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# 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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### ABSTRACT

**Objective:** To assess the efficacy, tolerability, and safety of brexpiprazole as adjunctive therapy to antidepressant treatments (ADTs) in adults with major depressive disorder (as defined by *DSM-IV-TR* criteria) and inadequate response to ADTs.

**Method:** Patients with historical inadequate response to 1–3 ADTs were enrolled. All patients entered a prospective 8-week phase on physician-determined, open-label ADT. Those with inadequate response were randomized to ADT + brexpiprazole 2 mg/d or ADT + placebo for 6 weeks. The study was conducted between July 2011 and May 2013. The primary efficacy end point was change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. The key secondary end point was change from baseline to week 6 in Sheehan Disability Scale (SDS) mean score. The efficacy population comprised all patients who had  $\geq 1$  dose of study drug in the double-blind phase and both baseline and  $\geq 1$  postrandomization MADRS scores. The efficacy population per final protocol included patients from the efficacy population who met amended randomization criteria of inadequate response throughout prospective treatment.

**Results:** Brexpiprazole ( $n = 175$ ) reduced mean MADRS total score versus placebo ( $n = 178$ ) at week 6 in the efficacy population per final protocol ( $-8.36$  vs  $-5.15$ ,  $P = .0002$ ). Brexpiprazole improved SDS mean score versus placebo ( $-1.35$  vs  $-0.89$ ,  $P = .0349$ ). The most common treatment-related adverse events were weight gain (brexpiprazole, 8.0%; placebo, 3.1%) and akathisia (7.4% vs 1.0%).

**Conclusions:** Adjunctive brexpiprazole therapy demonstrated efficacy and was well tolerated in patients with major depressive disorder and inadequate response to ADTs.

**Trial Registration:** ClinicalTrials.gov identifier: NCT01360645

*J Clin Psychiatry* 2015;76(9):1224–1231  
dx.doi.org/10.4088/JCP.14m09688

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Effective treatment of patients with major depressive disorder (MDD) not responding adequately to first-line antidepressant treatment (ADT) remains an important unmet need.<sup>1,2</sup> For inadequate response to an optimized trial of first-line ADT, current guidelines recommend switching ADT, adding a second ADT or adding adjunctive therapy with a non-ADT.<sup>1,3</sup> Adjunctive second-generation antipsychotic therapies such as olanzapine,<sup>4</sup> quetiapine,<sup>5,6</sup> and aripiprazole<sup>7</sup> are associated with significant improvements in treatment response and remission; however, their side effect profile may limit use in clinical practice.<sup>8,9</sup> Prominent side effects vary from drug to drug,<sup>10,11</sup> ie, weight gain with olanzapine,<sup>12</sup> sedation with quetiapine,<sup>5</sup> and akathisia with aripiprazole.<sup>7</sup> Thus, there is ongoing interest in identifying adjunctive strategies that offer the rapid efficacy of antipsychotics while reducing frequency and burden of side effects.

Serotonergic (5-HT), dopaminergic (D), and noradrenergic systems appear to play important roles in ADT mechanisms of action.<sup>13,14</sup> Brexpiprazole is a rationally designed serotonin-dopamine activity modulator, with partial agonism at serotonin 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors at similar potency, and potent antagonism at 5-HT<sub>2A</sub> and norepinephrine  $\alpha_{1B}$  and  $\alpha_{2C}$  receptors.<sup>15</sup> The therapeutic potential of brexpiprazole as an adjunctive treatment for depression has been demonstrated in animal models.<sup>16</sup> Brexpiprazole differs from aripiprazole in terms of its lower intrinsic activity at the D<sub>2</sub> receptor.<sup>15</sup> Brexpiprazole binds to 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, with around 10 times higher affinity than aripiprazole.<sup>15</sup> In addition, brexpiprazole is equipotent at 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, and D<sub>2</sub> receptors, while the relative potencies of aripiprazole at these receptors differ.<sup>15</sup> Brexpiprazole's partial agonism with low intrinsic D<sub>2</sub> receptor activity suggests a potential stabilizing effect on dopaminergic function and low potential to induce side effects (extrapyramidal symptoms, hyperprolactinemia, tardive dyskinesia) associated with blockade of dopamine transmission.<sup>17</sup> Preclinical models have confirmed the low potential of brexpiprazole to induce antipsychotic-related side effects.<sup>15,18</sup> In particular, we predicted that brexpiprazole's 5-HT<sub>2A</sub>/D<sub>2</sub> receptor binding profile, along with the low intrinsic D<sub>2</sub> activity, may predict low rates of activation-like side effects (akathisia, insomnia, or restlessness).<sup>15</sup> Furthermore, brexpiprazole has a moderate affinity, relative to D<sub>2</sub>/5-HT<sub>1A</sub> receptor affinity, for histamine H<sub>1</sub>,<sup>15</sup> which may result in low levels of sedation.

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A phase 2, placebo-controlled study (reference 19 and data on file, Otsuka, Princeton, New Jersey) of patients with MDD who had shown inadequate response to ADT suggested that adjunctive brexpiprazole  $1.5 \pm 0.5$  mg/d was efficacious and well tolerated. Efficacy of adjunctive brexpiprazole (3 mg/d) was demonstrated in a phase 3 study (NCT01360632; the Polaris trial) in patients with MDD and inadequate ADT response.<sup>20</sup> The present phase 3 study (331-10-228; NCT01360645, the Pyxis trial) objectives were to evaluate efficacy, safety, and tolerability of brexpiprazole at a fixed dose of 2 mg/d as adjunctive therapy in patients with MDD and inadequate response to ADTs.

## METHOD

### Patients

Patients were recruited at 59 study centers in the United States (74.9% of patients), Poland (9.7%), France (8.5%), Canada (4.8%), and Slovakia (2.1%). The study included outpatients aged 18–65 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria for a single or recurrent nonpsychotic episode of MDD<sup>21</sup> of at least 8 weeks' duration. During the current episode, patients must have reported an inadequate response, defined as <50% reduction in symptoms via patient self-reports on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ),<sup>22</sup> to an adequate trial of between 1 and 3 ADTs, including their most recent drug treatment. Eligible patients had a 17-item Hamilton Depression Rating Scale (HDRS-17)<sup>23,24</sup> total score  $\geq 18$  both at screening and on the first day of prospective treatment. Key exclusion criteria and concomitant medication regulations are provided (see eAppendix 1 at Psychiatrist.com).

The study was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline. The protocol was approved by independent ethics committees, and all patients provided informed consent to participate.

### Study Design

This randomized, double-blind, placebo-controlled, fixed-dose study was conducted between July 2011 and May 2013 and comprised a screening phase (7–28 days), an 8-week single-blind prospective treatment phase, and a 6-week double-blind randomized treatment phase (Figure 1A).

During the 8-week prospective treatment phase, all patients received single-blind placebo adjunctive to standard ADT (Table 1). Patients who were switched from a previous ADT had a washout period of at least 24 hours before initiating treatment. Antidepressant treatment was titrated from the starting dose to the maximum-tolerated dose to optimize the potential for response.

During prospective treatment, patients' outcomes were assessed to determine eligibility to enter the randomized treatment phase. Patients were eligible for randomization if

- Availability of effective antidepressant treatments with better tolerability profiles remains a significant unmet need for patients with major depressive disorder (MDD); clinical use of adjunctive second-generation antipsychotics can be limited by their tolerability profiles.
- Adjunctive brexpiprazole 2 mg improved depressive symptoms compared with antidepressant monotherapy in patients with MDD and inadequate response to antidepressant treatment.
- Brexpiprazole was well tolerated in this population.

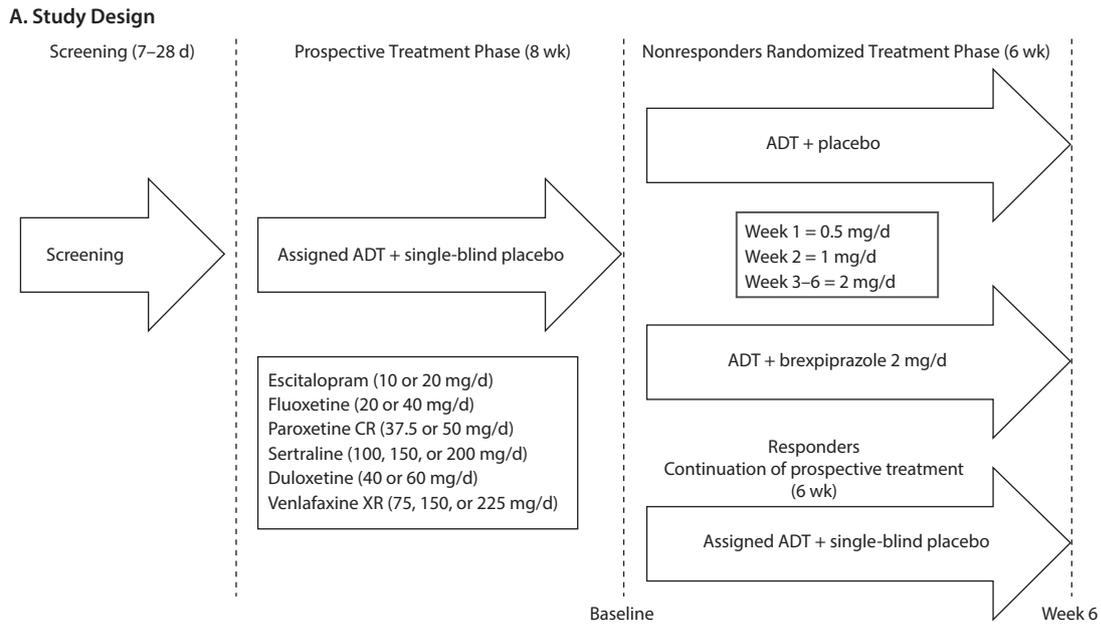
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they had inadequate response to the prospective ADT, had a negative drug screen, and were considered suitable for adjunctive therapy by the investigator. Inadequate response was initially defined as <50% reduction from the start of ADT in HDRS-17 total score, HDRS-17 total score  $\geq 14$ , and Clinical Global Impressions-Improvement scale (CGI-I)<sup>25</sup> score  $\geq 3$  at the end of prospective treatment. While this study was ongoing, additional analyses were performed on data from a completed phase 2 study of similar design (reference 19 and data on file, Otsuka, Princeton, New Jersey). It was found that a number of patients in that study had seemingly adequate improvement in Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-I scores at various times during the prospective treatment period, but subsequent worse scores at time of randomization. These patients did not show a consistent lack of response and would have been considered adequate responders if evaluated at another time point during the prospective phase. A number of these patients showed significant improvement again during the randomized phase, even if they were continuing on ADT alone. In order to exclude patients with seemingly variable response to ADT, this study's protocol was amended to specify that patients had to meet more refined inadequate response criteria throughout prospective treatment (HDRS-17 score  $\geq 14$ ; <50% reduction from baseline in HDRS-17, as well as <50% reduction in MADRS total score between start of prospective treatment and each scheduled visit, and CGI-I score  $\geq 3$  at each scheduled visit) to be eligible for randomization and also to blind the investigator to the revised criteria. Eligible patients were randomized to receive double-blind ADT + brexpiprazole or ADT + placebo (1:1) for 6 weeks. The ADT dose in the randomized phase was the same as the last dose from the prospective phase. Randomization was conducted via an interactive voice or web response system using a fixed-block, computer-generated randomization schedule with a block size of 4 and stratified by study center.

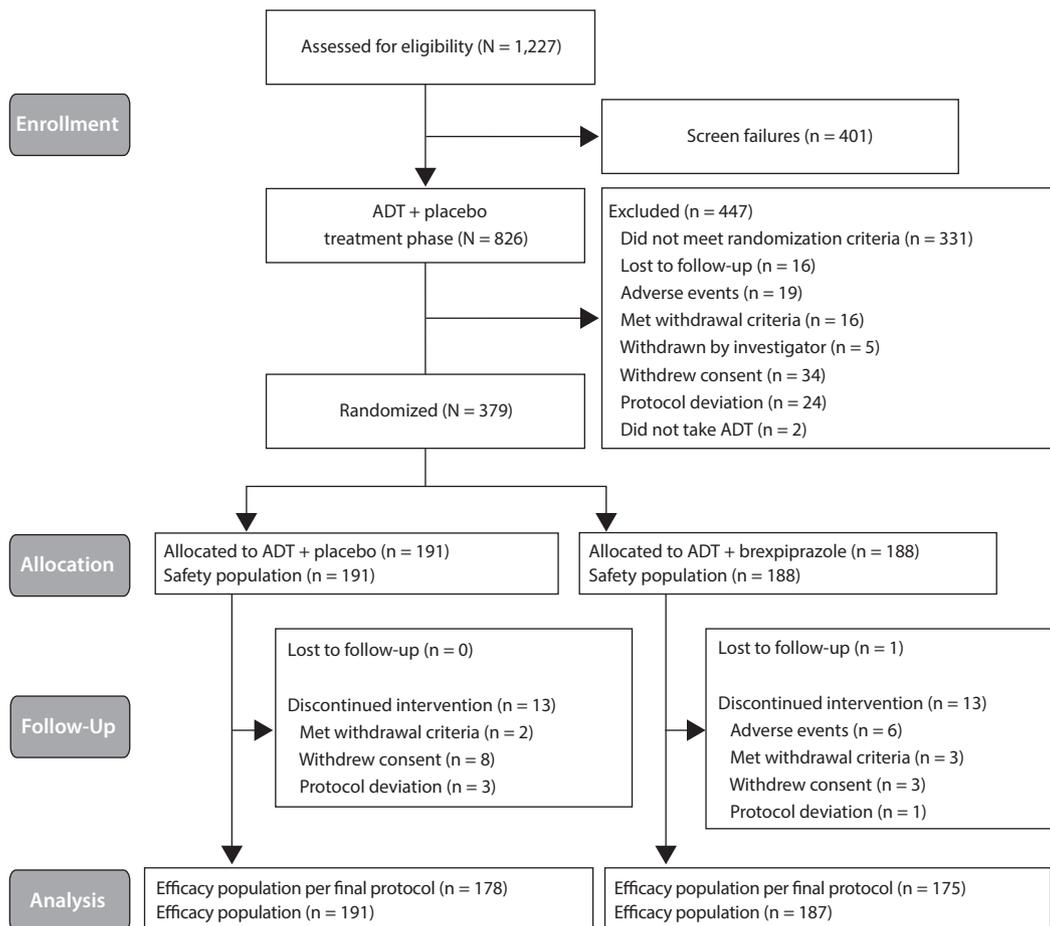
Patients who responded to ADT during prospective treatment continued to receive single-blind placebo plus the same ADT for an additional 6 weeks. Patients who completed the additional 6 weeks of ADT and eligible patients who completed the randomized treatment phase were invited to participate in an open-label rollover study (331-10-238; ClinicalTrials.gov identifier: NCT01360866).

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**Figure 1. Study Design and Patient Disposition<sup>a</sup>**



**B. Patient Disposition**



<sup>a</sup>Doses of ADT shown are target doses. Patients visited the study center at weekly intervals for the first 4 weeks and then every 2 weeks during the prospective treatment phase, and at weekly intervals (weeks 1 to 6) during the randomized treatment phase. Abbreviations: ADT=antidepressant treatment, CR=controlled release, XR=extended release.

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## Outcome Measures

Efficacy assessments were made at baseline (end of prospective treatment) and during randomized treatment. The MADRS<sup>26</sup> was administered at each weekly visit using the Structured Interview Guide.<sup>27</sup> Patients completed the Sheehan Disability Scale (SDS)<sup>28,29</sup> at baseline and at weeks 3 and 6. The HDRS-17 and Hamilton Anxiety Rating Scale (HARS)<sup>25,30,31</sup> were administered using Structured Interview Guides<sup>32,33</sup> at baseline and at week 6. At each visit, the investigator rated patients with the Clinical Global Impressions-Severity of Illness scale (CGI-S)<sup>25</sup> and CGI-I from start of prospective phase or from baseline. Patients completed the Inventory of Depressive Symptomatology–Self-Report (IDS-SR)<sup>34</sup> at each visit.

Safety and tolerability were evaluated by recording treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Extrapyramidal symptom scales were administered at each visit, including the Simpson-Angus Scale (SAS),<sup>35</sup> Abnormal Involuntary Movement Scale (AIMS),<sup>25</sup> and Barnes Akathisia Rating Scale (BARS).<sup>36</sup> Clinical laboratory tests and a 12-lead electrocardiogram (ECG) were conducted every 2 weeks, and vital signs were measured at each visit. Suicidality was monitored at each visit using the Columbia-Suicide Severity Rating Scale.<sup>37,38</sup> Patients completed the Massachusetts General Hospital Sexual Functioning Questionnaire<sup>39</sup> at baseline and at week 6. Least squares (LS) mean change in body weight at week 6 was derived from an analysis of covariance model, with treatment as factors and baseline value as covariate, on observed case data.

## Data Analysis

Sample size calculations were based on a predicted between-group difference of 3.0 points (SD=8.5) in mean MADRS total score change from baseline to week 6.<sup>19</sup> A sample size of 340 evaluable patients (170 in each treatment group) was projected to yield at least 90% power to detect treatment effects at a 2-tailed significance level of .05. It was planned to randomize 370 patients (185 in each treatment group) to allow for 5%–10% nonevaluable patients.

The safety population included all patients who received at least 1 dose of brexpiprazole or placebo during the randomized treatment phase. The efficacy population comprised all patients in the safety population who had MADRS scores at baseline and on at least 1 occasion after randomization. The efficacy population per final protocol included all patients from the efficacy population who met the amended randomization criteria for inadequate response. The statistical analysis plan prespecified the analyses of the efficacy population per final protocol as well as the efficacy population. Data reported here focus on the efficacy population per final protocol, since inadequate response was more reliably assessed and this population is more homogenous. Detailed outcomes for the efficacy population are provided in Supplementary eTable 1.

Baseline was defined as the last available measurement prior to starting the randomized treatment phase. The

primary efficacy end point was change from baseline to week 6 in MADRS total score. The primary analysis was conducted by fitting a mixed model repeated-measures analysis with an unstructured variance covariance structure. The model included fixed class effect terms for treatment, study center, visit week, and an interaction term of treatment by visit week. The model also included the interaction term of baseline MADRS total scores by visit week as covariates.

The key secondary efficacy end point was change from baseline to week 6 in SDS mean score. A hierarchical testing procedure was used in order to maintain overall experiment-wise type I error rate at .05. Other secondary efficacy end points were analyzed at a nominal .05 level (2-sided). MADRS response was defined as  $\geq 50\%$  reduction from baseline in MADRS total score. CGI-I response was defined as a score of 1 (very much improved) or 2 (much improved). MADRS remission was defined as a MADRS total score of  $\leq 10$  with  $\geq 50\%$  reduction from baseline. Further details are given in eAppendix 1.

## RESULTS

### Patients

Three hundred seventy-nine patients were randomized to brexpiprazole (n=188) or placebo (n=191) (Figure 1B). The randomized treatment phase was completed by 174/188 (92.6%) brexpiprazole and 178/191 (93.2%) placebo patients. The efficacy population included 187 and 191 patients in the brexpiprazole and placebo groups, respectively, while the efficacy population per final protocol included 175 and 178 patients, respectively.

Demographic and baseline psychiatric characteristics and baseline MADRS total and SDS mean scores were similar between treatment groups (Table 1). Investigator-assigned ADTs were relatively well balanced between the 2 groups. The mean baseline CGI-I score was 3.5 in both groups, indicating that the study population was moderately ill and showed minimal improvement despite 8 weeks of prospective ADT. During the current episode, 81.7%, 16.5%, and 1.9% of randomized patients had 1, 2, and 3 prior ADT failures, respectively.

### Efficacy Assessments

**MADRS score (primary end point).** Mean reduction from baseline to week 6 in MADRS total score was greater for brexpiprazole compared with placebo (LS mean =  $-8.36$  vs  $-5.15$ ; LS mean difference =  $-3.21$  [95% CI,  $-4.87$  to  $-1.54$ ],  $P = .0002$ ; efficacy population per final protocol) with difference between treatment groups apparent from the first week onward (Figure 2).

Similar results were seen for brexpiprazole versus placebo in the efficacy population (LS mean =  $-8.27$  vs  $-5.15$ ; LS mean difference =  $-3.12$  [95% CI,  $-4.70$  to  $-1.54$ ],  $P = .0001$ ) (Supplementary eFigure 1).

**Secondary end points.** In the efficacy population per final protocol, brexpiprazole produced a greater reduction from baseline to week 6 than placebo in mean SDS score

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**Table 1. Demographic and Baseline Clinical Characteristics and Assigned Antidepressant Treatment (safety population)**

Variable	ADT+ Placebo (n=191)	ADT+ Brexpiprazole (n=188)
<b>Demographic characteristic</b>		
Age, mean (SD), y	45.2 (11.3)	44.1 (11.6)
BMI (kg/m <sup>2</sup> ), mean (SD)	29.6 (7.1)	29.9 (6.8)
Female sex, n (%)	137 (71.7)	130 (69.1)
White, n (%)	166 (86.9)	163 (86.7)
<b>Clinical characteristic<sup>a</sup></b>		
Duration of current episode, mean (SD), mo	13.7 (17.1)	13.5 (14.2)
Recurrent episodes, n (%)	171 (89.5)	167 (88.8)
No. of lifetime episodes, mean (SD)	3.8 (2.9)	3.8 (3.2)
MADRS total score, mean (SD)	27.1 (5.6)	26.6 (5.8)
SDS score, mean (SD)	6.3 (2.1)	6.0 (2.0)
HDRS-17 total score, mean (SD)	21.6 (4.2)	21.2 (4.0)
CGI-S score, mean (SD)	4.2 (0.6)	4.1 (0.6)
IDS-SR total score, mean (SD)	37.1 (11.9)	36.6 (10.5)
CGI-I score, mean (SD)	3.5 (0.6)	3.5 (0.6)
HARS total score, mean (SD)	17.7 (5.9)	17.5 (5.7)
<b>Assigned antidepressant treatment<sup>b</sup></b>		
Escitalopram, n (%)	39 (20.4)	41 (21.8)
Fluoxetine, n (%)	29 (15.2)	23 (12.2)
Paroxetine CR, n (%)	21 (11.0)	26 (13.8)
Sertraline, n (%)	26 (13.6)	28 (14.9)
Duloxetine, n (%)	41 (21.5)	40 (21.3)
Venlafaxine XR, n (%)	35 (18.3)	30 (16.0)

<sup>a</sup>Measured at baseline, ie, the end of the 8-week prospective treatment phase.

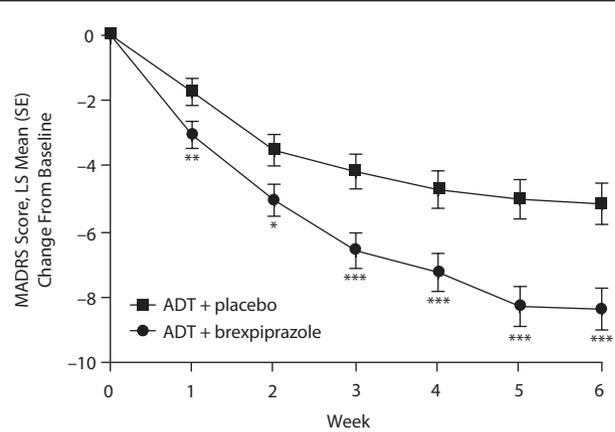
<sup>b</sup>No more than 2 of every 6 patients at each center were to be assigned to the same ADT without approval by the medical monitor. ADTs (target doses) were escitalopram (target dose: 10–20 mg/d), fluoxetine (20–40 mg/d), paroxetine CR (37.5–50 mg/d), sertraline (100–200 mg/d), duloxetine (40–60 mg/d), and venlafaxine XR (75–225 mg/d).

Abbreviations: ADT=antidepressant treatment, BMI=body mass index, CGI-I=Clinical Global Impression-Improvement scale, CGI-S=Clinical Global Impression-Severity of Illness scale, CR=controlled release, HARS=Hamilton Anxiety Rating Scale, HDRS-17=17-item Hamilton Depression Rating Scale, IDS-SR=Inventory of Depressive Symptomatology–Self-Report, MADRS=Montgomery-Asberg Depression Rating Scale, SD=standard deviation, SDS=Sheehan Disability Scale, XR=extended release.

( $P=.0349$ ; Table 2). Brexpiprazole produced numerical improvements on work/school, social life, and family life subscales. Greater improvements from baseline to week 6 in the brexpiprazole group compared with placebo were also seen in physician-rated HDRS-17 and CGI-S ( $P<.001$ ; Table 2). Greater improvement in the brexpiprazole group compared with placebo was seen in CGI-I score at week 6 ( $P=.0003$ ) and change from baseline to week 6 in HARS total score ( $P=.0376$ ; Table 2). There was a higher proportion of responders at week 6, whether defined by MADRS score ( $P=.0429$ ) or CGI-I ( $P=.0002$ ), in the brexpiprazole group compared with placebo (Table 2). Secondary end point outcomes for the efficacy population were similar to those for the efficacy population per final protocol (Supplementary eTable 1).

**Safety and tolerability assessments.** The most frequent TEAEs ( $\geq 5\%$ ) in patients receiving brexpiprazole were weight gain (8.0%) and akathisia (7.4%) (Table 3), which were generally considered by investigators to be mild to moderate. Activating side effects such as restlessness, insomnia, and anxiety were reported by only a few patients (restlessness,

**Figure 2. LS Mean (SE) Change From Baseline in MADRS Score for Efficacy Population per Final Protocol<sup>a,b</sup>**



<sup>a</sup>Baseline mean MADRS scores were 27.3 for ADT + placebo (n=178) and 26.9 for ADT + brexpiprazole (n=175).

<sup>b</sup>P values are based on mixed model repeated-measures analysis.

\* $P<.05$ .

\*\* $P<.01$ .

\*\*\* $P<.001$ .

Abbreviations: ADT=antidepressant treatment, LS=least squares, MADRS=Montgomery-Asberg Depression Rating Scale, SE=standard error.

6/188 [3.2%] vs 0%; insomnia, 4/188 [2.1%] vs 4/191 [2.1%]; anxiety, 7/188 [3.7%] vs 3/191 [1.6%], for brexpiprazole vs placebo, respectively). Somnolence, fatigue, and sedation were also uncommon (somnolence, 8/188 [4.3%] vs 1/191 [0.5%]; fatigue, 3/188 [1.6%] vs 3/191 [1.6%]; and sedation, 2/188 [1.1%] vs 0%). No suicide, attempted suicide, or deaths were reported during the study.

Mean body weight change at week 6 (observed cases) was 1.64 kg for brexpiprazole vs 0.36 kg for placebo (LS mean difference=1.28 kg,  $P<.0001$ ). An increase in body weight of  $\geq 7\%$  from baseline at any visit was seen in 9/187 (4.8%) brexpiprazole patients versus 5/190 (2.6%) placebo patients.

Mean prolactin concentrations in the brexpiprazole group increased from baseline to last visit by 8.3 ng/mL in female patients and 2.2 ng/mL in male patients (baseline=10.0 and 7.5 ng/mL, respectively); smaller mean changes were seen in the placebo group (female=+0.3 ng/mL, male=+0.3 ng/mL; baseline=9.9 and 7.1 ng/mL, respectively). There were no reports of amenorrhea or gynecomastia, and only 2 patients receiving brexpiprazole (compared with 1 patient in the placebo group) reported decreased libido. One hyperprolactinemia TEAE was reported for a female patient in the brexpiprazole group. An increase in prolactin concentration  $> 3$  times the upper limit of normal range was recorded at week 2 for 1 male patient receiving brexpiprazole; the value returned to baseline level by the last visit.

Mean changes from baseline to last visit (fasting values) for brexpiprazole versus placebo groups were  $-0.83$  versus  $-3.38$  mg/dL for triglycerides (baseline=135.22 vs 135.53 mg/dL),  $-0.40$  vs  $-0.30$  mg/dL for glucose (baseline=93.62 vs 94.22 mg/dL),  $+1.21$  vs  $+0.82$  mg/dL for high-density lipoprotein cholesterol (baseline=61.09 vs 61.08 mg/dL),

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**Table 2. Secondary Efficacy End Points: Mean Change From Baseline in Psychiatric Scale Scores to Week 6 (efficacy population per final protocol)**

Scale	Change From Baseline, LS Mean (SE)		Difference in Change From Baseline	
	ADT+ Placebo (n = 178)	ADT+ Brexpiprazole (n = 175)	LS Mean (95% CI)	P Value <sup>a</sup>
	SDS, mean	-0.89 (0.17)	-1.35 (0.17)	-0.46 (-0.88 to -0.03)
SDS work/school	-0.96 (0.23)	-1.11 (0.23)	-0.15 (-0.70 to 0.41)	.6080
SDS social life	-1.02 (0.19)	-1.57 (0.19)	-0.55 (-1.01 to -0.08)	.0224
SDS family life	-0.70 (0.19)	-1.31 (0.20)	-0.62 (-1.09 to -0.14)	.0113
HDRS-17 total	-3.59 (0.49)	-5.89 (0.51)	-2.29 (-3.47 to -1.12)	.0002
CGI-S	-0.57 (0.07)	-0.91 (0.07)	-0.34 (-0.53 to -0.15)	.0006
IDS-SR total	-6.05 (0.75)	-7.59 (0.77)	-1.54 (-3.52 to 0.44)	.1270
CGI-I	...	...	-0.42 <sup>b</sup> (-0.65 to -0.19)	.0003
HARS total	-2.70 (0.43)	-3.79 (0.45)	-1.09 (-2.13 to -0.06)	.0376
MADRS responders <sup>c</sup>	15.7 <sup>d</sup>	23.4 <sup>d</sup>	1.54 (1.01 to 2.35) <sup>e</sup>	.0429
CGI-I responders <sup>f</sup>	26.4 <sup>d</sup>	43.4 <sup>d</sup>	1.69 (1.27 to 2.27) <sup>e</sup>	.0002
MADRS remitters <sup>g</sup>	9.0 <sup>d</sup>	14.9 <sup>d</sup>	1.67 (0.97 to 2.90) <sup>e</sup>	.0671

<sup>a</sup>SDS, CGI-S, IDS-SR: mixed-model repeated measures analysis; HDRS-17, HARS: analysis of covariance; CGI-I: Cochran-Mantel-Haenszel (CMH) row mean score differ test; response and remission rates: CMH general association test.

<sup>b</sup>Value represents the difference between brexpiprazole and placebo CGI-I values.

<sup>c</sup>Defined as patients having  $\geq 50\%$  reduction from baseline in MADRS total score.

<sup>d</sup>Percentage of patients with response or remission.

<sup>e</sup>Ratio (95% CI) of response or remission rates.

<sup>f</sup>Defined as very much improved or much improved.

<sup>g</sup>Defined as patients with MADRS total score  $\leq 10$  and  $\geq 50\%$  reduction in MADRS total score from baseline.

Abbreviations: ADT = antidepressant treatment, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale, HDRS-17 = 17-item Hamilton Depression Rating Scale, IDS-SR = Inventory of Depressive Symptomatology-Self-Report, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, SE = standard error.

**Table 3. Treatment-Emergent Adverse Events (safety population)**

Variable	ADT + Placebo (n = 191), n (%)	ADT + Brexpiprazole (n = 188), n (%)
At least 1 TEAE <sup>a</sup>	89 (46.6)	111 (59.0)
SAE <sup>b</sup>	2 (1.0)	2 (1.1)
Discontinuation due to TEAE <sup>c</sup>	0	6 (3.2)
TEAEs occurring in $\geq 5\%$ of patients in ADT + brexpiprazole group		
Weight gain	6 (3.1)	15 (8.0)
Akathisia	2 (1.0)	14 (7.4)

<sup>a</sup>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.

<sup>b</sup>Brexpiprazole: syncope and fracture, abdominal pain. Placebo: atrial fibrillation, pneumonia.

<sup>c</sup>Brexpiprazole: abdominal pain, diarrhea, akathisia, headache, parkinsonism, anorgasmia.

Abbreviations: ADT = antidepressant treatment, SAE = serious adverse event, TEAE = treatment-emergent adverse event.

+2.60 vs +0.84 mg/dL for total cholesterol (baseline = 205.88 vs 209.69 mg/dL), and +1.37 vs -0.02 mg/dL for low-density lipoprotein cholesterol (baseline = 118.21 vs 122.61 mg/dL). Metabolic-related TEAEs were reported by 2 brexpiprazole patients (dyslipidemia; hypercholesterolemia) and 1 placebo patient (increased triglycerides). A change in fasting triglycerides from normal ( $< 150$  mg/dL) to high (200 to  $< 500$  mg/dL) levels occurred during randomized treatment in 15/115 (13.0%) and 5/119 (4.2%) brexpiprazole and placebo patients, respectively. Among patients who did not meet any criteria for metabolic syndrome at baseline,

3 or more criteria were met during randomized treatment by 3/133 (2.3%) brexpiprazole versus 2/148 (1.4%) placebo patients.

There were no other consistent differences between treatment groups in clinical laboratory results, vital signs, and ECGs.

Two of the 3 extrapyramidal symptom rating scales used showed small increases in mean scores for the brexpiprazole group over the randomized treatment phase. Least squares mean changes from baseline to last visit for brexpiprazole versus placebo were 0.18 versus -0.02 for SAS total score (LS mean difference = 0.20,  $P = .0038$ ), 0.03 versus 0.04 for AIMS total score (LS mean difference = -0.01,  $P = .8663$ ), and 0.14 versus -0.04 for BARS global score (LS mean difference = 0.18,  $P = .0005$ ). One patient from the brexpiprazole group discontinued treatment due to akathisia.

No suicidal behavior was reported on the Columbia-Suicide Severity Rating Scale. During randomized treatment, a similarly low proportion of patients in the brexpiprazole and placebo groups reported emergent (9/188 [4.8%] vs 12/191 [6.3%]) or worsening (3/188 [1.6%] vs 4/191 [2.1%]) suicidal ideation.

No emergent sexual dysfunction was observed on the Massachusetts General Hospital Sexual Functioning Questionnaire; total and individual item scores were similar between treatment groups. Change from baseline to last visit in overall sexual satisfaction score for brexpiprazole and placebo groups indicated comparable improvement (LS mean = -0.27 vs -0.20; LS mean difference = -0.07,  $P = .5421$ ).

In this trial, adjunctive brexpiprazole 2 mg/d improved depressive symptoms, measured by MADRS, compared with ADT monotherapy in patients with MDD and inadequate response to standard ADTs. Changes from baseline in other physician-rated depression scales (HDRS-17 and CGI-S) confirmed this effect. Brexpiprazole also improved social functioning, based on SDS mean score, compared with ADT monotherapy; the effect of brexpiprazole was largest on the disruptive effects of symptoms on social life, family life, and home responsibilities. It is perhaps unsurprising that brexpiprazole did not significantly improve work and school life compared with placebo. The length of time these patients have continued to experience depressive symptoms despite treatment will most likely have had considerable impacts on employment and education that cannot be resolved within the 6-week timeframe of this study.

A clinically relevant change in depression has been defined as a difference of at least 2 points over placebo in MADRS total score<sup>40,41</sup>; in this study, the difference between brexpiprazole and placebo was more than 3 points. The absolute reduction in MADRS total score observed with adjunctive brexpiprazole in this study (8.4; placebo, 5.2) was at the lower end of the range reported in pivotal studies of adjunctive aripiprazole versus placebo (8.8 vs 5.8; 8.5 vs 5.7; 10.1 vs 6.4) in patients with MDD and inadequate response to ADT.<sup>42–44</sup> However, as the placebo response was lower in this brexpiprazole study than the aripiprazole studies, the difference over placebo was comparable. The difference over placebo in reduction of MADRS total score observed with brexpiprazole was also similar to that reported with adjunctive quetiapine extended release (XR) in similar studies (300 mg: 15.0 vs 12.2; 14.7 vs 11.7).<sup>45,46</sup> It should be noted that direct comparisons between studies are limited by methodological differences. For example, fixed doses of brexpiprazole and quetiapine XR were evaluated, while aripiprazole was dosed flexibly. Furthermore, the studies of quetiapine XR did not include a prospective ADT phase, which may have resulted in differences between studies in the patient population.

Brexpiprazole was well tolerated in this study, with few patients discontinuing due to TEAEs or reporting SAEs. The most frequently reported TEAEs in the brexpiprazole group were weight gain and akathisia. Incidence of akathisia with brexpiprazole was lower than that reported in a meta-analysis<sup>47</sup> of randomized studies of adjunctive aripiprazole. Mean changes from baseline in SAS total score and BARS global score in the brexpiprazole group were small and lower than those reported in pivotal studies of adjunctive aripiprazole.<sup>42,44</sup> Incidences of insomnia and fatigue were low and comparable in adjunctive brexpiprazole and ADT monotherapy groups; restlessness, somnolence, and sedation were infrequently reported in the adjunctive brexpiprazole group. Brexpiprazole did not appear to have clinically relevant adverse effects on prolactin or metabolic parameters. Overall, the tolerability profile of brexpiprazole

reflected its receptor pharmacology—low intrinsic activity at D<sub>2</sub> receptors and moderately low affinity for receptors associated with sedation and weight gain.<sup>15</sup> Adjunctive brexpiprazole did not induce or worsen suicidal ideation and, as compared with ADT monotherapy, did not have any adverse effect on sexual function.

Defining a coherent group of patients with true inadequate response in a prospective trial (as well as responders) has proven difficult using standardized rating scales.<sup>48</sup> Here, our trial protocol was amended during the study to capture more refined criteria for inadequate response, in a blinded fashion, and reflect all visits during the prospective ADT trial period. The statistical analysis plan prespecified analyses of both the efficacy population and efficacy population per final protocol, and results were consistent across the 2 analyses.

Limitations of this study include lack of active comparator group and relatively short duration of the randomized treatment phase. If short-term efficacy of adjunctive brexpiprazole is confirmed in subsequent studies, documented maintenance of efficacy and safety of adjunctive brexpiprazole will be necessary with prolonged continuous therapy.

In conclusion, in this phase 3, randomized, placebo-controlled study, adjunctive brexpiprazole demonstrated efficacy and was well tolerated in patients with MDD and inadequate response to standard ADTs.

**Submitted:** November 26, 2014; accepted May 14, 2015.

**Online first:** August 4, 2015.

**Drug names:** aripiprazole (Abilify and others), duloxetine (Cymbalta and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), sertraline (Zoloft and others), venlafaxine (Effexor XR and others).

**Potential conflicts of interest:** Dr Thase has received grants from Agency for Healthcare Research and Quality, Alkermes, Forest, National Institute of Mental Health, Otsuka, PharmaNeuroboost, and Roche; has acted as an advisor or consultant for Alkermes, AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly, Forest Laboratories, Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, Lundbeck, MedAvante, Merck, Neuroonetics, Novartis, Ortho-McNeil Pharmaceuticals, Otsuka, PamLab, Pfizer, Shire, Sunovion, and Takeda; has received royalties from American Psychiatric Association, Guilford Publications, Herald House, and W. W. Norton & Company; and holds equity in MedAvante Inc. Dr Thase's spouse is an employee of Peloton Advantage. Drs Youakim, Skuban, Hobart, Zhang, McQuade, Carson, Nyilas, and Sanchez and Ms Augustine are employees of Otsuka Pharmaceutical Development & Commercialization. Dr Eriksson is an employee of H. Lundbeck A/S.

**Funding/support:** Funding for this study was provided by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, New Jersey) and H. Lundbeck A/S (Valby, Denmark).

**Role of the sponsor:** The sponsors were responsible for the study design and conduct and the collection, management, analysis, and interpretation of the data. The authors, some of whom are employed by the sponsors, were also responsible for writing and reviewing this article. All authors approved the final version.

**Previous presentation:** Presented at the 22nd European Congress of Psychiatry; March 1–4, 2014; Munich, Germany • and the American Psychiatric Association Annual Meeting; May 3–7, 2014; New York, New York.

**Acknowledgment:** Jennifer Stewart, MSc (QXV Communications, Macclesfield, United Kingdom), provided writing support, which was funded by Otsuka Pharmaceutical Development & Commercialization, Inc. (Princeton, New Jersey) and H. Lundbeck A/S (Valby, Denmark).

**Supplementary material:** Available at Psychiatrist.com.

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## **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

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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)**

Scale	ADT + placebo (n=191)	ADT + brexpiprazole (n=187)	Difference in change from baseline	
	Change from baseline		LS mean (95% CI)	P-value <sup>g</sup>
	LS mean (SE)			
SDS mean	-0.91 (0.17)	-1.35 (0.17)	-0.45 (-0.86, -0.03)	.0372 <sup>†</sup>
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 <sup>†</sup>
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 <sup>a</sup> (-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 <sup>b</sup>	14.7 <sup>c</sup>	23.5 <sup>c</sup>	1.63 (1.09, 2.44) <sup>d</sup>	.0176
CGI-I responders <sup>e</sup>	27.7 <sup>c</sup>	44.4 <sup>c</sup>	1.61 (1.23, 2.10) <sup>d</sup>	.0003
MADRS remitters <sup>f</sup>	8.4 <sup>c</sup>	14.4 <sup>c</sup>	1.68 (0.98, 2.86) <sup>d</sup>	.0586

<sup>†</sup>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.

<sup>a</sup>Value represents the difference between brexpiprazole and placebo CGI-I values.

<sup>b</sup>Defined as patients having ≥50% reduction from baseline in MADRS total score.

<sup>c</sup>Percentage of patients with response or remission.

<sup>d</sup>Ratio (95% CI) of response or remission rates.

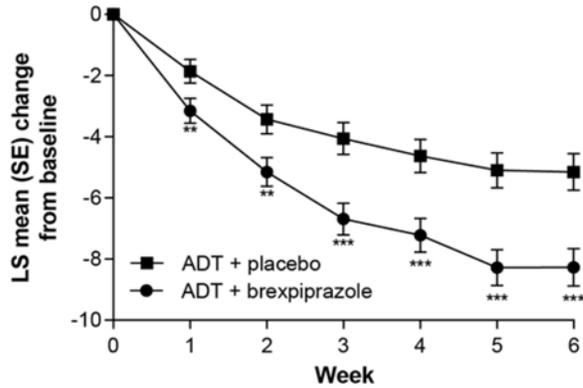
<sup>e</sup>Defined as very much improved or much improved.

<sup>f</sup>Defined as patients with MADRS total score  $\leq 10$  and  $\geq 50\%$  reduction in MADRS total score from baseline.

<sup>g</sup>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 benztropine 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  $\geq 50\%$  reduction from baseline in MADRS total score.

MADRS remission was defined as a MADRS total score of  $\leq 10$  and  $\geq 50\%$  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.