ClinicalTrials.gov PRS
Protocol Registration and Results System

ID: 13267A Randomised Placebo-controlled Duloxetine-referenced Study of Efficacy and Safety of 15 and 20 mg of Vortioxetine (Lu AA21004) in Acute Treatment of Major Depressive Disorder in Adults NCT01140906

Protocol Registration and Results Preview

Close

Randomised Placebo-controlled Duloxetine-referenced Study of Efficacy and Safety of 15 and 20 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:	NCT01140906

Purpose

The purpose of the study is to evaluate the efficacy, tolerability and the safety of two fixed doses of vortioxetine in the treatment of major depressive disorder.

Condition	Intervention	Phase
Major Depressive Disorder	Drug: Placebo Drug: Vortioxetine (Lu AA21004) Drug: Duloxetine	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study

Official Title: A Randomised, Double-blind, Parallel-group, Placebo-controlled, Duloxetine-referenced, Fixed-dose Study Evaluating the Efficacy and Safety of Lu AA21004 (15 and 20 mg/Day) in the Acute Treatment of Adult 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 8 Weeks of Treatment. [Time Frame: Baseline and Week 8] [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:

- Proportion of Responders at Week 8 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline) [Time Frame: Week 8] [Designated as safety issue: No]

- Change in Clinical Status Using CGI-I Score at Week 8 [Time Frame: Week 8] [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.

- Change From Baseline in MADRS Total Score After 8 Weeks of Treatment in Patients With Baseline HAM-A Total Score ≥20 [Time Frame: Baseline and Week 8] [Designated as safety issue: No]

- Proportion of Remitters at Week 8 (Remission Defined as a MADRS Total Score <=10) [Time Frame: Week 8] [Designated as safety issue: No]

- Change From Baseline in SDS Total Score After 8 Weeks of Treatment [Time Frame: Baseline and Week 8] [Designated as safety issue: No]
  The Sheehan Disability Scale (SDS) comprises self-rated items designed to measure impairment. The patient rates the extent to which his or her (1) work, (2) social life or leisure activities and (3) home life or family responsibilities are impaired on a 10-point visual analogue scales, on which 0 = normal functioning and 10 = severe functional impairment. The three items may be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). The higher the score, the more severe.

- Change From Baseline in ASEX Total Score After 8 Weeks of Treatment [Time Frame: Baseline and Week 8] [Designated as safety issue: Yes]
  The Arizona Sexual Experience Scale (ASEX) is a 5-item, patient self-rated scale that evaluates a patient's recent sexual experience. Patients are asked to assess their own experience over the last week (for example, "How strong is your sex drive?", "Are your orgasms satisfying?") and respond on a 6-point scale for each item. The ASEX is used to identify individuals with sexual dysfunction. Possible total score ranges from 5 to 30, with the higher score indicating more patient sexual dysfunction. A negative change indicates a lower sexual dysfunction.

- Potential Discontinuation Symptoms After Abrupt Discontinuation of Treatment With Vortioxetine [Time Frame: Change from Week 8 in DESS total score analyzed at Week 10] [Designated as safety issue: Yes]
  The Discontinuation-Emergent Signs and Symptoms Scale (DESS) was designed to evaluate possible effects of discontinuation of antidepressant therapy. It is a clinician-rated instrument that queries for signs and symptoms on a 43-item checklist (for example, agitation, insomnia, fatigue, and dizziness) to assess whether the item (event) is discontinuation-emergent. A new or worsened event reported after discontinuation of therapy scores 1 point on the checklist, and the DESS total score is the sum of all positive scores on the checklist. A higher score indicates more symptoms.

Enrollment: 607
Study Start Date: May 2010
Primary Completion Date: September 2011

Arms	Assigned Interventions
Placebo Comparator: Placebo	Drug: Placebo capsules, daily, orally
Experimental: Vortioxetine: 15 mg	Drug: Vortioxetine (Lu AA21004) encapsulated tablets, daily, orally Other Names: • Brintellix
Experimental: Vortioxetine: 20 mg	Drug: Vortioxetine (Lu AA21004) encapsulated tablets, daily, orally Other Names: • Brintellix
Duloxetine: 60 mg Active Reference	Drug: Duloxetine encapsulated capsules, daily, orally Other Names: • Cymbalta®

Eligibility

Ages Eligible for Study: 18 Years to 75 Years
Genders Eligible for Study: Both
Inclusion Criteria:

- The patient has recurrent MDD as the primary diagnosis according to DSM-IV-TR™ criteria (classification code 296.3x)
- The patient has a MADRS total score >=26
- The patient has a CGI-S score >=4
- The patient has had the current episode of MDE for >3 months

Exclusion Criteria:

- Any current anxiety psychiatric disorder as defined in the DSM-IV TR
- Current diagnosis or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV TR
- Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-IV TR
- Use of any psychoactive medication 2 weeks prior to screening and during the study
- The patient is at significant risk of suicide or has a score >=5 on Item 10 (suicidal thoughts) of the MADRS, or has attempted suicide within 6 months prior to the Screening Visit

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

Responsible Party: H. Lundbeck A/S
Study ID Numbers: 13267A
2009-017523-26 [EudraCT Number]
Health Authority: Belgium: Federal Agency for Medicinal Products and Health Products
Estonia: The State Agency of Medicine
Finland: Finnish Medicines Agency
France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)
Germany: Federal Institute for Drugs and Medical Devices
Latvia: State Agency of Medicines
Lithuania: State Medicine Control Agency - Ministry of Health
Norway: Norwegian Medicines Agency
Russia: Ministry of Health of the Russian Federation
Slovakia: State Institute for Drug Control
South Africa: Medicines Control Council
Sweden: Medical Products Agency
Ukraine: State Pharmacological Center - Ministry of Health

Study Results

Participant Flow

Recruitment Details	Patients were selected from psychiatric settings (private practices), outpatient clinics, and inpatient hospitals.
Pre-Assignment Details	At the Baseline Visit, patients who fulfilled the selection criteria were assigned to treatment with either placebo, vortioxetine 15 or 20 mg/day, or duloxetine 60 mg/day in a 1:1:1:1 ratio.

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg	Total (Not public)
Arm/Group Description	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally	
Period Title: **Overall Study**					
Started	158	151	151	147	607
Completed	133	117	125	131	506
Not Completed	25	34	26	16	101
Reason Not Completed					
Adverse Event	7	10	17	7	41
Lack of Efficacy	6	8	2	1	17
Non-compliance	0	1	0	1	2

Protocol Violation	5	3	2	1	11
Withdrawal of consent	6	6	2	2	16
Lost to Follow-up	1	1	0	2	4
Administrative or other reason	0	5	3	2	10
(Not Public)	Not Completed = 25 Total from all reasons = 25	Not Completed = 34 Total from all reasons = 34	Not Completed = 26 Total from all reasons = 26	Not Completed = 16 Total from all reasons = 16	

Baseline Characteristics

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg	Total
▼ Arm/Group Description	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally	
Overall Number of Baseline Participants	158	151	151	147	**607**
▼ Baseline Analysis Population Description [Not specified]					
Age, Continuous Mean (Standard Deviation) Units: years	48.1 (13.1)	47.0 (14.6)	46.2 (13.4)	45.6 (13.6)	46.7 (13.7)
Gender, Male/Female Measure Type: Number Units: participants					
Female	110	97	91	102	400
Male	48	54	60	45	207
MADRS baseline total score [1] Mean (Standard Deviation) Units: units on a scale	31.5 (3.6)	31.8 (3.4)	31.2 (3.4)	31.2 (3.5)	31.4 (3.5)
	[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. 9 of the items are based on patient report, and 1 is based on the rater's observation of the patients. Total score from 0 to 60. The higher the score, the more severe.				
CGI-S baseline severity score [1] Mean (Standard Deviation) Units: units on a scale	4.9 (0.7)	4.9 (0.6)	4.8 (0.7)	4.8 (0.7)	4.8 (0.7)
	[1] 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.				
HAM-A baseline total					

score [1] Mean (Standard Deviation) Units: units on a scale	20.8 (6.6)	21.3 (6.8)	20.4 (6.9)	20.5 (6.7)	20.8 (6.7)
	[1] 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.				
SDS total baseline score [1] Mean (Standard Deviation) Units: units on a scale	19.8 (6.0)	20.6 (5.3)	20.7 (4.8)	20.5 (4.4)	20.4 (5.2)
	[1] The Sheehan Disability Scale (SDS) comprises self-rated items designed to measure impairment. The patient rates the extent to which his or her (1) work, (2) social life or leisure activities and (3) home life or family responsibilities are impaired on a 10-point visual analogue scales, on which 0 = normal functioning and 10 = severe functional impairment. The three items may be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). The higher the score, the more severe.				

Outcome Measures

1. Primary Outcome

Title:	Change From Baseline in MADRS Total Score After 8 Weeks of Treatment.
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 8
Safety Issue?	No

Outcome Measure Data

Analysis Population Description

Full-analysis set (FAS), mixed model for repeated measurements (MMRM)

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	158	149	151	146
Mean (Standard Error) Units: units on a scale	-11.70 (0.76)	-17.23 (0.79)	-18.79 (0.78)	-21.15 (0.77)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.53
	Confidence Interval	(2-Sided) 95% -7.66 to -3.40
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.09
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-7.09
	Confidence Interval	(2-Sided) 95% -9.21 to -4.97
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.08
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 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	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-9.45
	Confidence Interval	(2-Sided) 95% -11.55 to -7.35
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.07
	Estimation Comments	[Not specified]

2. Secondary Outcome

Title:	Proportion of Responders at Week 8 (Response Defined as a >=50% Decrease in the MADRS Total Score From Baseline)
▼ Description:	[Not specified]
Time Frame:	Week 8
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS, last observation carried forward (LOCF), Logistic Regression

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg

Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	158	149	151	146
Measure Type: Number Units: percentage of patients	32	57	62	74

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Wald's test. Since p-value <0.025, hierarchically testing continued.
	Method	Other [Adjusted Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)

	Estimated Value	2.80
	Confidence Interval	(2-Sided) 95% 1.76 to 4.47
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Wald's test. Since p-value <0.025, hierarchically testing continued.
	Method	Other [Adjusted Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	3.36
	Confidence Interval	(2-Sided) 95% 2.10 to 5.36
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 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	Other [Adjusted Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	5.94
	Confidence Interval	(2-Sided) 95% 3.61 to 9.78
	Estimation Comments	[Not specified]

3. Secondary Outcome

Title:	Change in Clinical Status Using CGI-I Score at Week 8
▼ 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 8
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS, MMRM

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	158	149	151	146
Mean (Standard Error) Units: units on a scale	2.86 (0.09)	2.18 (0.09)	1.92 (0.09)	1.75 (0.09)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.69
	Confidence Interval	(2-Sided) 95% -0.94 to -0.44
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.13
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of	P-Value	<0.0001

Hypothesis	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.95
	Confidence Interval	(2-Sided) 95% -1.20 to -0.70
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.13
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 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	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-1.12
	Confidence Interval	(2-Sided) 95% -1.36 to -0.87
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.13

	Estimation Comments	[Not specified]

4. Secondary Outcome

Title:	Change From Baseline in MADRS Total Score After 8 Weeks of Treatment in Patients With Baseline HAM-A Total Score ≥20
▼ Description:	[Not specified]
Time Frame:	Baseline and Week 8
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

FAS, MMRM

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	89	87	80	80
Mean (Standard Error) Units: units on a scale	-12.20 (1.09)	-17.44 (1.08)	-18.62 (1.15)	-20.91 (1.10)

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0007
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-5.24
	Confidence Interval	(2-Sided) 95% -8.25 to -2.22
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.53
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-6.42
	Confidence Interval	(2-Sided) 95% -9.53 to -3.31
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.58
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 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	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-8.71
	Confidence Interval	(2-Sided) 95% -11.73 to -5.69
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.54
	Estimation Comments	[Not specified]

5. Secondary Outcome

Title:	Proportion of Remitters at Week 8 (Remission Defined as a MADRS Total Score <=10)
▼ Description:	[Not specified]
Time Frame:	Week 8
Safety Issue?	No

▼ Outcome Measure Data ✓

▼ Analysis Population Description

FAS, LOCF, Logistic Regression

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg

▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	158	149	151	146
Measure Type: Number Units: percentage of patients	19	35	38	54

▼ Statistical Analysis 1 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0016
	Comments	Wald's test. Since p-value <0.025, hierarchically testing continued.
	Method	Other [Adjusted Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.32

	Confidence Interval	(2-Sided) 95% 1.37 to 3.91
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0002
	Comments	Wald's test. Since p-value <0.025, hierarchically testing continued.
	Method	Other [Adjusted Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.65
	Confidence Interval	(2-Sided) 95% 1.58 to 4.44
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.0001
	Comments	Wald's test. This treatment arm was not in the testing sequence. A nominal p-value is provided.
	Method	Other [Adjusted for Odds Ratio]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	5.01
	Confidence Interval	(2-Sided) 95% 2.99 to 8.37
	Estimation Comments	[Not specified]

6. Secondary Outcome

Title:	Change From Baseline in SDS Total Score After 8 Weeks of Treatment
▼ Description:	The Sheehan Disability Scale (SDS) comprises self-rated items designed to measure impairment. The patient rates the extent to which his or her (1) work, (2) social life or leisure activities and (3) home life or family responsibilities are impaired on a 10-point visual analogue scales, on which 0 = normal functioning and 10 = severe functional impairment. The three items may be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). The higher the score, the more severe.
Time Frame:	Baseline and Week 8
Safety Issue?	No

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS, MMRM

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	115	97	107	99
Mean (Standard Error) Units: units on a scale	-4.46 (0.82)	-7.70 (0.89)	-8.38 (0.85)	-11.39 (0.85)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0054
	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.24
	Confidence Interval	(2-Sided) 95% -5.51 to -0.97
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.16
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	As soon as an endpoint was non-significant at the 0.025 level of significance, the testing procedure was stopped for all subsequent endpoints.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of	P-Value	0.0005

Hypothesis	Comments	Since p-value <0.025, hierarchically testing continued.
	Method	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-3.92
	Confidence Interval	(2-Sided) 95% -6.11 to -1.73
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.11
	Estimation Comments	To adjust for multiplicity the two doses of vortioxetine were tested separately versus placebo in the primary and key secondary efficacy analyses at a Bonferroni-corrected significance level of 0.025.

▼ Statistical Analysis 3 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Duloxetine 60 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	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-6.93
	Confidence Interval	(2-Sided) 95% -9.16 to -4.70
	Parameter Dispersion	Type: Standard Error of the mean Value: 1.13

	Estimation Comments	[Not specified]

7. Secondary Outcome

Title:	Change From Baseline in ASEX Total Score After 8 Weeks of Treatment
▼ Description:	The Arizona Sexual Experience Scale (ASEX) is a 5-item, patient self-rated scale that evaluates a patient's recent sexual experience. Patients are asked to assess their own experience over the last week (for example, "How strong is your sex drive?", "Are your orgasms satisfying?") and respond on a 6-point scale for each item. The ASEX is used to identify individuals with sexual dysfunction. Possible total score ranges from 5 to 30, with the higher score indicating more patient sexual dysfunction. A negative change indicates a lower sexual dysfunction.
Time Frame:	Baseline and Week 8
Safety Issue?	Yes

▼ Outcome Measure Data ✔

▼ Analysis Population Description

FAS, MMRM

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	156	147	148	144
Mean (Standard Error) Units: units on a scale	0.28 (0.42)	-0.39 (0.43)	-0.20 (0.43)	-1.25 (0.42)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.2524
	Comments	A nominal p-value is provided.
	Method	Other [MMRM]

	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.67
	Confidence Interval	(2-Sided) 95% -1.83 to 0.48
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.59
	Estimation Comments	No correction for multiplicity was made.

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4186
	Comments	A nominal p-value is provided.
	Method	Other [MMRM]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.48
	Confidence Interval	(2-Sided) 95% -1.64 to 0.68
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.59
	Estimation Comments	No correction for multiplicity was made.

8. Secondary Outcome

Title:	Potential Discontinuation Symptoms After Abrupt Discontinuation of Treatment With Vortioxetine

▼ Description:	The Discontinuation-Emergent Signs and Symptoms Scale (DESS) was designed to evaluate possible effects of discontinuation of antidepressant therapy. It is a clinician-rated instrument that queries for signs and symptoms on a 43-item checklist (for example, agitation, insomnia, fatigue, and dizziness) to assess whether the item (event) is discontinuation-emergent. A new or worsened event reported after discontinuation of therapy scores 1 point on the checklist, and the DESS total score is the sum of all positive scores on the checklist. A higher score indicates more symptoms.
Time Frame:	Change from Week 8 in DESS total score analyzed at Week 10
Safety Issue?	Yes

▼ Outcome Measure Data ✔

▼ Analysis Population Description

All Patients Completed Set (APCS), OC, Analysis of Covariance (ANCOVA)

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
▼ Arm/Group Description:	capsules, daily, orally	encapsulated tablets, daily, orally	encapsulated tablets, daily, orally	encapsulated capsules, daily, orally
Number of Participants Analyzed	121	116	120	127
Mean (Standard Error) Units: units on a scale	0.15 (0.30)	0.01 (0.31)	0.72 (0.31)	2.28 (0.30)

▼ Statistical Analysis 1 ✔

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 15 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.7372
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	-0.14
	Confidence Interval	(2-Sided) 95% -0.95 to 0.67
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.41
	Estimation Comments	[Not specified]

▼ Statistical Analysis 2 ✓

Statistical Analysis Overview	Comparison Groups	Placebo, Vortioxetine 20 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.1690
	Comments	A nominal p-value is provided.
	Method	ANCOVA
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.56
	Confidence Interval	(2-Sided) 95% -0.24 to 1.37
	Parameter Dispersion	Type: Standard Error of the mean Value: 0.41
	Estimation Comments	[Not specified]

Adverse Events

Time Frame	Serious Adverse Events: 8-week double-blind treatment period and 4-week safety follow-up period Other Adverse Events: 8-week double-blind treatment period

Additional Description	
Source Vocabulary Name	[Not specified]
Assessment Type	[Not specified] NOTE : An Assessment Type for Table Default has not been specified.

Arm/Group Title	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
Arm/Group Description	[Not specified] NOTE : An entry in Arm/Group Description is recommended.	[Not specified] NOTE : An entry in Arm/Group Description is recommended.	[Not specified] NOTE : An entry in Arm/Group Description is recommended.	[Not specified] NOTE : An entry in Arm/Group Description is recommended.

Serious Adverse Events

	Placebo	Vortioxetine 15 mg	Vortioxetine 20 mg	Duloxetine 60 mg
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	0/158 (0%)	0/151 (0%)	2/151 (1.32%)	3/147 (2.04%)
Injury, poisoning and procedural complications				
Intentional overdose [A]	0/158 (0%)	0/151 (0%)	0/151 (0%)	1/147 (0.68%)
Lumbar vertebral fracture [A]	0/158 (0%)	0/151 (0%)	0/151 (0%)	1/147 (0.68%)
Investigations				
Blood pressure decreased [A]	0/158 (0%)	0/151 (0%)	1/151 (0.66%)	0/147 (0%)
Nervous system disorders				
Dizziness [A]	0/158 (0%)	0/151 (0%)	1/151 (0.66%)	0/147 (0%)
Psychiatric disorders				
Intentional self-injury [A]	0/158 (0%)	0/151 (0%)	1/151 (0.66%)	0/147 (0%)
Self injurious behaviour [A]	0/158 (0%)	0/151 (0%)	0/151 (0%)	1/147 (0.68%)
Reproductive system and breast disorders				
Vaginal haemorrhage [A]	0/110 (0%)	0/97 (0%)	0/91 (0%)	1/102 (0.98%)

Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 14.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse	5%

Events				
	Placebo	**Vortioxetine 15 mg**	**Vortioxetine 20 mg**	**Duloxetine 60 mg**
	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)	Affected / at Risk (%)
Total	44/158 (27.85%)	61/151 (40.4%)	70/151 (46.36%)	67/147 (45.58%)
Gastrointestinal disorders				
Diarrhoea [A]	6/158 (3.8%)	6/151 (3.97%)	11/151 (7.28%)	9/147 (6.12%)
Dry mouth [A]	5/158 (3.16%)	5/151 (3.31%)	9/151 (5.96%)	14/147 (9.52%)
Nausea [A]	16/158 (10.13%)	40/151 (26.49%)	48/151 (31.79%)	45/147 (30.61%)
General disorders				
Fatigue [A]	4/158 (2.53%)	6/151 (3.97%)	5/151 (3.31%)	8/147 (5.44%)
Nervous system disorders				
Dizziness [A]	10/158 (6.33%)	7/151 (4.64%)	7/151 (4.64%)	15/147 (10.2%)
Headache [A]	12/158 (7.59%)	16/151 (10.6%)	19/151 (12.58%)	16/147 (10.88%)
Skin and subcutaneous tissue disorders				
Hyperhidrosis [A]	6/158 (3.8%)	5/151 (3.31%)	0/151 (0%)	11/147 (7.48%)

Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 14.0

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 results of this study will be published at the discretion of H. Lundbeck A/S. H. Lundbeck A/S will ensure that the authorship of all publications based on this study is in accordance with the criteria defined by the International Committee of Medical Journal Editors (ICMJE).

The primary publication must be published before any secondary publications.

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