A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 [vortioxetine] in patients with major depressive disorder

Alvarez E, Perez V, Dragheim M, Loft H, Artigas F.
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KEY FINDINGS

- Brintellix® (vortioxetine) was statistically significantly superior to placebo ($p<0.0001$) as assessed by MADRS at 6 weeks[1]
- Brintellix was efficacious in treating the symptoms of depression (assessed by MADRS or HAM-D_{24}) in severely depressed patients (MADRS ≥30), including those with substantial baseline levels of anxiety symptoms (HAM-A ≥20)[1]
- Nausea, hyperhidrosis, and vomiting were the only Brintellix adverse events reported with an incidence statistically significantly higher than placebo ($p<0.05$)[1*]

*Please refer to the Australian Approved Brintellix Product Information for full safety and tolerability data.[2]

Efficacy

Lundbeck

Brintellix® vortioxetine

Introduction

Brintellix is a multimodal antidepressant – it has a direct effect on receptor activity as well as serotonin (5-HT) reuptake inhibition.[1]

This is the first double-blind, randomized, placebo controlled study to evaluate the efficacy, safety and tolerability of Brintellix in patients with major depressive disorder (MDD). Venlafaxine XR (225 mg/d) was used as the active reference.[1]

Method[1]

Inclusion criteria

- Age 18–65 years
- Current major depressive episode (MDE; according to DSM-IV-TR criteria)
- MADRS score ≥30 at the baseline visit

Selected exclusion criteria

- Current psychiatric disorder other than MDD (as defined in DSM-IV-TR)
- Presence or history of a clinically significant neurological disorder
- Current or past history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, or any substance abuse disorder within the previous 6 months
- Patients at risk of suicide including those patients with a score of ≥5 on item 10 of MADRS scale
- Patients already receiving psychotherapy
- Pregnant or breastfeeding
- Hypersensitivity or non-response to venlafaxine
- Current depressive symptoms were resistant to two adequate antidepressant treatments of at least a 6-week duration
- Previous exposure to Brintellix
- Patients taking medication that could interfere with the study (e.g. psychoactive medications, interacting medicines)

Study design

- Patients assessed from baseline to week 6
- Double-blind treatment, randomised, placebo-controlled, active reference (venlafaxine)
- 429 patients randomised (1:1:1:1) to 5 or 10 mg/d Brintellix, placebo or 225 mg/d venlafaxine

Primary endpoint

- MADRS change from baseline to week 6 vs. placebo (FAS, LOCF)

Secondary endpoints

- MADRS, HAM-D_{24}, CGI-I, CGI-S, HAM-A
- Remission (defined as MADRS ≤10, 17-item HAM-D (HAM-D_{17}) ≤7 or as a CGI-S score ≤2)
- Response (defined as ≥50% decrease from baseline in MADRS or HAM-D_{24} total score, or a CGI-I score ≤2 at all time points)
- Tolerability assessments

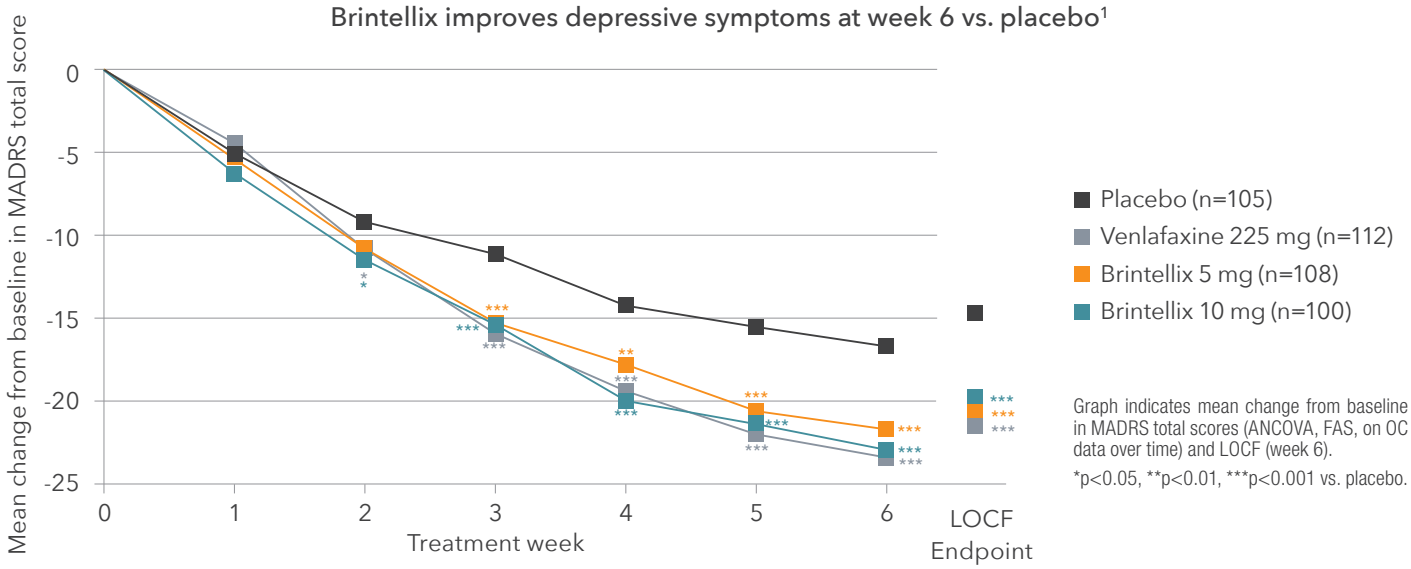
Study limitation

- Lack of generalisability due to a fairly homogeneous group that may not be reflective of the MDD population as a whole

Results[1]

Primary endpoint

- Both doses of Brintellix were statistically significantly superior to placebo (p<0.0001) in mean change from baseline in MADRS score at week 6
- Treatment differences from placebo were 5.9 points (Brintellix 5 mg) and 5.7 points (Brintellix 10 mg) at week 6 (LOCF)
- Venlafaxine was included as a reference for study validation, not for comparison of effect size



Graph indicates mean change from baseline in MADRS total scores (ANCOVA, FAS, on OC data over time) and LOCF (week 6).

*p<0.05, **p<0.01, ***p<0.001 vs. placebo.

Key secondary endpoints

HAM-D24

- Brintellix 5 mg and 10 mg statistically significantly improved HAM-D24 scores from week 1 onwards, compared with placebo (p<0.05)

HAM-A

- Brintellix 5 mg and 10 mg statistically significantly improved anxiety symptoms at 6 weeks, compared with placebo (p<0.05)

Tolerability and safety

- The majority of adverse events (AEs) experienced by patients were mild or moderate. The incidence of severe AEs was 4% in the placebo group, 6% in the Brintellix groups, and statistically significantly higher at 12% in the venlafaxine group (p=0.026)
- For the majority of patients reporting nausea, it was transient and mild or moderate in intensity
- Brintellix 5 mg and 10 mg had similar levels of treatment-emergent sexual dysfunction (TESD) compared to placebo[1†]

†In clinical studies the incidence of TESD reported with Brintellix increased with dose[2]

- No clinically relevant changes over time were seen in the weight, vital signs, or ECG parameters
- For Brintellix, nausea (5 and 10 mg), hyperhidrosis (10 mg), and vomiting (10 mg) were the only AEs reported with an incidence statistically significantly higher than placebo (p<0.05) in this study

Preferred term	Brintellix 5 mg (n=108)	Brintellix 10 mg (n=100)	Placebo (n=105)
Nausea	29.6%***	38.0%***	9.5%
Hyperhidrosis	2.8%	10.0%*	1.9%
Vomiting	1.9%	9.0%**	1.0%

*p<0.05, **p<0.01, ***p<0.001 vs. placebo.

Please refer to the Australian Approved Brintellix Product Information for full safety and tolerability data. Brintellix Product Information: Nausea: 8.1% (Placebo); 20.5% (Brintellix 5 mg); 22.6% (Brintellix 10 mg). Hyperhidrosis: 1.7% (Placebo); 2.3% (Brintellix 5 mg); 2.3% (Brintellix 10 mg). Vomiting: 1.1% (Placebo); 2.7% (Brintellix 5 mg); 3.6% (Brintellix 10 mg). Placebo: n= 1968; Brintellix 5 mg: n=1157; Brintellix 10 mg: n= 1042.[2]

Once-daily Brintellix
available in four tablet strengths[2]

§The starting and recommended dose in adults is 10 mg once daily. For patients ≥65 years, the recommended starting dose is 5 mg once daily.[2]

PBS Information: This product is not listed on the PBS.

Please review the full Product Information before prescribing.
Product Information is available by calling Lundbeck on 1300 721 277.

Minimum Product Information: Brintellix® (vortioxetine hydrobromide). **Pharmacology:** BRINTELLIX has multimodal activity, which is a combination of two pharmacological modes of action: direct modulation of serotonin receptor activity and inhibition of the serotonin transporter. Nonclinical data suggest that this leads to modulation of neurotransmission in several systems, including serotonin, norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems. **Indications:** Treatment of major depressive disorder in adults including prevention of relapse. BRINTELLIX is not indicated for paediatric use. **Dosage & Administration:** To be taken with or without food. Adults: 10 mg once daily; depending on individual response maximum 20 mg once daily or reduced to 5 mg once daily. Elderly (≥65 years): 5 mg once daily; increase to 10 mg once daily if required. Dosage adjustment may be required for strong CYP2D6 inhibitors or CYP450 inducers. Treatment for at least 6 months is recommended for consolidation of response. **Contraindications:** Hypersensitivity to any component of BRINTELLIX. Concomitant treatment with MAOIs or treatment within 14 days of MAOIs. **Precautions:** Clinical worsening and suicide risk; neuroleptic malignant syndrome; serotonin syndrome; activation of mania/hypomania; aggression/agitation; seizures; haemorrhage; hyponatraemia; severe hepatic impairment; severe renal impairment; raised intraocular pressure; angle-closure glaucoma; pregnancy (Category B3); electroconvulsive therapy; breastfeeding is not recommended; interference with urine drug screens. **Interactions:** MAOIs (see full PI for details); serotonergic medicines including *opioids (including tramadol)* and triptans; St John's Wort; cytochrome P450 inducers e.g. rifampicin; cytochrome P450 inhibitors e.g. bupropion; antiplatelets; anticoagulants; lithium; tryptophan; medicines lowering the seizure threshold including SSRIs, SNRIs, tricyclics, neuroleptics, mefloquine, tramadol. **Adverse Effects:** nausea; vomiting; diarrhoea; constipation; dizziness; generalised pruritus; hyponatraemia*. For all other adverse events see full PI. **Date of TGA approval:** 31 March 2014. **Date of TGA update:** 07 March 2022. **Date of Minimum PI:** 22 March 2022. **Please note changes to minimum product information in italics.*

Glossary: AE: adverse event; ANCOVA: Analysis of Covariance; CGI-I: Clinical Global Impression – Improvement scale; CGI-S: Clinical Global Impression – Severity scale; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision; ECG: electrocardiogram; FAS: Full-analysis set; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D_{17}: 17-item Hamilton Depression Scale; HAM-D_{24}: 24-item Hamilton Depression Scale; LOCF: last observation carried forward; MADRS: Montgomery–Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; OC: observed cases; TESD: treatment-emergent sexual dysfunction.

References: 1. Alvarez E, *et al. Int J Neuropsychopharmacol* 2012; 15(5):589–600. **2.** Brintellix® Australian Approved Product Information.

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