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Supplementary Material

Article Title: Adjunctive Brexpiprazole 1 and 3 mg for Patients With Major Depressive Disorder Following Inadequate Response to Antidepressants: A Phase 3, Randomized, Double-Blind Study

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Supplementary eTable 1. Secondary Efficacy Endpoints: Mean Change in Psychiatry Scale Scores From Baseline at Week 6 (Efficacy Population)

	ADT + Placebo (n=218)	ADT + Brexpiprazole 1 mg (n=225)			ADT + Brexpiprazole 3 mg (n=226)		
	Change From Baseline	Change From Baseline	Difference in Change From Baseline		Change From Baseline	Difference in Change From Baseline	
Scale	LS Mean (SE)	LS Mean (SE)	LS Mean (95% CI)	*P*-Value	LS Mean (SE)	LS Mean (95% CI)	*P*-Value
SDS mean	-0.84 (0.13)	-1.33 (0.14)	-0.49 (-0.87,-0.12)	.0091	-1.21 (0.13)	-0.37 (-0.73, -0.00)	.0474
SDS work / school	-0.73 (0.17)	-1.16 (0.17)	-0.43 (-0.91, 0.04)	.0741	-0.91 (0.18)	-0.18 (-0.66, 0.31)	.4774
SDS social life	-0.91 (0.15)	-1.39 (0.15)	-0.48 (-0.89, -0.07)	.0214	-1.31 (0.15)	-0.40 (-0.80, 0.01)	.0540
SDS family life	-0.80 (0.15)	-1.35 (0.15)	-0.55 (-0.97, -0.14)	.0093	-1.28 (0.16)	-0.48 (-0.90, -0.06)	.0256
CGI-S	-0.75 (0.06)	-0.86 (0.06)	-0.11 (-0.28, 0.06)	.2015	-0.90 (0.06)	-0.15 (-0.32, 0.02)	.0852
IDS-SR	-5.42 (0.67)	-7.02 (0.66)	-1.60 (-3.40, 0.20)	.0812	-6.94 (0.66)	-1.52 (-3.33, 0.29)	.1001
HAM-D17	-4.80 (0.37)	-5.47 (0.36)	-0.67 (-1.63, 0.29)	.1732	-6.14 (0.36)	-1.34 (-2.31, -0.37)	.0066
HAM-A	-3.33 (0.32)	-3.43 (0.31)	-0.10 (-0.93, 0.73)	.8164	-3.89 (0.31)	-0.55 (-1.39, 0.28)	.1939
MADRS responders[a]	15.1[b]	23.1[b]	1.53[c] (1.06, 2.20)	.0248	22.1[b]	1.51 (1.03, 2.21)[c]	.0326

MADRS remitters[d]	11.9[b]	15.1[b]	1.30[c] (0.81, 2.07)	.2843	13.7[b]	1.19 (0.74, 1.92)[c]	.4640
CGI-I	–	–	-0.16[e] (-0.33, 0.02)	.0755	–	-0.20 (-0.39, 0.00)	.0527

[a]Defined as patients having >50% reduction from baseline in MADRS total score

[b]Percentage of patients with MADRS response or remission

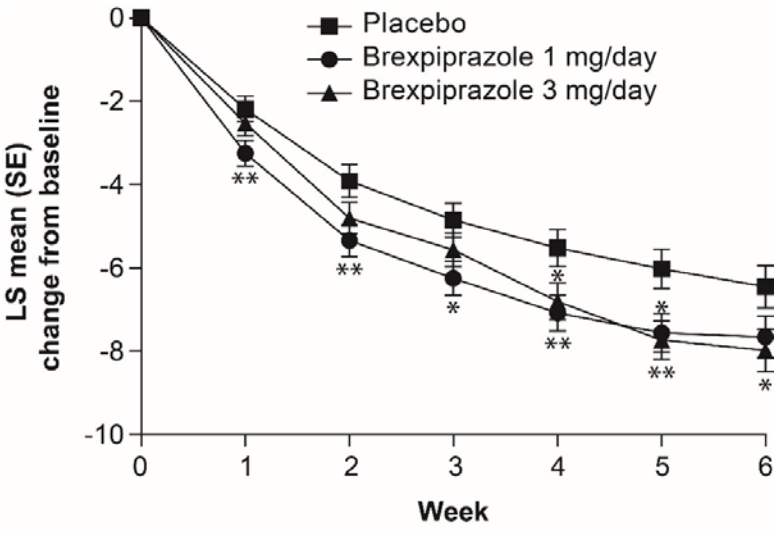
[c]Ratio of response or remission rate

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

[e]Value represents the difference between brexpiprazole and ADT monotherapy CGI-I values

ADT = antidepressant therapy, 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



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

Abbreviations: SE = standard error, MADRS = Montgomery–Åsberg Depression Rating Scale, LS = least squares.

eAppendix 1

A Phase 3, Randomized, Double-Blind Study of Adjunctive Brexpiprazole for Patients with Major Depressive Disorder Following Inadequate Response to Antidepressants

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METHODS

Exclusion Criteria

Exclusion criteria included treatment during the current depressive episode with adjunctive antipsychotic medication for >3 weeks; electroconvulsive therapy; initiating psychotherapy; hospitalization; hallucinations or delusions during the current episode; previous inadequate response to electroconvulsive therapy; previous vagus nerve stimulation or deep brain stimulation; current diagnosis of other psychiatric or medical condition; serious risk of suicide; substance abuse or alcoholism; abnormal laboratory test or electrocardiogram results.

Concomitant Medication Regulations

Treatment with monoamine oxidase inhibitors was not permitted within 14 days prior to the study. Treatment with benzodiazepines, hypnotics or oral neuroleptics was not permitted within 7 days prior to the study. Treatment with long-acting approved neuroleptics was not permitted within 1.5 cycles prior to the study. Short-term use of benzodiazepines (lorazepam maximum 6 mg/day or oxazepam maximum 90 mg/day) or non-benzodiazepine sleep aids (maximum 7 days in any treatment phase) was allowed to manage symptoms, if necessary. Anticholinergics (maximum 4 mg/day benzatropine equivalent) or propranolol (maximum 60 mg/day) were allowed to manage extrapyramidal symptoms, if necessary.

Data analysis

The primary efficacy endpoint was change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score from baseline to Week 6. The primary analysis

was conducted by fitting a mixed-model repeated measures (MMRM) analysis with an unstructured variance covariance structure using change from baseline to Week 6 in MADRS total score as the dependent variable based on the observed cases dataset. The primary analysis used the Kenward-Rogers type of degrees of freedom. The primary comparison between adjunctive brexpiprazole 1 mg, 3 mg and placebo groups at Week 6 was estimated as the difference between least squares means using the computing software procedure PROC MIXED. Comparisons between brexpiprazole 1 mg versus placebo and brexpiprazole 3 mg versus placebo were tested using Hochberg's procedure to adjust for multiplicity and maintain type I error at .05 (two-tailed). If the larger of the two *P*-values was ≤.05 in favor of brexpiprazole, both doses of brexpiprazole were significantly better than placebo. If the larger of the two *P*-values was >.05, then the smaller *P*-value was compared with .025. If the smaller of the two *P*-values was ≤.025 in favor of brexpiprazole, then this dose was significantly better than placebo.

The key secondary efficacy endpoint was change in Sheehan Disability Scale mean score from baseline to Week 6 analyzed by using the same MMRM model as in the primary efficacy analysis. To control for overall experiment-wise type I error a hierarchical testing procedure was used, so that if the primary efficacy analysis was statistically significant at an alpha level of .025 (two-sided) for either the brexpiprazole 1 mg versus placebo or the brexpiprazole 3 mg versus placebo comparison, then the corresponding comparison of the key secondary efficacy analysis was also tested at an alpha level of .025 (two-sided). A hierarchical testing procedure was also used for the SDS individual items scores to control for multiplicity and maintain overall type I error at .05. If the SDS mean score analysis was statistically significant then the individual item scores were tested in the following order: family life, social life and work/school.

The other secondary endpoints were analyzed at a nominal .05 level. Change in Clinical Global Impression – Severity of Illness Scale score and IDS-SR = Inventory of Depressive Symptomatology (Self-Report) total score from baseline to Week 6 was analyzed by fitting the same MMRM model used for the primary efficacy analysis. Change in 17-item Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale total scores from baseline to Week 6 were analyzed by ANCOVA with baseline value as covariate and treatment and trial site as main effects. Change in Clinical Global Impression – Improvement Scale score from baseline to Week 6 was analyzed by the Cochrane-Mantel-Haenszel (CMH) row mean score differ test controlling for trial site. The proportion of MADRS responders (>50% reduction from baseline in MADRS total score) during the 6-week double-blind phase; and proportion of patients with MADRS remission (defined as MADRS total score ≤10 and ≥50% reduction in MADRS total score from baseline) were analyzed by the CMH general association test controlling for trial site.

Treatment-emergent adverse events were defined as adverse events which started on or after the beginning of the double-blind phase, or those which worsened, became serious or drug-related, or resulted in discontinuation, dose reduction of study drug or death during the double-blind phase. Least squares mean change in body weight at Week 6 was derived from an ANCOVA model with treatment as factors and baseline value as covariate, on observed case data.