy:

N/A

Evidence for comparator:

N/A - the test IMP, Folic acid is being used versus a placebo only

Actual start date of recruitment	01 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 164
Worldwide total number of subjects	164
EEA total number of subjects	164

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)	151
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

164 patients have been recruited and randomised. 83 patients were allocated to Folic Acid and 81 patients were allocated to Placebo.

Pre-assignment

Screening details:

Screening commenced following consent and prior to patient randomisation in order to confirm eligibility. Detailed screening information was described in the protocol.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Folic Acid

Arm description:

5mg folic acid

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

Dosage and administration details:

5mg tablet taken orally, once daily for 12 weeks

Arm title	Placebo

Arm description:

folic acid-matched-placebo

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

Dosage and administration details:

5mg tablet taken orally, once daily for 12 weeks

Number of subjects in period 1	Folic Acid	Placebo
Started	83	81
Completed	74	69
Not completed	9	12
Lost to follow-up	9	12

Baseline characteristics

Reporting groups	
Reporting group title	Folic Acid
Reporting group description:	
5mg folic acid	
Reporting group title	Placebo
Reporting group description:	
folic acid-matched-placebo	

Reporting group values	Folic Acid	Placebo	Total
Number of subjects	83	81	164
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	55.4	56.2	
standard deviation	± 5.1	± 5.9	-
Gender categorical			
Units: Subjects			
Female	83	81	164
Male	0	0	0
Patient subgroup			
Units: Subjects			
Healthy Woman	67	66	133
Breast Cancer Survivor	14	14	28
Endometrial Cancer Survivor	2	1	3
BMI			
Units: Subjects			
≤ 30	64	63	127
> 30	19	18	37
Baseline Folate			
Units: µg/L			
arithmetic mean	7.8	7.6	
standard deviation	± 3.1	± 3.1	-
Hot flushes at screening			
Units: integer			
arithmetic mean	85	85	

standard deviation	± 37	± 51	-

End points

End points reporting groups	
Reporting group title	Folic Acid
Reporting group description: 5mg folic acid	
Reporting group title	Placebo
Reporting group description: folic acid-matched-placebo	

Primary: Change in daily Hot Flush Score at 12 weeks from randomisation based on the composite score B calculation	
End point title	Change in daily Hot Flush Score at 12 weeks from randomisation based on the composite score B calculation
End point description: The mean change and associated standard deviation of composite score B between randomisation and week 12 will be presented for both treatment arms and statistically compared between the groups using a two-sample t-test. The difference in the mean change along with the 95% CI will be presented.	
End point type	Primary
End point timeframe: between randomisation and week 12	

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	69		
Units: score				
arithmetic mean (standard deviation)	-6.98 (± 10.30)	-4.57 (± 9.46)		

Statistical analyses

Statistical analysis title	Unadjusted: primary analysis
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.149
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.68
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	1.66

Statistical analysis title	Adjusted: secondary analysis
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.72
upper limit	0.49

Secondary: Change in daily Hot Flush Score at 12 weeks from randomisation based on the composite score B calculation - secondary outcome sensitivity analysis: multiple imputation

End point title	Change in daily Hot Flush Score at 12 weeks from randomisation based on the composite score B calculation - secondary outcome sensitivity analysis: multiple imputation

End point description:

A sensitivity analysis which accounts for missing data via multiple-imputation for the primary outcome analysis. Patients are required to have data available for week 1 to be included in the multiple imputation analysis. This analysis will be performed via a regression based imputation model using a bootstrap approach. Details are provided in the SAP.

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: score				
arithmetic mean (standard deviation)	-6.78 (± 10.2)	-4.09 (± 9.82)		

Statistical analyses

Statistical analysis title	Unadjusted analysis - t-test
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.099
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.88
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	1.63

Statistical analysis title	Adjusted analysis - linear regression model
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	-2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.87
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	1.56

Secondary: Change in daily Hot Flush Score based on the composite score B calculation - secondary outcome multilevel model

End point title	Change in daily Hot Flush Score based on the composite score B calculation - secondary outcome multilevel model

End point description:

The longitudinal nature of the primary outcome data will allow multivariable mixed model regression to investigate repeated measurements from baseline through to 12 weeks as random effects, incorporating clinically relevant baseline covariates and stratification factors as fixed effects.

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: integer	80	78		

Statistical analyses

Statistical analysis title	multilevel mixed-effects model
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	1.39

Secondary: Change in daily Hot Flush Score at 4 weeks from randomisation based on the composite score B calculation

End point title	Change in daily Hot Flush Score at 4 weeks from randomisation based on the composite score B calculation

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 4

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: score				
arithmetic mean (standard deviation)	-3.96 (± 8.28)	-3.93 (± 8.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in daily Hot Flush Score at 8 weeks from randomisation based on the composite score B calculation

End point title	Change in daily Hot Flush Score at 8 weeks from randomisation based on the composite score B calculation

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 8

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: score				
arithmetic mean (standard deviation)	-5.84 (± 9.19)	-4.49 (± 8.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in Hot Flush Severity at week 4 based on the severity score B calculation

End point title	Change from randomisation in Hot Flush Severity at week 4 based on the severity score B calculation

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 4

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	76		
Units: score				
arithmetic mean (standard deviation)	-0.09 (± 0.23)	-0.06 (± 0.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in Hot Flush Severity at week 8 based on the severity score B calculation

End point title	Change from randomisation in Hot Flush Severity at week 8 based on the severity score B calculation

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 8

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	71		
Units: score				
arithmetic mean (standard deviation)	-0.12 (± 0.37)	-0.06 (± 0.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in Hot Flush Severity at week 12 based on the severity score B calculation

End point title	Change from randomisation in Hot Flush Severity at week 12 based on the severity score B calculation

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	68		
Units: score				
arithmetic mean (standard deviation)	-0.17 (± 0.39)	-0.09 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in Hot Flush Severity based on the severity score B calculation - multilevel model

End point title	Change from randomisation in Hot Flush Severity based on the severity score B calculation - multilevel model

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: integer	80	78		

Statistical analyses

Statistical analysis title	multilevel mixed-effects model
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.253
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.03

Secondary: Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 4 as calculated using frequency score B

End point title	Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 4 as calculated using frequency score B

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 4

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	77		
Units: score				
arithmetic mean (standard deviation)	-1.70 (± 3.34)	-2.05 (± 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 8 as calculated using frequency score B

End point title	Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 8 as calculated using frequency score B

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 8

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	74		
Units: score				
arithmetic mean (standard deviation)	-2.65 (± 3.77)	-2.57 (± 4.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 12 as calculated using frequency score B

End point title	Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) at week 12 as calculated using frequency score B

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	69		
Units: score				
arithmetic mean (standard deviation)	-3.29 (± 4.34)	-2.59 (± 4.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) as calculated using frequency score B - multilevel model

End point title	Change from randomisation in daily frequency of hot flushes (mild, moderate and severe) as calculated using frequency score B - multilevel model

End point description:

End point type	Secondary

End point timeframe:

between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: integer	80	78		

Statistical analyses

Statistical analysis title	multilevel mixed-effects model
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.979
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	0.94

Secondary: The number of responders at weeks 4, 8 and 12; defined as a reduction in daily Hot Flush Score of ≥50% from randomisation as calculated using composite score B

End point title	The number of responders at weeks 4, 8 and 12; defined as a reduction in daily Hot Flush Score of ≥50% from randomisation as calculated using composite score B

End point description:

End point type	Secondary

End point timeframe:

between week 4 and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	81		
Units: integer				
week 4	14	15		
week 8	20	28		
week 12	27	24		

Statistical analyses

Statistical analysis title	multilevel mixed-effects model
Comparison groups	Folic Acid v Placebo

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.08

Secondary: Utian Quality of Life week 4

End point title	Utian Quality of Life week 4

End point description:

The mean and standard deviation of the change from randomisation in QoL data as measured by the UQoL Scale at week 4

End point type	Secondary

End point timeframe:

between randomisation and week 4

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	77		
Units: score				
arithmetic mean (standard deviation)				
Occupational score	-1.37 (± 5.39)	-1.83 (± 5.08)		
Health score	-0.58 (± 4.68)	-0.34 (± 3.75)		
Emotional score	1.06 (± 4.76)	-0.05 (± 4.01)		
Sexual score	-0.06 (± 1.98)	-0.60 (± 2.35)		
Total score	-0.95 (± 12.43)	-2.82 (± 9.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Utian Quality of Life week 8

End point title	Utian Quality of Life week 8

End point description:

The mean and standard deviation of the change from randomisation in QoL data as measured by the UQoL Scale at week 8

End point type	Secondary

End point timeframe:
between randomisation and week 8

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	74		
Units: score				
arithmetic mean (standard deviation)				
Occupational score	-0.83 (± 5.16)	-2.42 (± 6.04)		
Health score	0.30 (± 4.69)	-0.78 (± 4.20)		
Emotional score	1.34 (± 5.11)	-0.54 (± 5.12)		
Sexual score	0.08 (± 2.37)	-0.59 (± 2.69)		
Total score	0.88 (± 12.54)	-4.34 (± 12.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Utian Quality of Life week 12

End point title	Utian Quality of Life week 12

End point description:

The mean and standard deviation of the change from randomisation in QoL data as measured by the UQoL Scale at week 12

End point type	Secondary

End point timeframe:
between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	71		
Units: score				
arithmetic mean (standard deviation)				
Occupational score	-0.75 (± 6.13)	-1.24 (± 5.87)		
Health score	0.25 (± 4.67)	-0.27 (± 4.32)		
Emotional score	1.22 (± 5.06)	0.27 (± 5.78)		
Sexual score	-0.04 (± 2.61)	-0.27 (± 1.96)		
Total score	0.68 (± 13.35)	-1.51 (± 13.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Utian Quality of Life - multilevel models	
End point title	Utian Quality of Life - multilevel models
End point description:	
The change in QoL from randomisation will then be investigated over time using multilevel mixed-effects model	
End point type	Secondary
End point timeframe:	
between randomisation and week 12	

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: integer	81	81		

Statistical analyses

Statistical analysis title	Occupational score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.767
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	4.03

Statistical analysis title	Health score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	1.3

Statistical analysis title	Emotional score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	5.01

Statistical analysis title	Sexual score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.089
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	2.93

Statistical analysis title	Total score
Comparison groups	Folic Acid v Placebo

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.569
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.38
upper limit	9.79

Secondary: Greene Climacteric Scale week 4

End point title	Greene Climacteric Scale week 4

End point description:

Change from randomisation in other menopausal symptoms using the Greene Climacteric Scale at week 4

End point type	Secondary

End point timeframe:

between randomisation and week 4

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: score				
arithmetic mean (standard deviation)				
Psychological score	-2.31 (± 4.56)	-2.21 (± 4.78)		
Psychological (anxiety) score	-1.46 (± 2.77)	-1.35 (± 2.66)		
Psychological (depression) score	-0.85 (± 2.40)	-0.86 (± 2.63)		
Somatic score	-1.64 (± 4.01)	-1.64 (± 3.06)		
Vasomotor score	-0.95 (± 1.90)	-1.24 (± 1.77)		
Sexual Dysfunction score	-0.13 (± 0.92)	-0.21 (± 0.99)		
Total score	-5.03 (± 8.33)	-5.29 (± 7.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Greene Climacteric Scale week 8

End point title	Greene Climacteric Scale week 8

End point description:

Change from randomisation in other menopausal symptoms using the Greene Climacteric Scale at week 8

End point type	Secondary
End point timeframe: between randomisation and week 8	

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	73		
Units: score				
arithmetic mean (standard deviation)				
Psychological score	-3.05 (± 4.90)	-2.68 (± 5.35)		
Psychological (anxiety) score	-1.97 (± 2.99)	-1.58 (± 2.96)		
Psychological (depression) score	-1.08 (± 2.53)	-1.11 (± 2.81)		
Somatic score	-1.77 (± 3.22)	-1.59 (± 2.93)		
Vasomotor score	-1.05 (± 2.06)	-1.40 (± 1.76)		
Sexual Dysfunction score	-0.21 (± 1.00)	-0.14 (± 0.99)		
Total score	-6.08 (± 8.72)	-5.81 (± 8.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Greene Climacteric Scale week 12

End point title	Greene Climacteric Scale week 12
End point description: Change from randomisation in other menopausal symptoms using the Greene Climacteric Scale at week 12	
End point type	Secondary
End point timeframe: between randomisation and week 12	

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	72		
Units: score				
arithmetic mean (standard deviation)				
Psychological score	-3.39 (± 5.43)	-2.72 (± 5.71)		
Psychological (anxiety) score	-2.06 (± 3.28)	-1.42 (± 3.13)		
Psychological (depression) score	-1.32 (± 2.94)	-1.31 (± 2.98)		
Somatic score	-1.86 (± 3.48)	-2.08 (± 3.40)		
Vasomotor score	-1.23 (± 1.95)	-1.50 (± 2.05)		
Sexual Dysfunction score	-0.08 (± 0.96)	-0.40 (± 1.15)		
Total score	-6.56 (± 9.27)	-6.71 (± 9.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Greene Climacteric Scale - multilevel models

End point title	Greene Climacteric Scale - multilevel models

End point description:

End point type	Secondary

End point timeframe:
between randomisation and week 12

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: integer	81	81		

Statistical analyses

Statistical analysis title	Psychological score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.679
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.55
upper limit	3.92

Statistical analysis title	Psychological (anxiety) score
Comparison groups	Folic Acid v Placebo

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.413
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	2.58

Statistical analysis title	Psychological (depression) score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	1.83

Statistical analysis title	Somatic score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.619
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.68
upper limit	1.59

Statistical analysis title	Vasomotor score

Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.537
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	1.64

Statistical analysis title	Sexual Dysfunction score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.165
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.23
upper limit	0.21

Statistical analysis title	Total score
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.988
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	5.16

Other pre-specified: Change in serum folate level at week 12 from baseline

End point title	Change in serum folate level at week 12 from baseline
End point description:	

End point type	Other pre-specified
End point timeframe:	
between randomisation and week 12	

End point values	Folic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: value				
arithmetic mean (standard deviation)	11.06 (± 3.86)	0.66 (± 3.15)		

Statistical analyses

Statistical analysis title	t-test
Comparison groups	Folic Acid v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	10.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.18
upper limit	11.61
Variability estimate	Standard error of the mean
Dispersion value	0.61

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting was from commencement of treatment to 30 days after completion of trial treatment.

Adverse event reporting additional description:

The collection and reporting of AEs were in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Details of all SAEs were documented and reported from the date of informed consent until 30 days after the administration of last dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Folic Acid

Reporting group description:

Each patient received folic acid (5mg) once daily by mouth for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Patients received a folic acid-matched-tablet once daily by mouth for 12 weeks.

Serious adverse events	Folic Acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	2 / 81 (2.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal Calculi			

subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (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: 5 %

Non-serious adverse events	Folic Acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 83 (14.46%)	7 / 81 (8.64%)	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Night sweats			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 83 (2.41%)	3 / 81 (3.70%)	
occurrences (all)	2	6	
Flatulence			
subjects affected / exposed	4 / 83 (4.82%)	4 / 81 (4.94%)	
occurrences (all)	5	7	
Abdominal discomfort			

subjects affected / exposed	1 / 83 (1.20%)	1 / 81 (1.23%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	5 / 83 (6.02%)	1 / 81 (1.23%)	
occurrences (all)	5	1	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 83 (2.41%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	2 / 83 (2.41%)	0 / 81 (0.00%)	
occurrences (all)	3	0	
Pruritus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 81 (1.23%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal colic	Additional description: Renal Calculi		
subjects affected / exposed	1 / 83 (1.20%)	0 / 81 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2014	Change in IMP supplier and formulation from capsules to tablets
27 February 2015	MHRA requested changes to SAE reporting period, unblinding procedure and removal of additional definition of postmenopausal women (requiring FSH testing)
02 September 2015	Changes to exclusion criteria (introduction of drug washout periods), use of Patient Advertisement and Patient Invitation Letter
24 November 2015	Inclusion of Patient Identification Centres, optional telephone visits at weeks 4 and/or 8, Patient Booklet.
29 March 2017	-Sample size re-evaluated due to slower than anticipated recruitment rate. In accordance with guidance from the DMC, TSC, TMG and Trial Statisticians, the power has been reduced from 90% to 80% and the expected dropout rate has been reduced from 30% to 10%. This has resulted in a reduction in the sample size required from 236 patients to 162 patients - Study duration extended to allow the sample size to be recruited -Contraindicated medication list clarified - Contact details updated including the randomisation telephone number
06 August 2018	Temporary Halt due to lack of IMP and restart to trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 February 2017	Recruitment delays led to IMP expiry and the trial required halting so funding for a further batch of IMP could be secured which was produced and released to sites following approval of the updated Simplified IMPD submitted as part of substantial amendment AM08.	20 June 2017

11 May 2018	The IMP stock at them was due to expire on 04th August 2018. On the FOAM trial, each patient is dispensed one bottle of IMP following randomisation containing their entire 12 week supply of folic acid. This means that randomisation of patients after 11th May 2018 couldn't take place as the IMP expiry date would not cover an extended treatment window. Due to the slower than anticipated recruitment and the relatively short IMP expiration dates, much of the IMP that was packaged towards the beginning of the study expired prior to use. This resulted in a lack of funds to produce an additional batch of IMP required to recruit the trial to target. Subsequent funding for a further batch of IMP was secured which was produced and released to sites following approval of the updated Simplified IMPD submitted as part of substantial amendment AM08. Further funds were acquired for this final batch of IMP and as per former advice received from the MHRA helpline on 06-Apr-2017, the trial halted and the team advised to automatically restart the study and resume recruitment as soon as this new IMP was ready to be dispatched.	26 September 2018

Notes:

Limitations and caveats

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

This study failed to identify a statistically significant benefit for folic acid (over placebo). Therefore, the use of folic acid would not be recommended as an alternative therapy for HRT in symptomatic postmenopausal women based on the findings.

Notes: