A randomised, double-blind study in adults with major depressive disorder with an inadequate response to a single course of selective serotonin reuptake inhibitor or serotonin–noradrenaline reuptake inhibitor treatment switched to vortioxetine or agomelatine

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KEY FINDINGS

- Brintellix® (vortioxetine) was statistically significantly superior to agomelatine in treating depressive symptoms, as measured by MADRS (primary endpoint: change from baseline at week 8; p=0.0018), in patients who had an inadequate response to prior treatment with an SSRI or SNRI[1]
  - The statistically significant (p<0.05) difference in favour of Brintellix was seen early (at 3 or 4 weeks) and was sustained (at 8 and 12 weeks)[1]
- The robustness of this finding was shown by consistent statistically significant (p<0.05) improvements with Brintellix compared with agomelatine in secondary efficacy analyses including measures of overall functioning (measured by the Sheehan Disability Scale) and health-related quality of life (measured by EuroQol 5 Dimensions)[1]
- This study appears to be the first large double-blind randomised study to have shown a statistically significant (p<0.05) and clinically relevant difference in efficacy between two classes of antidepressants in a patient population of inadequate SSRI/SNRI responders[1]

Efficacy

Lundbeck

Brintellix® vortioxetine

Introduction

In patients with major depressive disorder (MDD), initial treatment is usually antidepressant monotherapy, often with a selective serotonin reuptake inhibitor. Following inadequate response to treatment, clinical guidelines recommend switching pharmacological class as one viable option.[1,2]

Brintellix is a multimodal antidepressant that is thought to modulate neurotransmission through two modes of action: direct effects on serotonin (5-HT) receptor activity and 5-HT reuptake.[1] Agomelatine is an antidepressant that is thought to exert its effects by melatonergic agonism (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonism.[1]

Method

Key inclusion criteria[1]

- Aged ≥18 to ≤75 years
- Primary diagnosis of a single episode of MDD or recurrent MDD (DSM-IV-TR criteria)
- Current major depressive episode of <12 months' duration (Mini International Neuropsychiatric Interview)
- MADRS total score ≥22 and item 1 (apparent sadness) score ≥3
- Inadequate response to SSRI or SNRI monotherapy (other than fluoxetine and fluvoxamine) for ≥6 weeks before screening

Key exclusion criteria[1]

- Previous exposure to Brintellix or history of lack of response to agomelatine
- Current Axis I disorder other than generalised anxiety disorder or social anxiety disorder
- History of a 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
- Any substance abuse disorder in the previous 2 years
- History of a clinically significant neurological disorder, neurodegenerative disorder or any Axis II disorder that might compromise participation in the study
- Serious risk of suicide on the basis of the investigator's clinical judgement, and those who had a score ≥5 on item 10 of the MADRS scale (suicidal thoughts) or suicide attempt within <6 months
- Receiving formal cognitive or behavioural therapy or systematic psychotherapy
- Pregnant or breastfeeding
- Taking disallowed concomitant medication, or rifampicin or ciprofloxacin

Study design[1]

Following a screening period of 4–10 days, eligible patients were randomised and switched directly from SSRI or SNRI to

- Brintellix (10–20 mg/day), or
- Agomelatine (25–50 mg/day)

for 12 weeks of double-blind treatment.

Investigators gradually decreased SSRI or SNRI dose, to the minimum therapeutic dose, in the week before baseline, then optimised vortioxetine or agomelatine dose for each patient by flexible-dose design for the first 4 weeks.

Patients were assessed at baseline and weeks 1, 2, 3, 4, 8 and 12.

Primary endpoint[1]

- Change from baseline to week 8 in MADRS total score (MMRM) using a non-inferiority test followed by a superiority test

Secondary endpoints[1]

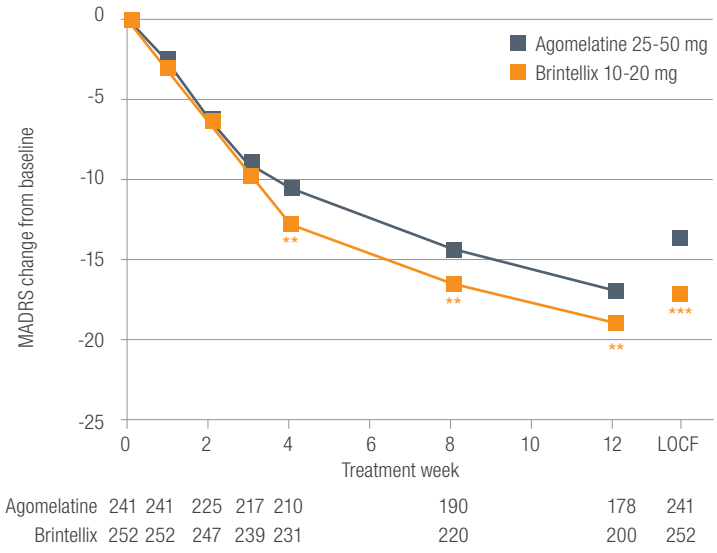
- Response and remission rates
- Anxiety symptoms (Hamilton Anxiety Rating Scale)
- Severity of illness and global improvement (Clinical Global Impression)
- Overall functioning (Sheehan Disability Scale)
- Health-related quality of life (EuroQol 5 Dimensions)
- Productivity (Work Limitations Questionnaire)
- Family functioning (Depression and Family Functioning Scale)

Results[1]

Primary endpoint

- At week 8, mean change from baseline in MADRS total score was -16.5 for Brintellix (n=252) and -14.4 points for agomelatine (n=241) (FAS, MMRM)
- The mean difference for Brintellix to agomelatine was -2.2 (95% CI: -3.5 to -0.8; p=0.0018)
- Non-inferiority was established, as the upper bound of the 95% CI for the comparison was -0.81 MADRS points – ie, less than the non-inferiority margin of +2 MADRS points
- In addition, significantly superior efficacy was established as the upper bound of the 95% confidence limit was also less than 0

Comparison of Brintellix and agomelatine efficacy on depressive symptoms, according to estimated changes in MADRS total scores – the primary outcome measure[1¶]



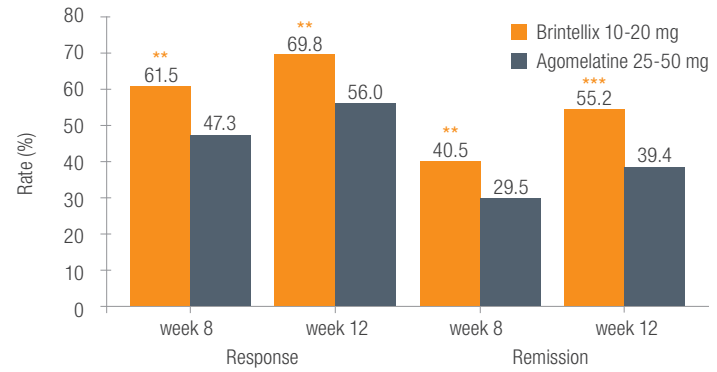
¶Data shown for baseline to week 12 were analysed using the FAS and MMRM, data shown for LOCF at week 12 were analysed using the FAS and ANCOVA, and patient numbers at each visit are shown below the x-axis for each treatment group.

**p<0.01, ***p<0.001 vs. agomelatine.

Secondary endpoints[1]

Brintellix was statistically significantly (p<0.05) superior to agomelatine in terms of response and remission.

Comparison of Brintellix and agomelatine efficacy on response and remission rates, according to MADRS total scores – secondary outcome measures[1‡]



‡Data were analysed by logistic regression using the FAS and LOCF; response was defined as ≥50% improvement from baseline in MADRS total score; and remission was defined as MADRS total score ≤10.**p<0.01, ***p<0.001 vs. agomelatine.

Brintellix showed statistically significant improvements compared with agomelatine according to other secondary endpoints (p<0.05)

- Measures of depressive symptoms, severity of illness and global improvement, overall functioning and health-related quality of life at week 4 onwards (based on MADRS, HAM-A, Clinical Global Impression, Sheehan Disability Scale and EuroQol 5 Dimensions scores)
- Productivity at week 8 (based on the Work Limitations Questionnaire)
- Family functioning at weeks 8 and 12 (based on Depression and Family Functioning Scale)

Safety outcomes[1]

Key safety findings included (p values not reported)

- Fewer patients withdrew from the study because of TEAEs with Brintellix than with agomelatine (5.5% vs. 8.3%)
- Similar incidence of treatment-emergent sleep-related symptoms for the two treatment groups (11.1% vs. 10.7%, based on somnolence, insomnia and sleep disorder data)

TEAEs with incidence ≥5% in either treatment group in the 12-week treatment period[1]

Preferred term	Brintellix 10–20 mg, n (%) (n=253)	Agomelatine 25–50 mg, n (%) (n=242)
Patients with TEAEs	137 (54.2)	127 (52.5)
Nausea	41 (16.2)	22 (9.1)
Headache	26 (10.3)	32 (13.2)
Dizziness	18 (7.1)	28 (11.6)
Somnolence	10 (4.0)	19 (7.9)

Please refer to the Australian Approved Brintellix Product Information for full safety and tolerability data. Brintellix Product Information: Nausea: 22.6% (Brintellix 10 mg); 27.2% (Brintellix 20 mg); 8.1% (Placebo). Headache: 12.7% (Brintellix 10 mg); 12.4% (Brintellix 20 mg); 12.9% (Placebo). Dizziness: 5.2% (Brintellix 10 mg); 6.3% (Brintellix 20 mg); 5.3% (Placebo). Somnolence: 2.9% (Brintellix 10 mg); 3.3% (Brintellix 20 mg); 2.3% (Placebo). Brintellix 10 mg: n= 1042; Brintellix 20 mg, n=812; Placebo: n= 1968.[2]

Study limitations[1]

- Absence of placebo in the comparison makes it difficult to know whether the less effective treatment, agomelatine, was efficacious
- Symptoms of discontinuation from previous therapy may have influenced efficacy of Brintellix and/or agomelatine
- Exclusion of patients with unsatisfactory response to classes of antidepressants other than SSRIs and SNRIs means the results may not be generalisable to other antidepressant classes, apart from tricyclic antidepressants (which have a similar mechanism of action)
- Exclusion of patients with comorbid conditions means that the results may not be generalisable to MDD patients with high comorbidity

Brintellix (vortioxetine) was non-inferior and statistically significantly superior to agomelatine as measured by MADRS (primary endpoint: change from baseline at week 8; p=0.0018) in MDD patients with previous inadequate response to a single course of SSRI or SNRI monotherapy. Brintellix was well tolerated.[1]

Once-daily Brintellix
available in four tablet strengths[3]

§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.[3]

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: ANCOVA: analysis of covariance; CI: confidence interval; DSM-IV-TR: Diagnostic and statistical manual of mental disorders, fourth edition, text revision; FAS: full analysis set; HAM-A: Hamilton Anxiety Rating Scale; LOCF: last observation carried forward; MADRS: Montgomery–Åsberg Depression Rating Scale; MMRM: mixed model for repeated measures; SNRI: serotonin and noradrenaline reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TEAE: treatment-emergent adverse event.

References: 1. Montgomery SA, *et al. Hum Psychopharmacol Clin Exp* 2014; 29(5):470–482. **2.** Bauer M, *et al. World J Biol Psychiatry* 2007; 8(2): 67–104. **3.** Brintellix® Australian Approved Product Information.

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