THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Efficacy and Safety of Adjunctive Brexpiprazole 2 mg in Major Depressive Disorder: A Phase 3, Randomized, Placebo-Controlled Study in Patients With Inadequate Response to Antidepressants

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DOI Number: 10.4088/JCP.14m09688

List of Supplementary Material for the article

1. **eTable 1** Secondary Efficacy Endpoint: Mean Psychiatric Scale Scores at Baseline and Mean Change From Baseline to Week 6 (Efficacy Population)
2. **eFigure 1** LS Mean (SE) Change From Baseline in MADRS Score for Efficacy Population
3. **eAppendix 1** Exclusion Criteria, Concomitant Medication Regulations, and Data Analysis

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Supplementary eTable 1. Secondary Efficacy Endpoints: Mean Psychiatric Scale Scores at Baseline and Mean Change from Baseline to Week 6 (Efficacy Population)

	ADT + placebo (*n*=191)	ADT + brexpiprazole (*n*=187)		
	Change from baseline		Difference in change from baseline	
Scale	LS mean (SE)		LS mean (95% CI)	*P*-value[g]
SDS mean	-0.91 (0.17)	-1.35 (0.17)	-0.45 (-0.86, -0.03)	.0372[†]
SDS work/school	-0.90 (0.22)	-1.09 (0.22)	-0.19 (-0.73, 0.34)	.4771
SDS social life	-1.04 (0.18)	-1.54 (0.19)	-0.50 (-0.96, -0.04)	.0323
SDS family life	-0.73 (0.19)	-1.33 (0.19)	-0.60 (-1.07, -0.13)	.0129[†]
HAM-D17 total	-3.55 (0.47)	-5.89 (0.48)	-2.34 (-3.47, -1.22)	.0001
CGI-S	-0.58 (0.07)	-0.91 (0.07)	-0.34 (-0.52, -0.15)	.0004
IDS-SR total	-5.52 (0.73)	-7.49 (0.74)	-1.96 (-3.87, -0.06)	.0435
CGI-I	–	–	-0.39[a] (-0.60, -0.17)	.0005
HAM-A total	-2.77 (0.42)	-3.94 (0.43)	-1.17 (-2.17, -0.17)	.0219
MADRS responders[b]	14.7[c]	23.5[c]	1.63 (1.09, 2.44)[d]	.0176
CGI-I responders[e]	27.7[c]	44.4[c]	1.61 (1.23, 2.10)[d]	.0003
MADRS remitters[f]	8.4[c]	14.4[c]	1.68 (0.98, 2.86)[d]	.0586

[†]For SDS, *P*-value considered to be statistically significantly superior to placebo within the formal testing strategy. A hierarchical testing procedure was applied to the SDS individual item scores. If the SDS mean score analysis was statistically significant, a Hochberg procedure would be applied to the three individual item scores to control multiplicity and to maintain the overall type I error rate at .05. If the largest *P*-value was <.05, then all three SDS individual item scores were statistically significant. If the largest *P*-value was >.05 and the second largest *P*-value was <.025, then the two corresponding SDS individual item scores were statistically significant. If the second largest *P*-value was >.025, statistical significance was declared for the remaining SDS individual item score if the *P*-value was <.0167.

[a]Value represents the difference between brexpiprazole and placebo CGI-I values.

[b]Defined as patients having ≥50% reduction from baseline in MADRS total score.

[c]Percentage of patients with response or remission.

[d]Ratio (95% CI) of response or remission rates.

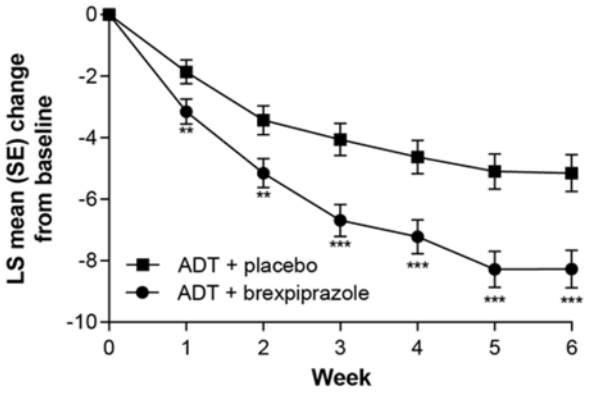
[e]Defined as very much improved or much improved.

[f]Defined as patients with MADRS total score ≤10 and ≥50% reduction in MADRS total score from baseline.

[g]SDS, CGI-S, IDS-SR: mixed-model repeated measures analysis; HAM-D17, HAM-A: analysis of covariance; CGI-I: Cochran-Mantel-Haenszel (CMH) row mean score differ test; response and remission rates: CMH general association test.

Abbreviations: ADT = antidepressant treatment; CGI-I = Clinical Global Impression – Improvement Scale; CGI-S = Clinical Global Impression – Severity of Illness Scale; CI = confidence interval; HAM-A = Hamilton Anxiety Rating Scale; HAM-D17 = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology (Self-Report); LS = least squares; MADRS = Montgomery Åsberg Depression Rating Scale; SDS = Sheehan Disability Scale; SE = standard error.

