Clinical trial results:
A single centre, double blind, non-inferiority study to evaluate the antidepressant activity of Viotra™ compared with amitriptyline in the treatment of major depressive disorder (MDD) in patients who have an unsatisfactory response / are resistant to SSRIs.

Summary

EudraCT number	2013-000719-26
Trial protocol	GB
Global end of trial date	29 October 2015

Results information

Result version number	v1 (current)
This version publication date	12 October 2016
First version publication date	12 October 2016

Trial information

Trial identification

Sponsor protocol code	ETS6103-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02014363
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	e-Therapeutics plc
Sponsor organisation address	17 Blenheim Office Park, Oxfordshire, United Kingdom, OX29 8LN
Public contact	Clinical Operations Manager, e-Therapeutics plc, 44 1993880000, contact@etherapeutics.co.uk
Scientific contact	Clinical Operations Manager, e-Therapeutics plc, 44 1993880000, contact@etherapeutics.co.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2015
Global end of trial reached?	Yes
Global end of trial date	29 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the antidepressant activity of Viotra™ is not inferior to amitriptyline in subjects who have an unsatisfactory response to / are resistant to treatment with SSRIs.

Protection of trial subjects:

Patients were assessed regularly with regards to the status of their depressive episode. Safety assessments such as blood sampling for the assessment of haematological and clinical chemistry parameters, ECG assessments and pregnancy tests were performed periodically.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2013
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: 367
Worldwide total number of subjects	367
EEA total number of subjects	367

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)	365
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After 6 wks treatment with citalopram, subjects who had a HAMD-17 score of ≥12 at the end of the lead-in phase were randomised to take low or high-dose tramadol or standard dose amitriptyline. The subjects visited the site at weeks 1, 2, 4, 6, and 8 for assessment of their mental state and safety and were followed up 28 days after the final visit.

Pre-assignment

Screening details:

Patients with confirmed major depressive disorder and with HAM-D score of ≥18 started 6 wk run-in with citalopram. Patients with HAM-D score ≥12 at the end of the run in were potentially eligible for randomisation.

Period 1

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

Blinding implementation details:

All medication dispensed during the blinded randomisation phase were identical in appearance. The blinded study medication was provided to the Investigator Site and dispensed to the patients. The blinded study medication code was recorded, to enable unblinding of treatments received after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	ETS6103 low dose

Arm description:

Low-dose of ETS6103

Arm type	Experimental
Investigational medicinal product name	ETS6103
Investigational medicinal product code	
Other name	Tramadol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

8-week treatment with one low-dose ETS6103 capsule taken once daily orally with water at between 19:00h and 21:00h.

Arm title	ETS6103 high dose

Arm description:

High dose of ETS6103

Arm type	Experimental
Investigational medicinal product name	ETS6103
Investigational medicinal product code	
Other name	Tramadol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

8-week treatment with one high-dose ETS6103 capsule taken once daily orally with water at between 19:00h and 21:00h.

Arm title	Amitriptyline

Arm description:	
Amitriptyline	
Arm type	Active comparator
Investigational medicinal product name	Amitriptyline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Weeks 1 & 2: one 75 mg amitriptyline capsule taken once daily orally with water at between 7-9pm (evening). Weeks 3 - 8: one 150mg amitriptyline capsule taken once daily orally with water at between 7-9pm (evening).

Number of subjects in period 1[1]	ETS6103 low dose	ETS6103 high dose	Amitriptyline
Started	55	54	55
Completed	38	35	31
Not completed	17	19	24
Consent withdrawn by subject	3	-	1
Adverse event, non-fatal	6	8	12
Other	1	-	1
Non-compliance	1	1	1
Lack of efficacy	6	10	9

Notes:

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

Justification: The number of patients enrolled reflects the numbers of patients screened and included in the safety analysis dataset. The number of patients in the baseline period is the number of patients randomised and included in the full analysis dataset.

