ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 04/22/2014

Randomised Placebo-controlled Venlafaxine-referenced Study of Efficacy and Safety of 5 and 10 mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder in Adults

This study has been completed.

Sponsor:	H. Lundbeck A/S
Collaborators:	
Information provided by (Responsible Party):	H. Lundbeck A/S
ClinicalTrials.gov Identifier:	NCT00839423

Purpose

The purpose of this Venlafaxine-referenced study is to evaluate the efficacy, safety and tolerability of two fixed doses of Vortioxetine in the acute treatment of Major Depressive Disorder (MDD).

Condition	Intervention	Phase
Major Depressive Disorder	Drug: Placebo Drug: Vortioxetine (Lu AA21004) Drug: Venlafaxine XL	Phase 2

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: Double-blind, Randomised, Placebo-controlled Study Comparing the Efficacy and Safety of Two Fixed Dosages of a Novel Antidepressant Compound to That of Placebo in Patients With Major Depressive Disorder

Further study details as provided by H. Lundbeck A/S:

Primary Outcome Measure:

- Change From Baseline in MADRS Total Score After 6 Weeks of Treatment [Time Frame: Baseline and Week 6] [Designated as safety issue: No]

The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe.

Secondary Outcome Measures:

- Change From Baseline in MADRS Total Score After 1 Week of Treatment [Time Frame: Baseline and Week 1] [Designated as safety issue: No]
- Change From Baseline in HAM-D 24 Total Score After 6 Weeks of Treatment [Time Frame: Baseline and Week 6] [Designated as safety issue: No]
  The 24-item Hamilton Depression Rating Scale (HAM-D) is based on the 21-item HAM-D plus an additional 3 items (helplessness, hopelessness, and worthlessness). The observer makes his/her assessment on the basis of a specific statement, content, tone, facial expression, and gestures of the patient during the interview, and scores each item from 0 to 2 or 0 to 4. Total score from 0 to 76. The higher the score, the more severe.
- Change From Baseline in HAM-A Total Score After 6 Weeks of Treatment [Time Frame: Baseline and Week 6] [Designated as safety issue: No]
  The Hamilton Anxiety Rating Scale (HAM-A) consists of 14 items that assess anxious mood, tension, fear, insomnia, intellectual (cognitive) symptoms, depressed mood, behaviour at interview, somatic (sensory), cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic, and somatic (muscular) symptoms. Each symptom is rated from 0 (absent) to 4 (maximum severity). Total score from 0 to 56. The higher the score, the more severe.
- Change From Baseline in CGI-S Score After 6 Weeks of Treatment [Time Frame: Baseline and Week 6] [Designated as safety issue: No]
  The Clinical Global Impression - Severity of Illness (CGI-S) is a 7-point scale rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The investigator should use his/her total clinical experience with this patient population to judge how mentally ill the patient is at the time of rating.
- Change in Clinical Status Using CGI-I Score at Week 6 [Time Frame: Week 6] [Designated as safety issue: No]
  The Clinical Global Impression - Global Improvement (CGI-I) is a 7-point scale rated from 1 (very much improved) to 7 (very much worse). The investigator rated the patient's overall improvement relative to baseline, whether or not, in the opinion of the investigator, this was entirely due to the drug treatment.
- Proportion of Responders at Week 6 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline) [Time Frame: Week 6] [Designated as safety issue: No]
- Proportion of Remitters at Week 6 (Remission is Defined as a MADRS Total Score <=10) [Time Frame: Week 6] [Designated as safety issue: No]

Enrollment: 426
Study Start Date: August 2006
Primary Completion Date: August 2007
Study Completion Date: September 2007

Arms	Assigned Interventions
Placebo Comparator: Placebo	Drug: Placebo capsules, daily, orally
Experimental: Vortioxetine (Lu AA21004) 5 mg	Drug: Vortioxetine (Lu AA21004) encapsulated tablets, daily, orally Other Names: Brintellix
Experimental: Vortioxetine (Lu AA21004) 10 mg	Drug: Vortioxetine (Lu AA21004) encapsulated tablets, daily, orally Other Names:

Arms	Assigned Interventions
	Brintellix
Venlafaxine XL 225 mg Active Reference	Drug: Venlafaxine XL capsules, daily, orally Other Names: Effexor®

Eligibility

Ages Eligible for Study: 18 Years to 65 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- MDE as primary diagnosis according to DSM-IV-TR criteria (classification code 296.xx)
- Current MDE duration of at least 3 months and less than 12 months
- The patient has a MADRS total score >=30

Exclusion Criteria:

- Any current psychiatric disorder other than MDD as defined in the DSM-IV TR
- Any substance disorder within the previous 6 months
- Female patients of childbearing potential who are not using effective contraception
- Use of any psychoactive medication 2 weeks prior to screening and during the study

Other protocol-defined inclusion and exclusion criteria may apply.

Contacts and Locations

Investigators

Study Director:	Email contact via H. Lundbeck A/S	LundbeckClinicalTrials@lundbeck.com

More Information

Results Publications:

Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol. 2012 Jun;15(5):589-600. doi: 10.1017/S1461145711001027. Epub 2011 Jul 18.

Responsible Party: H. Lundbeck A/S
Study ID Numbers: 11492A

	2006-001515-29 [EudraCT Number]
Health Authority:	Australia: Department of Health and Ageing Therapeutic Goods Administration Austria: Agency for Health and Food Safety Canada: Health Canada Czech Republic: State Institute for Drug Control Finland: Finnish Medicines Agency France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Italy: The Italian Medicines Agency Malaysia: Ministry of Health Slovakia: State Institute for Drug Control Spain: Spanish Agency of Medicines Sweden: Medical Products Agency

Study Results

Participant Flow

Recruitment Details	Outpatients with Major Depressive Episode (MDE) were recruited from psychiatric settings.
Pre-Assignment Details	Eligible patients were randomised equally (1:1:1:1) to one of the 4 treatment arms for a 6-week double-blind treatment period. The doses of Vortioxetine were 5 mg/day or 10 mg/day for 6 weeks. The dose of venlafaxine was 75 mg/day for 4 days, 150 mg/day for the following 3 days, and 225 mg/day for the remainder of the treatment period.

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Overall Study

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Started	105	108	100	113
Completed	87	98	82	93

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Not Completed	18	10	18	20
Adverse Event	4	3	7	16
Lack of Efficacy	6	6	3	2
Non-compliance	0	0	0	1
Protocol Violation	0	1	2	0
Withdrawal of consent	4	0	4	1
Lost to Follow-up	1	0	1	0
Administrative or other reasons	3	0	1	0

Baseline Characteristics

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Baseline Measures

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg	Total
Number of Participants	105	108	100	113	426
Age, Continuous [units: years] Mean (Standard Deviation)	42.0 (10.9)	43.8 (11.6)	42.3 (13.1)	45.0 (10.3)	43.3 (11.5)
Gender, Male/Female [units: participants]					
Female	69	70	66	62	267
Male	36	38	34	51	159
MADRS: Baseline Total Score [1] [units: units on a scale] Mean (Standard Deviation)	33.9 (2.7)	34.1 (2.6)	34.0 (2.8)	34.2 (3.1)	34.0 (2.8)

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg	Total
Baseline 24-item HAM-D Total Score [2] [units: units on a scale] Mean (Standard Deviation)	29.7 (5.0)	29.9 (5.4)	29.3 (5.6)	29.4 (5.0)	29.6 (5.2)
HAM-A: Baseline Total Score [3] [units: units on a scale] Mean (Standard Deviation)	22.9 (5.9)	21.7 (6.2)	22.3 (5.6)	22.0 (5.5)	22.2 (5.8)
CGI-S: Baseline Severity Score [4] [units: units on a scale] Mean (Standard Deviation)	5.1 (0.7)	5.2 (0.7)	5.1 (0.7)	5.2 (0.7)	5.2 (0.7)

[1] The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe.

[2] The 24-item Hamilton Depression Rating Scale (HAM-D) is based on the 21-item HAM-D plus an additional 3 items (helplessness, hopelessness, and worthlessness). The observer makes his/her assessment on the basis of a specific statement, content, tone, facial expression, and gestures of the patient during the interview, and scores each item from 0 to 2 or 0 to 4. Total score from 0 to 76. The higher the score, the more severe.

[3] The Hamilton Anxiety Rating Scale (HAM-A) consists of 14 items that assess anxious mood, tension, fear, insomnia, intellectual (cognitive) symptoms, depressed mood, behaviour at interview, somatic (sensory), cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic, and somatic (muscular) symptoms. Each symptom is rated from 0 (absent) to 4 (maximum severity). Total score from 0 to 56. The higher the score, the more severe.

[4] The Clinical Global Impression – Severity of Illness (CGI-S) is a 7-point scale rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The investigator should use his/her total clinical experience with this patient population to judge how mentally ill the patient is at the time of rating.

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in MADRS Total Score After 6 Weeks of Treatment
Measure Description	The Montgomery Åsberg Depression Rating Scale (MADRS) is a depression rating scale consisting of 10 items, each rated 0 (no symptom) to 6 (severe symptom). The 10 items represent the core symptoms of depressive illness. The rating should be based on a clinical interview with the patient, moving from broadly phrased questions about symptoms to more detailed ones, which allow a precise rating of severity, covering the last 7 days. Total score from 0 to 60. The higher the score, the more severe.
Time Frame	Baseline and Week 6

Safety Issue?	No

Analysis Population Description

Full-analysis set (FAS) – all patients in the all-patients-treated set (APTS) who had at least one valid baseline and one valid post-baseline assessment of the MADRS total score; Last Observation Carried Forward (LOCF)

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	112
Change From Baseline in MADRS Total Score After 6 Weeks of Treatment [units: units on a scale] Mean (Standard Error)	-14.50 (1.03)	-20.40 (1.01)	-20.20 (1.04)	-20.92 (0.99)

Statistical Analysis 1 for Change From Baseline in MADRS Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	The statistical model was an analysis of covariance (ANCOVA) of the change from baseline in MADRS total score (FAS, LOCF) with treatment and centre as fixed factors and the baseline MADRS score as a covariate. Null hypothesis: No difference between 10 mg Vortioxetine and placebo at Week 6. With 96 patients in each treatment arm and a standard deviation of 9 points, the power to detect a true effect of 3.7 points on the MADRS total score at Week 6 will be 80%.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A hierarchical hypothesis testing procedure was used. The comparison of 10 mg to placebo was primary. Since p-value was <0.05, hierarchically testing continued.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.70
	Confidence Interval	(2-Sided) 95% -8.49 to -2.91
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.42
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in MADRS Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	The statistical model was ANCOVA of the change from baseline in MADRS total score (FAS, LOCF) with treatment and centre as fixed factors and the baseline MADRS score as a covariate. Null hypothesis: No difference between 5 mg Vortioxetine and placebo at Week 6.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	The hierarchical hypothesis testing meant that comparison of 5 mg to placebo was performed at a 5% significance level since significance was achieved for the primary comparison of 10 mg to placebo. Since p-value <0.05, hierarchically testing contd.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)

	Estimated Value	-5.90
	Confidence Interval	(2-Sided) 95% -8.64 to -3.17
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.39
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in MADRS Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Venlafaxine 225 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	This treatment arm was not in the testing sequence. A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-6.42
	Confidence Interval	(2-Sided) 95% -9.13 to -3.72
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.38
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in MADRS Total Score After 1 Week of Treatment
Measure Description	
Time Frame	Baseline and Week 1
Safety Issue?	No

Analysis Population Description

FAS, LOCF. Please note that 1 patient in each Vortioxetine group did not have a valid MADRS assessment at Week 1, but were included in the analysis because they had a valid MADRS assessment after Week 1.

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	107	99	112
Change From Baseline in MADRS Total Score After 1 Week of Treatment [units: units on a scale] Mean (Standard Error)	-5.04 (0.50)	-5.26 (0.49)	-5.86 (0.51)	-4.50 (0.48)

Statistical Analysis 1 for Change From Baseline in MADRS Total Score After 1 Week of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	The statistical model was ANCOVA of the change from baseline in MADRS total score (FAS, LOCF) with treatment and centre as fixed factors and the baseline MADRS score as a covariate. Null hypothesis: No difference between 10 mg Vortioxetine and placebo at Week 1.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.2377
	Comments	The hierarchical procedure meant that the above hypothesis was tested at a 5% significance level since significance was achieved for both 10 and 5 mg at Week 6. Since p-value was >0.05, hierarchically testing stopped here.
	Method	ANCOVA

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.82
	Confidence Interval	(2-Sided) 95% -2.17 to 0.54
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.69
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in MADRS Total Score After 1 Week of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	The statistical model was ANCOVA of the change from baseline in MADRS total score (FAS, LOCF) with treatment and centre as fixed factors and the baseline MADRS score as a covariate. Null hypothesis: No difference between 5 mg Vortioxetine and placebo at Week 1.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7489
	Comments	The hierarchical procedure meant that the above hypothesis was not tested since significance was not achieved for 10 mg at Week 1. A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.22
	Confidence Interval	(2-Sided) 95% -1.54 to 1.11
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.67
	Estimation Comments	[Not specified]

Statistical Analysis 3 for Change From Baseline in MADRS Total Score After 1 Week of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Venlafaxine 225 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4142
	Comments	This treatment arm was not in the testing sequence. A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.54
	Confidence Interval	(2-Sided) 95% -0.77 to 1.85
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.67
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in HAM-D 24 Total Score After 6 Weeks of Treatment
Measure Description	The 24-item Hamilton Depression Rating Scale (HAM-D) is based on the 21-item HAM-D plus an additional 3 items (helplessness, hopelessness, and worthlessness). The observer makes his/her assessment on the basis of a specific statement, content, tone, facial expression, and gestures of the patient during the interview, and scores each item from 0 to 2 or 0 to 4. Total score from 0 to 76. The higher the score, the more severe.
Time Frame	Baseline and Week 6
Safety Issue?	No

Analysis Population Description

FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	111
Change From Baseline in HAM-D 24 Total Score After 6 Weeks of Treatment [units: units on a scale] Mean (Standard Error)	-12.23 (0.90)	-17.51 (0.89)	-17.57 (0.92)	-17.32 (0.88)

Statistical Analysis 1 for Change From Baseline in HAM-D 24 Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.28
	Confidence Interval	(2-Sided) 95% -7.69 to -2.88
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.22

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in HAM-D 24 Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.33
	Confidence Interval	(2-Sided) 95% -7.79 to -2.88
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.25
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in HAM-A Total Score After 6 Weeks of Treatment
Measure Description	The Hamilton Anxiety Rating Scale (HAM-A) consists of 14 items that assess anxious mood, tension, fear, insomnia, intellectual (cognitive) symptoms, depressed mood, behaviour at interview, somatic (sensory), cardiovascular, respiratory, gastrointestinal, genitourinary, autonomic, and somatic (muscular) symptoms. Each symptom is rated from 0 (absent) to 4 (maximum severity). Total score from 0 to 56. The higher the score, the more severe.
Time Frame	Baseline and Week 6
Safety Issue?	No

Analysis Population Description

FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	101	102	95	106
Change From Baseline in HAM-A Total Score After 6 Weeks of Treatment [units: units on a scale] Mean (Standard Error)	-8.41 (0.74)	-11.71 (0.75)	-11.41 (0.77)	-11.29 (0.73)

Statistical Analysis 1 for Change From Baseline in HAM-A Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0011
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.30
	Confidence Interval	(2-Sided) 95% -5.27 to -1.33
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.00

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in HAM-A Total Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0034
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.00
	Confidence Interval	(2-Sided) 95% -5.01 to -1.00
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.02
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Change From Baseline in CGI-S Score After 6 Weeks of Treatment
Measure Description	The Clinical Global Impression - Severity of Illness (CGI-S) is a 7-point scale rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). The investigator should use his/her total clinical experience with this patient population to judge how mentally ill the patient is at the time of rating.
Time Frame	Baseline and Week 6
Safety Issue?	No

Analysis Population Description
FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	111
Change From Baseline in CGI-S Score After 6 Weeks of Treatment [units: units on a scale] Mean (Standard Error)	-1.55 (0.14)	-2.45 (0.14)	-2.51 (0.15)	-2.58 (0.14)

Statistical Analysis 1 for Change From Baseline in CGI-S Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.90
	Confidence Interval	(2-Sided) 95% -1.28 to -0.52
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.19

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change From Baseline in CGI-S Score After 6 Weeks of Treatment

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.95
	Confidence Interval	(2-Sided) 95% -1.34 to -0.56
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.20
	Estimation Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Change in Clinical Status Using CGI-I Score at Week 6
Measure Description	The Clinical Global Impression - Global Improvement (CGI-I) is a 7-point scale rated from 1 (very much improved) to 7 (very much worse). The investigator rated the patient's overall improvement relative to baseline, whether or not, in the opinion of the investigator, this was entirely due to the drug treatment.
Time Frame	Week 6
Safety Issue?	No

Analysis Population Description

FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	111
Change in Clinical Status Using CGI-I Score at Week 6 [units: units on a scale] Mean (Standard Error)	2.64 (0.12)	2.05 (0.12)	2.04 (0.12)	1.96 (0.12)

Statistical Analysis 1 for Change in Clinical Status Using CGI-I Score at Week 6

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0003
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.58
	Confidence Interval	(2-Sided) 95% -0.90 to -0.27
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.16

	Estimation Comments	[Not specified]

Statistical Analysis 2 for Change in Clinical Status Using CGI-I Score at Week 6

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0003
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.60
	Confidence Interval	(2-Sided) 95% -0.92 to -0.27
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.16
	Estimation Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Proportion of Responders at Week 6 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline)
Measure Description	
Time Frame	Week 6
Safety Issue?	No

Analysis Population Description

FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	112
Proportion of Responders at Week 6 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline) [units: percentage of patients]	44.8	66.7	68.0	72.3

Statistical Analysis 1 for Proportion of Responders at Week 6 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline)

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.002
	Comments	A nominal p-value is provided.
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference %]
	Estimated Value	21.90
	Confidence Interval	(2-Sided) 95% 8.89 to 34.92
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Responders at Week 6 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline)

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	A nominal p-value is provided.
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference %]
	Estimated Value	23.34
	Confidence Interval	(2-Sided) 95% 10.05 to 36.43
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Proportion of Remitters at Week 6 (Remission is Defined as a MADRS Total Score <=10)
Measure Description	
Time Frame	Week 6
Safety Issue?	No

Analysis Population Description
FAS, LOCF

Reporting Groups

	Description
Placebo	capsules, daily, orally
Vortioxetine 5 mg	encapsulated tablets, daily, orally
Vortioxetine 10 mg	encapsulated tablets, daily, orally
Venlafaxine 225 mg	capsules, daily, orally

Measured Values

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
Number of Participants Analyzed	105	108	100	112
Proportion of Remitters at Week 6 (Remission is Defined as a MADRS Total Score <=10) [units: percentage of patients]	26.7	49.1	49.0	55.4

Statistical Analysis 1 for Proportion of Remitters at Week 6 (Remission is Defined as a MADRS Total Score <=10)

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 5 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	A nominal p-value is provided.
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference %]
	Estimated Value	22.41
	Confidence Interval	(2-Sided) 95% 9.74 to 35.07
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Remitters at Week 6 (Remission is Defined as a MADRS Total Score <=10)

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 10 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.001
	Comments	A nominal p-value is provided.
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference %]
	Estimated Value	22.33
	Confidence Interval	(2-Sided) 95% 9.39 to 35.28
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Serious Adverse Events: 6-week double-blind treatment period and 4-week safety follow-up period Other Adverse Events: 6-week double-blind treatment period
Additional Description	[Not specified]

Reporting Groups

	Description
Placebo	
Vortioxetine 5 mg	
Vortioxetine 10 mg	
Venlafaxine 225 mg	

Serious Adverse Events

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/105 (0%)	0/108 (0%)	2/100 (2%)	1/113 (0.88%)
Infections and infestations				
Varicella [A] *	0/105 (0%)	0/108 (0%)	1/100 (1%)	0/113 (0%)

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Brain neoplasm [A] *	0/105 (0%)	0/108 (0%)	0/100 (0%)	1/113 (0.88%)
Psychiatric disorders				
Depression [A] *	0/105 (0%)	0/108 (0%)	1/100 (1%)	0/113 (0%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA10_0

Other Adverse Events
Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	53/105 (50.48%)	63/108 (58.33%)	66/100 (66%)	78/113 (69.03%)
Eye disorders				
Vision blurred [A] *	2/105 (1.9%)	2/108 (1.85%)	1/100 (1%)	6/113 (5.31%)
Gastrointestinal disorders				
Constipation [A] *	1/105 (0.95%)	1/108 (0.93%)	3/100 (3%)	11/113 (9.73%)
Diarrhoea [A] *	5/105 (4.76%)	9/108 (8.33%)	7/100 (7%)	5/113 (4.42%)
Dry mouth [A] *	7/105 (6.67%)	8/108 (7.41%)	8/100 (8%)	19/113 (16.81%)
Nausea [A] *	10/105 (9.52%)	32/108 (29.63%)	38/100 (38%)	38/113 (33.63%)
Vomiting [A] *	1/105 (0.95%)	2/108 (1.85%)	9/100 (9%)	4/113 (3.54%)
General disorders				
Fatigue [A] *	6/105 (5.71%)	4/108 (3.7%)	6/100 (6%)	11/113 (9.73%)
Infections and infestations				
Nasopharyngitis [A] *	9/105 (8.57%)	8/108 (7.41%)	7/100 (7%)	4/113 (3.54%)
Nervous system disorders				

	Placebo	Vortioxetine 5 mg	Vortioxetine 10 mg	Venlafaxine 225 mg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dizziness [A] *	8/105 (7.62%)	7/108 (6.48%)	7/100 (7%)	14/113 (12.39%)
Headache [A] *	26/105 (24.76%)	23/108 (21.3%)	25/100 (25%)	32/113 (28.32%)
Tremor [A] *	3/105 (2.86%)	5/108 (4.63%)	0/100 (0%)	6/113 (5.31%)
Psychiatric disorders				
Anorgasmia [A] *	0/105 (0%)	0/108 (0%)	0/100 (0%)	7/113 (6.19%)
Insomnia [A] *	5/105 (4.76%)	7/108 (6.48%)	6/100 (6%)	14/113 (12.39%)
Reproductive system and breast disorders				
Ejaculation delayed [A] *	0/36 (0%)	0/38 (0%)	0/34 (0%)	4/51 (7.84%)
Erectile dysfunction [A] *	0/36 (0%)	0/38 (0%)	0/34 (0%)	4/51 (7.84%)
Skin and subcutaneous tissue disorders				
Hyperhidrosis [A] *	2/105 (1.9%)	3/108 (2.78%)	10/100 (10%)	17/113 (15.04%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA10_0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The main publication has to be published before any sub publication. The investigators shall obtain Lundbeck's written approval before publishing any publication relating to Vortioxetine, the Study, the Protocol and/or the results recorded during the Study.

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