Supplementary eFigure 1. LS mean (SE) change from baseline in MADRS score for efficacy population.



Baseline mean MADRS scores. ADT + placebo, 27.1, *n*=191; ADT + brexpiprazole, 26.6, *n*=187.

**P*<.05, ***P*<.01, ****P*<.001; mixed-model repeated measures analysis.

Abbreviations: ADT = antidepressant treatment; LS = least squares; MADRS = Montgomery Åsberg Depression Rating Scale; SE = standard error.

eAppendix 1

Efficacy and Safety of Adjunctive Brexpiprazole in Major Depressive Disorder: A Phase 3, Randomized, Placebo-controlled Study in Patients with Inadequate Response to Antidepressants

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METHODS

Exclusion Criteria

Key exclusion criteria were as follows: treatment during the current episode with adjunctive antipsychotics, initiating or changing psychotherapy; electroconvulsive therapy (ECT); hospitalization during the current episode; occurrence of hallucinations or delusions during the current episode; current diagnosis of other psychiatric or serious medical condition; serious risk of suicide; substance abuse or dependence; previous inadequate response to ECT; previous vagus nerve stimulation or deep brain stimulation; and exclusionary laboratory test values or electrocardiogram (ECG) results.

Concomitant Medication Regulations

Treatment with monoamine oxidase inhibitors was not permitted within 14 days prior to the study. Use of benzodiazepines, hypnotics, and oral neuroleptics was not allowed within 7 days prior to the study. Use of long-acting approved neuroleptics was not allowed within 1.5 cycles prior to the study. Short-term use of oral benzodiazepines (maximum dose: lorazepam 6 mg/day or oxazepam 90 mg/day) or non-benzodiazepine sleep aids (maximum 7 days in any treatment phase) was allowed during the study to manage symptoms, if necessary. Anticholinergics (maximum dose: 4 mg/day benzatropine equivalent) or propranolol (maximum dose: 60 mg/day) were permitted for the management of EPS, if necessary. Concomitant medication was to be avoided for at least 12 hours prior to efficacy and safety assessments.

Data Analysis

The primary analysis was conducted by fitting a mixed-model repeated measures (MMRM) analysis with an unstructured variance covariance structure in which change from baseline to week 6 in MADRS total score was the dependent variable based on the observed cases dataset. The Kenward-Roger type of degrees of freedom was used for the primary MMRM analysis. The primary comparison between the antidepressant treatment (ADT) + brexpiprazole and ADT + placebo groups was tested at a significance level of .05 and was estimated as the difference between LS means utilizing the computing software procedure PROC MIXED.

The key secondary efficacy endpoint was the change from baseline to week 6 in Sheehan Disability Scale (SDS) mean score, which was analyzed by fitting the same MMRM model as that used in the primary analysis. A hierarchical testing procedure was used in order to maintain the overall experiment-wise type I error rate at .05. Thus, the comparison between

the ADT + brexpiprazole and ADT + placebo groups was only to be tested at an alpha level of .05 (two-sided) if the primary efficacy analysis was statistically significant. A hierarchical testing procedure was also applied to the SDS individual item scores (Table S1).

Other secondary efficacy endpoints were analyzed at a nominal .05 level (two-sided). Change from baseline to weeks 1, 2, 3, 4, and 5 in MADRS total score, and change from baseline to week 6 in Clinical Global Impression ─ Severity of illness (CGI-S) score and Inventory of Depressive Symptomatology (Self-Report) (IDS-SR) total score, were analyzed using the same MMRM model as the primary efficacy analysis. Change from baseline to week 6 in Hamilton Depression Rating Scale (HAM-D17) and Hamilton Anxiety Rating Scale (HAM-A) total scores was analyzed using analysis of covariance (ANCOVA) with baseline value as covariate, and treatment and study center as main effects. Clinical Global Impression – Improvement (CGI-I) score (change from baseline) at week 6 was analyzed by the Cochran-Mantel-Haenszel (CMH) row mean score differ test controlling for study center.

MADRS response was defined as ≥50% reduction from baseline in MADRS total score. MADRS remission was defined as a MADRS total score of ≤10 and ≥50% reduction from baseline in MADRS total score. A CGI-I response was defined as a score of 1 (very much improved) or 2 (much improved). Response and remission rates were analyzed by the CMH general association test controlling for study center.

Treatment-emergent adverse events (TEAEs) were defined as those that started on or after the first day of the randomized treatment phase, or those that continued from the prospective treatment phase and worsened, became serious or drug-related, or resulted in death or discontinuation, interruption, or dose reduction of study drug during the randomized treatment phase. MMRM analysis was applied to changes from baseline to the last visit in Simpson Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Massachusetts General Hospital Sexual Functioning Questionnaire scores.