Baseline characteristics

Reporting groups	
Reporting group title	ETS6103 low dose
Reporting group description: Low-dose of ETS6103	
Reporting group title	ETS6103 high dose
Reporting group description: High dose of ETS6103	
Reporting group title	Amitriptyline
Reporting group description: Amitriptyline	

Reporting group values	ETS6103 low dose	ETS6103 high dose	Amitriptyline
Number of subjects	55	54	55
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	55	54	55
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	39	40	36
Male	16	14	19

Reporting group values	Total		
Number of subjects	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)	164		
From 65-84 years	0		
85 years and over	0		

Gender categorical Units: Subjects			
Female	115		
Male	49		

Subject analysis sets

Subject analysis set title	Safety analysis set

End points

End points reporting groups

Reporting group title	ETS6103 low dose
Reporting group description: Low-dose of ETS6103	
Reporting group title	ETS6103 high dose
Reporting group description: High dose of ETS6103	
Reporting group title	Amitriptyline
Reporting group description: Amitriptyline	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who signed an informed consent and entered the lead-in phase	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: All subjects of the SA set who received at least one dose of randomised study medication with at least one on treatment measurement of the primary variable after randomisation	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: All subjects of the FA set for whom no relevant protocol deviations were documented	

Primary: The mean difference in baseline-adjusted MADRS score at the end of treatment (week 8)

End point title	The mean difference in baseline-adjusted MADRS score at the end of treatment (week 8)
End point description:	
End point type	Primary
End point timeframe: Baseline (start of treatment) to week 8. For missing results for the efficacy variable MADRS, LOCF (last-observation-carried-forward) was applied.	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	39	
Units: Baseline-adjusted MADRS score				
least squares mean (standard error)	-6.1396 (± 1.64423)	-6.0076 (± 1.65174)	-11.3762 (± 1.7344)	

Statistical analyses

Statistical analysis title	Non-inferiority ETS6103 high vs. amitriptyline
Statistical analysis description:	
Noninferiority test - comparison ETS6103 high dose vs. amitriptyline, PP set	
Comparison groups	ETS6103 high dose v Amitriptyline
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9861 [1]
Method	ANCOVA

Notes:

[1] - One-sided p-value (Non-inferiority) 97.5% confidence interval (one-sided). Non-inferiority margin 2.5.

Statistical analysis title	Non-inferiority ETS6103 low vs. amitriptyline
Statistical analysis description:	
Noninferiority test - comparison ETS6103 low dose vs. amitriptyline, PP set	
Comparison groups	Amitriptyline v ETS6103 low dose
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9828 [2]
Method	ANCOVA

Notes:

[2] - One-sided p-value (Non-inferiority) 97.5% confidence interval (one-sided). Non-inferiority margin 2.5.

Secondary: The mean difference in baseline-adjusted MADRS score at week 1

End point title	The mean difference in baseline-adjusted MADRS score at week 1
End point description:	
End point type	Secondary
End point timeframe:	
Baseline (randomisation) to week 1	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[3]	54[4]	54[5]	
Units: Baseline adjusted MADRS score				
arithmetic mean (standard deviation)	-0.87 (± 6.588)	-1.7 (± 7.324)	-3.13 (± 5.306)	

Notes:

[3] - Full analysis dataset

[4] - Full analysis dataset

[5] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: The mean difference in baseline-adjusted MADRS score at week 2

End point title	The mean difference in baseline-adjusted MADRS score at week 2

End point description:

End point type	Secondary

End point timeframe:
Baseline (randomisation) to week 2

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[6]	54[7]	54[8]	
Units: Baseline-adjusted MADRS score				
arithmetic mean (standard deviation)	-2.17 (± 8.181)	-3.35 (± 8.175)	-5 (± 8.362)	

Notes:
[6] - Full analysis dataset
[7] - Full analysis dataset
[8] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: The mean difference in baseline-adjusted MADRS score at week 4

End point title	The mean difference in baseline-adjusted MADRS score at week 4

End point description:

End point type	Secondary

End point timeframe:
Baseline (randomisation) to week 4

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[9]	54[10]	54[11]	
Units: Baseline-adjusted MADRS score				
arithmetic mean (standard deviation)	-3.89 (± 10.225)	-4.93 (± 9.206)	-7.09 (± 9.495)	

Notes:
[9] - Full analysis dataset
[10] - Full analysis dataset
[11] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: The mean difference in baseline-adjusted MADRS score at week 6

End point title	The mean difference in baseline-adjusted MADRS score at week 6

End point description:

End point type	Secondary

End point timeframe:

Baseline (randomisation) to week 6

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[12]	54[13]	54[14]	
Units: Baseline adjusted MADRS score				
arithmetic mean (standard deviation)	-5.22 (± 11.12)	-5.93 (± 10.365)	-7.87 (± 9.798)	

Notes:

[12] - Full analysis dataset

[13] - Full analysis dataset

[14] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: Patients in remission

End point title	Patients in remission

End point description:

Patients with remission defined as ≤ 10 on the MADRS at the end of treatment (week 8).

End point type	Secondary

End point timeframe:

Baseline (randomisation) to end of treatment (week 8).

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[15]	54[16]	54[17]	
Units: Number of patients	7	11	17	

Notes:

[15] - Full analysis dataset

[16] - Full analysis dataset

[17] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: Patients responsing

End point title	Patients responsing

End point description:

Responders defined as ≥ 50% decrease from baseline in the MADRS at the end of treatment (week 8)

End point type	Secondary

End point timeframe:

Baseline (randomisation) to end of treatment (week 8).

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[18]	54[19]	54[20]	
Units: Number of patients	15	17	22	

Notes:

[18] - Full analysis dataset

[19] - Full analysis dataset

[20] - Full analysis dataset

Statistical analyses

No statistical analyses for this end point

Secondary: Mean difference in baseline-adjusted CGI severity at week 8

End point title	Mean difference in baseline-adjusted CGI severity at week 8

End point description:

End point type	Secondary

End point timeframe:

Baseline (week 0) to week 8.

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	50	48	
Units: Baseline-adjusted CGI				
arithmetic mean (standard deviation)	-1 (± 1.294)	-0.98 (± 1.505)	-1.21 (± 1.458)	

Statistical analyses

Statistical analysis title	CGI-S comparison low dose ETS6103 and amitriptylin

Statistical analysis description:	
Baseline-adjusted CGI severity scores were compared between low dose ETS6103 and amitriptyline and high dose ETS6103 and amitriptyline using the ANCOVA model. The model statements were comparable to the primary efficacy parameter, whereas the test was based on superiority.	
Comparison groups	ETS6103 low dose v Amitriptyline
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5089
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1727
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3444
upper limit	0.6898
Variability estimate	Standard error of the mean
Dispersion value	0.26047

Statistical analysis title	CGI-S comparison high dose ETS6103 and amitriptyli
Statistical analysis description:	
Baseline-adjusted CGI severity scores were compared between low dose ETS6103 and amitriptyline and high dose ETS6103 and amitriptyline using the ANCOVA model. The model statements were comparable to the primary efficacy parameter, whereas the test was based on superiority.	
Comparison groups	Amitriptyline v ETS6103 high dose
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4417
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2232
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3503
upper limit	0.7967
Variability estimate	Standard error of the mean
Dispersion value	0.28889

Secondary: The mean difference in CGI improvement at week 1

End point title	The mean difference in CGI improvement at week 1
End point description:	

End point type	Secondary

End point timeframe:
Baseline (week 0) to week 1.

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	51	42	
Units: CGI improvement score				
arithmetic mean (standard deviation)	3.67 (± 0.953)	3.57 (± 1.153)	3.48 (± 1.131)	

Statistical analyses

Statistical analysis title	CGI-I low dose ETS6103 and amitriptyline wk1
Statistical analysis description: CGI-I analysis of absolute scales for week 1 - comparison low dose ETS6103 vs. Amitriptyline	
Comparison groups	ETS6103 low dose v Amitriptyline
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3883
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1905
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2461
upper limit	0.6271
Variability estimate	Standard error of the mean
Dispersion value	0.2197

Statistical analysis title	CGI-I high dose ETS6103 and amitriptyline wk1
Statistical analysis description: CGI-I analysis of absolute scales for week 1 - comparison high dose ETS6103 vs. Amitriptyline	
Comparison groups	Amitriptyline v ETS6103 high dose
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.699
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0924

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3808
upper limit	0.5657
Variability estimate	Standard error of the mean
Dispersion value	0.23826

Secondary: The mean difference in CGI improvement at week 2	
End point title	The mean difference in CGI improvement at week 2
End point description:	
End point type	Secondary
End point timeframe:	
Baseline (week 0) to week 2.	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	51	43	
Units: CGI improvement score				
arithmetic mean (standard deviation)	3.46 (± 1.051)	3.31 (± 1.191)	3.26 (± 1.432)	

Statistical analyses

Statistical analysis title	CGI-I high dose ETS6103 and amitriptyline wk2
Statistical analysis description:	
CGI-I analysis of absolute scales for week 2 - comparison high dose ETS6103 vs. Amitriptyline	
Comparison groups	ETS6103 high dose v Amitriptyline
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.831
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0579
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4795
upper limit	0.5954
Variability estimate	Standard error of the mean
Dispersion value	0.2706

Statistical analysis title	CGI-I low dose ETS6103 and amitriptyline wk2
Statistical analysis description: CGI-I analysis of absolute scales for week 2 - comparison low dose ETS6103 vs. Amitriptyline	
Comparison groups	Amitriptyline v ETS6103 low dose
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4408
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3172
upper limit	0.7222
Variability estimate	Standard error of the mean
Dispersion value	0.26156

Secondary: The mean difference in CGI improvement at week 4	
End point title	The mean difference in CGI improvement at week 4
End point description:	
End point type	Secondary
End point timeframe: Baseline (week 0) to week 4.	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	51	43	
Units: CGI improvement				
arithmetic mean (standard deviation)	3 (± 1.111)	3.08 (± 1.262)	2.86 (± 1.407)	

Statistical analyses

Statistical analysis title	CGI-I high dose ETS6103 and amitriptyline wk4
Statistical analysis description: CGI-I analysis of absolute scales for week 4 - comparison high dose ETS6103 vs. Amitriptyline	
Comparison groups	Amitriptyline v ETS6103 high dose

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4308
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.218
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3291
upper limit	0.765
Variability estimate	Standard error of the mean
Dispersion value	0.27545

Statistical analysis title	CGI-I low dose ETS6103 and amitriptyline wk4
Statistical analysis description: CGI-I analysis of absolute scales for week 4 - comparison low dose ETS6103 vs. Amitriptyline	
Comparison groups	Amitriptyline v ETS6103 low dose
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5991
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1395
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3859
upper limit	0.665
Variability estimate	Standard error of the mean
Dispersion value	0.26444

Secondary: The mean difference in CGI improvement at week 6	
End point title	The mean difference in CGI improvement at week 6
End point description:	
End point type	Secondary
End point timeframe: Baseline (week 0) to week 6.	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	51	43	
Units: CGI improvement score				
arithmetic mean (standard deviation)	3 (± 1.305)	3.18 (± 1.452)	2.67 (± 1.393)	

Statistical analyses

Statistical analysis title	CGI-I high dose ETS6103 and amitriptyline wk6
Statistical analysis description: CGI-I analysis of absolute scales for week 6 - comparison high dose ETS6103 vs. Amitriptyline	
Comparison groups	ETS6103 high dose v Amitriptyline
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0922
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	1.0881
Variability estimate	Standard error of the mean
Dispersion value	0.29505

Statistical analysis title	CGI-I low dose ETS6103 and amitriptyline wk6
Statistical analysis description: CGI-I analysis of absolute scales for week 6 - comparison low dose ETS6103 vs. Amitriptyline	
Comparison groups	Amitriptyline v ETS6103 low dose
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2527
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3256
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2363
upper limit	0.8875
Variability estimate	Standard error of the mean
Dispersion value	0.2828

Secondary: The mean difference in CGI improvement at week 8	
End point title	The mean difference in CGI improvement at week 8
End point description:	
End point type	Secondary
End point timeframe: Baseline (week 0) to week 8	

End point values	ETS6103 low dose	ETS6103 high dose	Amitriptyline	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53	53	52	
Units: CGI improvement score				
arithmetic mean (standard deviation)	3.23 (± 1.625)	3.19 (± 1.798)	2.73 (± 1.773)	

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1382
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.4956
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1623
upper limit	1.1536
Variability estimate	Standard error of the mean
Dispersion value	0.33173

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Randomisation to end of 4-week follow-up visit.	
Adverse event reporting additional description: Interventional phase.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	ETS6103 Low dose
Reporting group description: AEs occurring in ETS6103 low-dose patients, during the interventional phase (between randomisation and 4-week follow-up visit).	
Reporting group title	ETS6103 High dose
Reporting group description: AEs occurring in ETS6103 high-dose patients, during the interventional phase (between randomisation and 4-week follow-up visit).	
Reporting group title	Amitriptyline
Reporting group description: AEs occurring in amitriptyline patients, during the interventional phase (between randomisation and 4-week follow-up visit).	

Serious adverse events	ETS6103 Low dose	ETS6103 High dose	Amitriptyline
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	1 / 55 (1.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 54 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol abuse			

subjects affected / exposed	0 / 55 (0.00%)	0 / 54 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ETS6103 Low dose	ETS6103 High dose	Amitriptyline
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 55 (78.18%)	50 / 54 (92.59%)	47 / 55 (85.45%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 55 (5.45%)	1 / 54 (1.85%)	2 / 55 (3.64%)
occurrences (all)	3	1	2
Blood pressure increased			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	3 / 55 (5.45%)
occurrences (all)	0	1	3
Mean cell volume increased			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	1 / 55 (1.82%)
occurrences (all)	1	2	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 55 (3.64%)	0 / 54 (0.00%)	3 / 55 (5.45%)
occurrences (all)	2	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 55 (10.91%)	5 / 54 (9.26%)	3 / 55 (5.45%)
occurrences (all)	6	5	3
Dizziness			
subjects affected / exposed	2 / 55 (3.64%)	5 / 54 (9.26%)	4 / 55 (7.27%)
occurrences (all)	2	5	4
Tremor			
subjects affected / exposed	0 / 55 (0.00%)	0 / 54 (0.00%)	8 / 55 (14.55%)
occurrences (all)	0	0	8
Somnolence			
subjects affected / exposed	0 / 55 (0.00%)	1 / 54 (1.85%)	5 / 55 (9.09%)
occurrences (all)	0	1	5

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 55 (5.45%)	7 / 54 (12.96%)	4 / 55 (7.27%)
occurrences (all)	3	7	4
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	3 / 55 (5.45%)	7 / 54 (12.96%)	26 / 55 (47.27%)
occurrences (all)	3	7	26
Vomiting			
subjects affected / exposed	3 / 55 (5.45%)	6 / 54 (11.11%)	6 / 55 (10.91%)
occurrences (all)	4	8	6
Nausea			
subjects affected / exposed	6 / 55 (10.91%)	5 / 54 (9.26%)	0 / 55 (0.00%)
occurrences (all)	6	7	0
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)	3 / 54 (5.56%)	4 / 55 (7.27%)
occurrences (all)	1	3	4
Dyspepsia			
subjects affected / exposed	0 / 55 (0.00%)	2 / 54 (3.70%)	4 / 55 (7.27%)
occurrences (all)	0	2	4
Constipation			
subjects affected / exposed	0 / 55 (0.00%)	0 / 54 (0.00%)	5 / 55 (9.09%)
occurrences (all)	0	0	5
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 55 (3.64%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	3 / 55 (5.45%)	3 / 54 (5.56%)	2 / 55 (3.64%)
occurrences (all)	3	3	2
Cough			
subjects affected / exposed	4 / 55 (7.27%)	1 / 54 (1.85%)	1 / 55 (1.82%)
occurrences (all)	4	1	1
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	3 / 55 (5.45%)	7 / 54 (12.96%)	0 / 55 (0.00%)
occurrences (all)	3	8	0
Hyperhidrosis			
subjects affected / exposed	4 / 55 (7.27%)	1 / 54 (1.85%)	2 / 55 (3.64%)
occurrences (all)	4	1	2
Rash			
subjects affected / exposed	1 / 55 (1.82%)	5 / 54 (9.26%)	0 / 55 (0.00%)
occurrences (all)	1	6	0
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	7 / 55 (12.73%)	8 / 54 (14.81%)	3 / 55 (5.45%)
occurrences (all)	7	8	3
Anxiety			
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	5 / 55 (9.09%)
occurrences (all)	1	1	5
Nightmare			
subjects affected / exposed	2 / 55 (3.64%)	4 / 54 (7.41%)	1 / 55 (1.82%)
occurrences (all)	2	4	1
Irritability			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	1 / 55 (1.82%)
occurrences (all)	1	2	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 55 (1.82%)	1 / 54 (1.85%)	2 / 55 (3.64%)
occurrences (all)	1	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 55 (1.82%)	2 / 54 (3.70%)	1 / 55 (1.82%)
occurrences (all)	1	2	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 55 (7.27%)	5 / 54 (9.26%)	0 / 55 (0.00%)
occurrences (all)	4	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2013	The MHRA guidelines on acceptable forms of effective contraception in UK clinical trials were applied. All subjects had to be fully informed about the prescribing information for citalopram, tramadol and amitriptyline.
05 September 2013	The company name was changed due to the merger of Harrison Clinical Research (HCR) with Synteract to become SynteractHCR (SHCR). Visit windows during the lead-in phase were added to allow flexibility without compromising the value of key efficacy variables and taking citalopram supply into account. Subjects who attended visit 2 early for any reason, had to complete the 2 weeks of treatment with 20mg citalopram before starting the 40mg citalopram The data documented in the Case Report Forms of lead-in subjects who were not randomised, had to be listed but not analysed. Typographical errors and inconsistencies were corrected.
24 April 2014	The recruitment period was extended to Q2 2015. Exclusion criterion 5 was amended to permit propanolol if a stable dose (minimum 30 days) had been prescribed for non-psychotropic reasons e.g. high blood pressure. Formal psychotherapy or alternative treatments was defined in exclusion criterion 7 as that administered by a specialist healthcare professional, using formal structured techniques. The exclusion of epilepsy or history of seizures in exclusion criterion 10 was clarified. Additional guidance on withdrawal criteria for subjects with a QTc interval of >500ms measured at visits 2 or 6 or >60ms increase from screening and guidance on ECG review timelines was added.
05 March 2015	Addition of LOCF (Last observation carried forward) technique for missing values of the MADRS score and CGI improvement. Revision of the classification of subsets in order to specify that subjects with at least one on treatment measurement of the primary variable after randomisation would be included in the FA set. Furthermore, all subjects of the FA set without relevant protocol deviations would be included in the PP set.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None

Notes: