Clinical trial results:
A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF SAGE-217 IN THE TREATMENT OF ADULTS WITH SEVERE POSTPARTUM DEPRESSION

Summary

EudraCT number	2020-001424-34
Trial protocol	GB
Global end of trial date	12 April 2022

Results information

Result version number	v1
This version publication date	27 April 2023
First version publication date	27 April 2023

Trial information

Trial identification

Sponsor protocol code	217-PPD-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04442503
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sage Therapeutics, Inc.
Sponsor organisation address	215 First Street, Cambridge, United States, 02142
Public contact	Handan Gunduz-Bruce, MD, MBA, Sage Therapeutics, Inc., +1 617949 2883, handan.gunduz-bruce@sagerx.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if treatment with SAGE-217 reduces depressive symptoms in adults with severe postpartum depression (PPD) compared to placebo.

Protection of trial subjects:

This study was conducted in accordance with applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, as well as local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 191
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	196
EEA total number of subjects	3

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)	196
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in study at 92 investigational sites in Spain, United Kingdom and United States from 8 June 2020 to 12 April 2022.

Pre-assignment

Screening details:

The study enrolled 200 subjects and of which 196 subjects received treatment.

Pre-assignment period milestones

Number of subjects started	200[1]
Number of subjects completed	196

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomised but not treated: 4

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: 200 subjects started the trial but only 196 received the study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received SAGE-217 matched-placebo capsules, orally, once daily for 14 days.

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

Dosage and administration details:

SAGE-217 matched-placebo oral capsules.

Arm title	Sage 217 50 mg

Arm description:

Subjects received SAGE-217, 50 mg, capsules, orally, once daily for 14 days.

Arm type	Experimental
Investigational medicinal product name	SAGE-217
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
SAGE-217 oral capsules.

Number of subjects in period 1	Placebo	Sage 217 50 mg
Started	98	98
Completed	86	84
Not completed	12	14
Physician decision	-	2
Adverse Event	1	1
Withdrawal by Subject	3	4
Lost to follow-up	8	6
Reason not Specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received SAGE-217 matched-placebo capsules, orally, once daily for 14 days.	
Reporting group title	Sage 217 50 mg
Reporting group description:	
Subjects received SAGE-217, 50 mg, capsules, orally, once daily for 14 days.	

Reporting group values	Placebo	Sage 217 50 mg	Total
Number of subjects	98	98	196
Age categorical Units: Subjects			
Adults (18-64 years)	98	98	196
Age continuous Units: years			
geometric mean	31.0	30.0	
standard deviation	± 5.95	± 5.90	-
Gender categorical Units: Subjects			
Female	98	98	196
Male	0	0	0

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received SAGE-217 matched-placebo capsules, orally, once daily for 14 days.	
Reporting group title	Sage 217 50 mg
Reporting group description:	
Subjects received SAGE-217, 50 mg, capsules, orally, once daily for 14 days.	

Primary: Change From Baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) Total Score at Day 15

End point title	Change From Baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) Total Score at Day 15
End point description:	
17-item HAM-D scale assesses severity of depression related to: depressed mood (sadness,hopeless,helpless,worthless),feelings of guilt,suicide,insomnia (early,middle,late), work and activities (slowness of thought and speech;impaired ability to concentrate;decreased motor activity), retardation,agitation,anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis,loss of weight, and insight. Individual items are scored on 3-point (0 to 2) or 5-point scale (0 to 4), with 0=none/absent and 4=most severe. Total score is sum of 17 items, from 0 to 52; higher score=more depression. Negative CFB=improvement. MMRM was used for analysis. Full Analysis Set (FAS)=all randomised subjects who received any amount of IP and had valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=subjects with data available for analyses.	
End point type	Primary
End point timeframe:	
Baseline and Day 15	

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 97, 98)	28.8 (± 2.34)	28.6 (± 2.49)		
Change from Baseline at Day 15 (n=90, 93)	-11.4 (± 8.50)	-15.6 (± 7.62)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change from Baseline at Day 15	
Comparison groups	Sage 217 50 mg v Placebo

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Least Square Mean Difference
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	1.16

Secondary: Change From Baseline in the 17-item HAM-D Total Score

End point title	Change From Baseline in the 17-item HAM-D Total Score

End point description:

17-item HAM-D scale assesses severity of depression related to: depressed mood (sadness,hopeless,helpless,worthless),feelings of guilt,suicide,insomnia (early,middle,late), work and activities (slowness of thought and speech;impaired ability to concentrate;decreased motor activity), retardation,agitation,anxiety (psychic and somatic), somatic symptoms (gastrointestinal and general), genital symptoms, hypochondriasis,loss of weight, and insight. Individual items are scored on 3-point (0 to 2) or 5-point scale (0 to 4), with 0=none/absent and 4=most severe. Total score is sum of 17 items, from 0 to 52; higher score=more depression. Negative CFB=improvement. MMRM was used for analysis. Full Analysis Set (FAS)=all randomised subjects who received any amount of IP and had valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Days 3, 28 and 45

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=97, 98)	28.8 (± 2.34)	28.6 (± 2.49)		
Change from Baseline at Day 3 (n=96, 98)	-6.3 (± 6.78)	-9.5 (± 7.40)		
Change from Baseline at Day 28 (n=85, 77)	-13.5 (± 8.77)	-16.3 (± 8.34)		
Change from Baseline at Day 45 (n=85, 84)	-14.8 (± 9.09)	-17.7 (± 8.40)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline at Day 3	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-1.4
Variability estimate	Standard error of the mean
Dispersion value	0.999

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change from Baseline at Day 45	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-1
Variability estimate	Standard error of the mean
Dispersion value	1.277

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline at Day 28	
Comparison groups	Placebo v Sage 217 50 mg

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	1.244

Secondary: Change From Baseline in Clinical Global Impressions - Severity Scale (CGI-S) Score

End point title	Change From Baseline in Clinical Global Impressions - Severity Scale (CGI-S) Score

End point description:

CGI-S is a 7-point Likert scale to rate the severity of subject's illness at time of assessment, relative to the clinician's past experience with subjects who had same diagnosis. Subject was assessed on severity of mental illness at time of rating as 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7= extremely ill subjects. Lower score indicates better outcome. A negative change from baseline indicates improvement. MMRM was used for analysis. FAS=all randomised subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=Number analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Day 15

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=97, 98)	4.9 (± 0.58)	5.0 (± 0.66)		
Change from Baseline at Day 15 (n=90, 93)	-1.6 (± 1.38)	-2.2 (± 1.51)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:	
Change from Baseline at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.196

Secondary: Percentage of Subjects With HAM-D Response

End point title	Percentage of Subjects With HAM-D Response

End point description:

17-item HAM-D scale=severity of depression related to:depressed mood,feelings of guilt, suicide, insomnia, work and activities (slowness of thought and speech; impaired ability to concentrate; decreased motor activity), retardation, agitation, anxiety(psychic and somatic),somatic symptoms(gastrointestinal and general),genital symptoms, hypochondriasis, loss of weight, and insight. Individual items are scored on 3-point (0to2) or 5-point scale (0to4), with 0=none/absent and 4=most severe. Total score=sum of 17 items, ranges from 0to52; higher score=more depression. Negative CFB=improvement. HAM-D response= ≥50% reduction in HAM-D total score from baseline. FAS=all randomised subjects who received any amount of IP and had valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=subjects with data available for analyses. Percentages are rounded off to nearest whole number.

End point type	Secondary

End point timeframe:

Days 15 and 45

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: percentage of participants				
number (not applicable)				
Day 15 (n= 90, 93)	38.9	57.0		
Day 45 (n= 85, 84)	54.1	61.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Day 45	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1661 [1]
Method	GEE Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.534
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.837
upper limit	2.812

Notes:

[1] - P-value are from a GEE for binary response model, with factors for treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time-point-by treatment interaction.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209 [2]
Method	GEE Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.112
upper limit	3.67

Notes:

[2] - P-value are from a generalized estimating equation (GEE) for binary response model, with factors for treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time-point-by treatment interaction.

Secondary: Percentage of Subjects With HAM-D Remission

End point title	Percentage of Subjects With HAM-D Remission

End point description:

HAM-D remission=having a HAM-D total score of <=7.17-item HAM-D scale=severity of depression related to the following symptoms: depressed mood (sadness,hopeless,helpless,worthless),feelings of guilt,suicide,insomnia (early,middle,late), work and activities(slowness of thought and speech;impaired ability to concentrate;decreased motor activity),retardation,agitation,anxiety (psychic and somatic),somatic symptoms (gastrointestinal and general),genital symptoms, hypochondriasis,loss of weight,and insight. Individual items are scored on 3-point (0 to 2) or 5-point scale (0 to 4), with 0=none/absent and 4=most severe. Total score=sum of 17 items, ranges from 0 to 52; higher score=more depression. Negative CFB=improvement. FAS=all randomised subjects who received any amount of IP and had valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I.n=subjects

End point type	Secondary
End point timeframe:	
Days 15 and 45	

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: percentage of participants				
number (not applicable)				
Day 15 (n= 90, 93)	16.7	26.9		
Day 45 (n= 85, 84)	29.4	44.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Day 45	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0226 [3]
Method	GEE Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.108
upper limit	3.915

Notes:

[3] - P-value are from a GEE for binary response model, with factors for treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time-point-by treatment interaction.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111 [4]
Method	GEE Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.781

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.876
upper limit	3.621

Notes:

[4] - P-value are from a GEE for binary response model, with factors for treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time-point-by treatment interaction.

Secondary: Percentage of Subjects With Clinical Global Impression - Improvement (CGI-I) Response

End point title	Percentage of Subjects With Clinical Global Impression - Improvement (CGI-I) Response

End point description:

CGI-I response was defined as having a CGI-I score of "very much improved" or "much improved." CGI-I employs a 7-point Likert scale to measure the overall improvement in the subject's condition posttreatment. The investigator rated the subject's total improvement whether or not it is due entirely to drug treatment. Response choices include 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse. The CGI-I was only rated at posttreatment assessments. FAS included all randomized subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I.Hamilton Rating Scale for Depression (HAM-D) total score. N=number analysed is the number of subjects available for analyses. n=Number analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Day 15

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	93		
Units: percentage of subjects				
number (not applicable)	46.7	66.7		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Day 15

Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089 [5]
Method	GEE
Parameter estimate	Odds ratio (OR)
Point estimate	2.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.223
upper limit	4.072

Notes:

[5] - P-value are from a GEE for binary response model, with factors for treatment, baseline HAMD-17 total score, baseline antidepressant use, assessment time point, and time-point-by treatment interaction.

Secondary: Change From Baseline in Hamilton Rating Scale for Anxiety (HAM-A) Total Score

End point title	Change From Baseline in Hamilton Rating Scale for Anxiety (HAM-A) Total Score

End point description:

14-item HAM-A was used to rate the severity of symptoms of anxiety. Each 14-items were defined by a series of symptoms, and measured both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The HAM-A total score was calculated as the sum of the 14 individual item scores. The scoring for HAM-A is calculated by assigning scores of 0 (not present) to 4 (very severe), with a total score range of 0 to 56 where <17 indicated mild severity, 18 to 24, mild to moderate severity, and 25 to 30, moderate to severe severity. A negative change from baseline in HAM-A total score indicated improvement. FAS included all randomized subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n= subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Day 15

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=97, 98)	24.7 (± 5.96)	24.4 (± 6.01)		
Change from Baseline at Day 15 (n= 90, 92)	-10.4 (± 7.15)	-13.0 (± 8.19)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline at Day 15

Comparison groups	Placebo v Sage 217 50 mg

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0235 [6]
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	-0.3
Variability estimate	Standard error of the mean
Dispersion value	0.98

Notes:

[6] - P-value is from a MMRM; the model includes treatment (SAGE-217 or placebo), baseline HAM-A total score, antidepressant use at baseline (Yes or No), assessment time point, and time point-by-treatment interaction as explanatory variables.

Secondary: Change From Baseline in the Montgomery Åsberg Depression Rating Scale (MADRS) Total Score

End point title	Change From Baseline in the Montgomery Åsberg Depression Rating Scale (MADRS) Total Score

End point description:

MADRS total score was calculated as sum of the 10 individual item scores. MADRS is a 10-item diagnostic questionnaire used to measure severity of depressive episodes in subjects with mood disorders. It includes questions on following: apparent sadness; reported sadness; inner tension; reduced sleep; reduced appetite; concentration difficulties; lassitude; inability to feel; pessimistic thoughts; and suicidal thoughts. Each item is rated on 7-point scale from 0 (no symptoms) to 6 (symptoms of maximum severity). Total score ranges 0 to 60 with higher score=more depression. A negative CFB in MADRS total score indicated improvement. FAS included all randomized subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I.N=subjects available for analysis. n=subjects with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Day 15

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 96, 98)	35.0 (± 4.81)	35.5 (± 5.37)		
Change from Baseline at Day 15 (n= 89, 92)	-14.1 (± 11.78)	-19.9 (± 12.00)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	1.706

Secondary: Change From Baseline in HAM-D Subscale

End point title	Change From Baseline in HAM-D Subscale
End point description: The 17-item HAM-D is comprised of individual ratings related to the following symptoms: depressed mood, feelings of guilt, suicide, insomnia, work and activities, retardation, agitation, anxiety, somatic symptoms, genital symptoms, hypochondriasis, loss of weight, and insight. HAM-D subscale scores will be calculated as the sum of the items comprising each subscale. Individual items are scored on either a 3-point (0 to 2) or a 5-point scale (0 to 4), with 0=none/absent and 4=most severe. FAS population. n=Number analysed is the number of subjects with data available for analyses.	
End point type	Secondary
End point timeframe: Baseline and Day 15	

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Core Subscale Baseline (n=97,98)	47.6 (± 6.96)	49.2 (± 6.79)		
CFB in Core Subscale at Day 15 (n=90,93)	-20.4 (± 18.49)	-27.7 (± 16.36)		
Anxiety Subscale Baseline (n=97,98)	52.6 (± 9.23)	51.2 (± 8.79)		
CFB in Anxiety Subscale at Day 15 (n=90,93)	-20.4 (± 17.28)	-26.0 (± 15.66)		
Bech-6-Subscale Baseline (n=97,98)	62.9 (± 6.14)	63.7 (± 5.64)		
CFB in Bech-6 Subscale at Day 15 (n=90,93)	-24.6 (± 21.37)	-34.3 (± 19.61)		
Meier Subscale Baseline (n=97,98)	56.3 (± 5.94)	56.9 (± 6.11)		

CFB in in Meier Subscale at Day 15 (n=90,93)	-22.5 (± 18.99)	-30.7 (± 17.23)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Change from Baseline in Meier Subscale at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	2.609

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline (CFB) in Core Subscale at Day 15	
Comparison groups	Sage 217 50 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0151
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	-1.2
Variability estimate	Standard error of the mean
Dispersion value	2.4

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: CFB in Anxiety Subscale at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0123
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	-1.3
Variability estimate	Standard error of the mean
Dispersion value	2.27

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: CFB in Bech-6 Subscale at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-8.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	-2.8
Variability estimate	Standard error of the mean
Dispersion value	2.96

Secondary: Change From Baseline in Self-Reported Measures of Depressive Symptoms, as Assessed by the Edinburgh Postnatal Depression Scale (EPDS) Total Score

End point title	Change From Baseline in Self-Reported Measures of Depressive Symptoms, as Assessed by the Edinburgh Postnatal Depression Scale (EPDS) Total Score

End point description:

The EPDS is a self-rated depressive symptom severity scale specific to the perinatal period which consists of 10 individual items. Each item is rated on a 4-point scale ranging from 0 to 3 points, where 0=minimal depression and 3=severe depression. The EPDS total score is calculated as the sum of the 10

individual item scores, ranging from 0 points to 30 points with a higher score indicating more depression. A negative change indicates improvement. FAS included all randomised subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=Number analysed is the number of subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Days 3, 8,15, 21, 28 and 45

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 97, 98)	20.0 (± 4.15)	21.1 (± 3.68)		
Change from Baseline at Day 3 (n= 94, 97)	-2.2 (± 4.50)	-4.2 (± 5.34)		
Change from Baseline at Day 8 (n= 95, 93)	-6.0 (± 6.20)	-8.9 (± 7.01)		
Change from Baseline at Day 15 (n= 89, 91)	-8.0 (± 6.41)	-10.8 (± 7.18)		
Change from Baseline at Day 21 (n= 81, 84)	-8.7 (± 6.65)	-10.9 (± 6.72)		
Change from Baseline at Day 28 (n= 85, 76)	-9.4 (± 6.48)	-11.6 (± 7.83)		
Change from Baseline at Day 45 (n= 85, 84)	-9.7 (± 7.40)	-12.3 (± 7.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-Reported Measures of Depressive Symptoms, as Assessed by the 9-item Patient Health Questionnaire (PHQ-9) Score

End point title	Change From Baseline in Self-Reported Measures of Depressive Symptoms, as Assessed by the 9-item Patient Health Questionnaire (PHQ-9) Score

End point description:

PHQ-9 is a self-rated depressive symptom severity scale to monitor severity over time for newly diagnosed subjects or in current treatment for depression. Scoring was based on responses to 9 specific questions as follows: 0=not at all; 1=several days; 2 = more than half the days; and 3=nearly every day. Score were calculated as the sum of the 9 individual item scores. PHQ-9 total score was categorised as: 1 to 4=minimal depression, 5 to 9=mild depression, 10 to 14 =moderate depression, 15 to 19=moderately severe depression; and 20 to 27 =severe depression. PHQ-9 total score ranges from 1 to 27 with a higher score=more depression. Negative CFB indicates reduced depression. MMRM was used for analysis. FAS=all randomised subjects who received any amount of IP and had a valid baseline and at least one valid post-baseline total score in at least one of HAM-D, HAM-A, MADRS, CGI-S, EPDS and PHQ-9, or at least 1 post-baseline value of CGI-I. n=subjects with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline, Days 3, 8,15, 21, 28 and 45

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	98		
Units: score on a scale				
least squares mean (standard error)				
Change from Baseline at Day 3(n=94,97)	-2.3 (± 0.462)	-2.0 (± 0.456)		
Change from Baseline at Day 8(n=95,93)	-5.9 (± 0.617)	-7.7 (± 0.620)		
Change from Baseline at Day 15(n=90,91)	-8.6 (± 0.652)	-10.5 (± 0.651)		
Change from Baseline at Day 21(n=81,84)	-9.0 (± 0.655)	-10.6 (± 0.651)		
Change from Baseline at Day 28(n=85,77)	-9.2 (± 0.692)	-10.5 (± 0.703)		
Change from Baseline at Day 45(n=85,84)	-9.8 (± 0.728)	-11.7 (± 0.731)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Change from Baseline at Day 3	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6912
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.649

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline at Day 8	
Comparison groups	Placebo v Sage 217 50 mg

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.874

Statistical analysis title	Statistical Analysis 5
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1846
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.987

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Change from Baseline at Day 21	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0811
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.924

Statistical analysis title	Statistical Analysis 6
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0625
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.031

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Change from Baseline at Day 15	
Comparison groups	Placebo v Sage 217 50 mg
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0444
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.922

Secondary: Percentage of Subjects With at Least One Treatment-Emergent Adverse Event (TEAE)

End point title	Percentage of Subjects With at Least One Treatment-Emergent Adverse Event (TEAE)

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subjects administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. A TEAE is defined as an AE with onset after the start of Investigational Product (IP), or any worsening of a pre-existing medical condition/AE with onset after the start of IP and throughout the study. Safety Set included all participants who were administered IP.

End point type	Secondary

End point timeframe:

Up to Day 45

End point values	Placebo	Sage 217 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	98		
Units: percentage of participants				
number (not applicable)	53.1	66.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From Baseline up to Day 45	
Adverse event reporting additional description:	
Safety Set included all subjects who were administered IP.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	SAGE-217 50 mg
Reporting group description:	
Subjects received SAGE-217, 50 mg, capsules, orally, once daily for 14 days.	
Reporting group title	Placebo
Reporting group description:	
Subjects received SAGE-217 matched-placebo capsules, orally, once daily for 14 days.	

Serious adverse events	SAGE-217 50 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Perinatal depression			
subjects affected / exposed	1 / 98 (1.02%)	0 / 98 (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: 2 %

Non-serious adverse events	SAGE-217 50 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 98 (66.33%)	52 / 98 (53.06%)	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	1 / 98 (1.02%)	4 / 98 (4.08%)	
occurrences (all)	1	4	
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 98 (0.00%)	3 / 98 (3.06%)	
occurrences (all)	0	4	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	1	3	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
White blood cells urine positive			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Blood urine present			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Red blood cells urine positive			

subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Prothrombin time prolonged			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Nitrite urine present			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 98 (13.27%)	10 / 98 (10.20%)	
occurrences (all)	19	11	
Headache			
subjects affected / exposed	9 / 98 (9.18%)	13 / 98 (13.27%)	
occurrences (all)	16	39	
Somnolence			
subjects affected / exposed	26 / 98 (26.53%)	5 / 98 (5.10%)	
occurrences (all)	33	5	
Sedation			
subjects affected / exposed	11 / 98 (11.22%)	1 / 98 (1.02%)	
occurrences (all)	12	1	
Memory impairment			
subjects affected / exposed	3 / 98 (3.06%)	0 / 98 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Tremor			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 98 (4.08%)	1 / 98 (1.02%)	
occurrences (all)	4	1	
Fatigue			

subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 98 (6.12%)	2 / 98 (2.04%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	5 / 98 (5.10%)	6 / 98 (6.12%)	
occurrences (all)	12	6	
Abdominal pain			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Dry mouth			
subjects affected / exposed	2 / 98 (2.04%)	3 / 98 (3.06%)	
occurrences (all)	2	3	
Constipation			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 98 (2.04%)	1 / 98 (1.02%)	
occurrences (all)	2	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 98 (3.06%)	1 / 98 (1.02%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Muscle twitching			
subjects affected / exposed	2 / 98 (2.04%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Myalgia			

subjects affected / exposed	3 / 98 (3.06%)	0 / 98 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	1 / 98 (1.02%)	2 / 98 (2.04%)	
occurrences (all)	2	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 98 (5.10%)	0 / 98 (0.00%)	
occurrences (all)	5	0	
Urinary tract infection			
subjects affected / exposed	5 / 98 (5.10%)	4 / 98 (4.08%)	
occurrences (all)	5	4	
Upper respiratory tract infection			
subjects affected / exposed	0 / 98 (0.00%)	2 / 98 (2.04%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2021	The summary of Amendment 1 was as follows: - Added COVID-19 questions to be asked to document information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 as part of medical history, AE collection, and prior/concomitant medication/procedure collection throughout the study; - Broadened the eligibility criteria to include women who were up to 12 months postpartum. The criterion for the diagnosis of PPD, including the onset of symptoms, remained the same per DSM-5. The extension to 12 months was instituted so that a broader population of subjects could be reached, consistent with DSM-5; -Clarified that a subject with an index pregnancy that resulted in neonatal/infant death would be excluded; -Added details on the estimand specified in the protocol per FDA request; -Removed the definition of overdose to align with current Sage practice and other protocols. Cases of overdose were to be collected as reported by the investigator and recorded as an AE; -Increased the number of sites where the study was to be conducted; -Indicated that urine and serum pregnancy tests were to be conducted at Screening and that the urine test was recommended to precede other Screening assessments. Qualifying criteria were to be based on serum test results; - Updated contraception requirements to specify the types of bilateral tubal occlusion procedures that were considered to be acceptable forms of contraception and which procedure type required at least 3 months postprocedure prior to Screening; -Aligned the prohibited medication section with medications listed as exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported