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Adjunctive Brexpiprazole and Functioning in Major Depressive Disorder: A Pooled Analysis of Six Randomized Studies Using the Sheehan Disability Scale

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Abstract

Background: Patients with major depressive disorder and inadequate response to antidepressant treatments may experience a prolonged loss of functioning. This post hoc analysis aimed to determine the effect of adjunctive brexpiprazole on functioning in such patients.
Methods: A pooled analysis of data from the 6-week, randomized, double-blind treatment phases of 6 studies of adjunctive brexpiprazole (2 and 3 mg/d in fixed-dose studies; 1–3 mg/d in flexible-dose studies) vs placebo in patients with major depressive disorder and inadequate response to antidepressant treatments (NCT01360645, NCT01360632, NCT02196506, NCT01727726, NCT00797966, NCT01052077). Functioning was measured by change in Sheehan Disability Scale score from baseline to week 6.
Results: Considering Sheehan Disability Scale mean score across all 6 studies (n = 2066 randomized), the least squares mean difference between antidepressant treatments + brexpiprazole and antidepressant treatments + placebo at week 6 was –0.40 (95% CI: –0.56, –0.23; $P < .0001$). Antidepressant treatments + brexpiprazole showed a greater benefit than antidepressant treatments + placebo on the social life (–0.45; –0.63, –0.27; $P < .001$) and family life (–0.50; –0.70, –0.31; $P < .001$) items but not on the work/studies item (–0.16; –0.38, 0.06; $P = .16$). Pooled analyses of just the (1) fixed-dose, (2) flexible-dose, and (3) Phase 3 studies showed the same pattern of benefits for antidepressant treatments + brexpiprazole.
Conclusions: Brexpiprazole, as adjunct to antidepressant treatments, improved functioning in patients with major depressive disorder and inadequate response to antidepressant treatments.

Keywords: brexpiprazole, functioning, Sheehan Disability Scale, depression, adjunctive

Introduction

Major depressive disorder (MDD) is associated with impairments across multiple domains of patient functioning, including work and school (affecting work performance and earnings, for example), social life and leisure activities, and family and home responsibilities (Kessler et al., 2003, 2006; Kessler, 2012). In clinical practice, improvement of functioning may lag behind

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Significance Statement

Patients with major depressive disorder are likely to experience problems with functioning in multiple environments: at work or school, in their social life and leisure activities, and in their family and home responsibilities. In particular, patients who do not fully respond to antidepressant treatment may suffer a prolonged loss of functioning. The present article describes the effects of brexpiprazole on functioning, based on pooled data for over 2000 patients from 6 randomized, controlled trials. Among patients with inadequate response to antidepressant treatment, brexpiprazole was shown to improve functioning over 6 weeks compared with placebo. Specifically, benefits were observed for brexpiprazole over placebo in the domains of social and family life.

improvement of mood, largely due to unresolved, functionally impairing symptoms such as fatigue, sleep/wake disturbance, and cognitive dysfunction (Saltiel and Silvershein, 2015).

Many patients with MDD fail to respond to antidepressant treatment (ADT) (Rush et al., 2006). Patients with inadequate response to ADT may experience a prolonged loss of functioning and quality of life (Mauskopf et al., 2009). One treatment option for such patients is the use of an adjunctive antipsychotic added to the existing ADT. A meta-analysis of 14 randomized, placebo-controlled studies showed that adjunctive atypical antipsychotics are efficacious for reducing depressive symptoms in MDD (Spielmans et al., 2013). However, the use of adjunctive atypical antipsychotics is associated with tolerability concerns, and little or no benefits have been observed on functioning or quality-of-life outcomes (Spielmans et al., 2013).

Brexpiprazole is a serotonin–dopamine activity modulator that acts as a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors and as an antagonist at serotonin 5-HT_{2A} and noradrenaline α_{1B}/α_{2C} receptors, all with subnanomolar potency (Maeda et al., 2014). The efficacy and safety of brexpiprazole as adjunct to ADT over 6 weeks have been demonstrated in 4 phase 3 studies (Pyxis, Polaris, Sirius, and Delphinus) (Thase et al., 2015a, 2015b; Hobart et al., 2018a, 2018b) in which brexpiprazole improved depressive symptoms vs placebo. The present article is a pooled analysis of data from the 4 short-term phase 3 studies, together with 2 short-term phase 2 studies (Studies 211 and 222; Thase et al., 2011, 2016), with the aim of determining the effect of adjunctive brexpiprazole on functioning in patients with inadequate response to ADTs.

Methods

This pooled analysis included 6 short-term, randomized, placebo-controlled studies of adjunctive brexpiprazole in patients with MDD and inadequate response to ADTs. Details of the included studies are given in Table 1. For a full description of the study designs and selection criteria, please refer to the primary publications (Thase et al., 2011, 2015a, 2015b, 2016; Hobart et al., 2018a, 2018b).

All studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline and local regulatory requirements. The study protocols were approved by relevant institutional review boards and independent ethics committees. All patients provided written informed consent prior to the start of the studies.

Study Design and Patients

Each of the 6 studies had a similar design, comprising an 8- or 10-week prospective treatment phase followed by a 6-week, randomized, double-blind treatment phase for patients who did not adequately respond to prospective treatment (Table 1). In the prospective treatment phase, eligible adult outpatients (see Table 1 for main inclusion criteria) received an investigator-determined, open-label ADT, together with single-blind placebo (in Pyxis, Polaris, Sirius, Study 211, and Study 222) or double-blind placebo (in Delphinus). During this phase, patients were assessed for inadequate response to prospective ADT (see Table 1 for definitions). Patients who did not meet the criteria for inadequate response (i.e., responders to prospective ADT) continued to receive the same open-label ADT and single- or double-blind placebo until the end of the study; these patients were not randomized or included in the analyses. Patients who did meet the criteria for inadequate response were randomized to double-blind treatment with adjunctive brexpiprazole or placebo (or quetiapine extended-release in Delphinus) for 6 weeks. Three studies used fixed doses of brexpiprazole and 3 used flexible doses; administered doses were in the range of 0.15–3 mg/d, depending on the study.

Assessments

This publication focuses on the Sheehan Disability Scale (SDS) (Sheehan, 1983; Sheehan et al., 1996; Sheehan and Sheehan, 2008), which was a key secondary efficacy outcome in each study. The SDS measures functional disability on 3 items: work/studies, social life, and family life. Patients use visual analogue scales to rate the extent to which each of these items has been disrupted by their symptoms, from 0 (not at all) to 10 (extremely). Patients can skip the work/studies item if they have not worked/studied in the last week for reasons unrelated to their disorder. The SDS mean score is calculated as the mean of the 3 individual item scores, or 2 items if work/studies is not reported (range 0 [best functioning] to 10 [worst functioning]). In all 6 studies, the SDS was completed at baseline (randomization) and week 6. In addition, Pyxis, Polaris, and Sirius collected SDS data at week 3 and Delphinus collected SDS data at weeks 2 and 4.

For details of the studies' primary efficacy outcomes (Montgomery–Åsberg Depression Rating Scale [MADRS] total score) and safety and tolerability outcomes, please refer to the primary publications and MDD clinical overviews (Thase et al., 2011, 2015a, 2015b, 2016; Nelson et al., 2016; Hobart et al., 2018a, 2018b).

Data Analysis

The brexpiprazole doses included in this post hoc analysis were 2 and 3 mg/d from the fixed-dose studies (the recommended dose range in MDD; Rexulti, 2018) and 1–3 mg/d from the flexible-dose studies. Brexpiprazole doses of <1 mg/d were investigated in some of the studies but were not included in this post hoc analysis because they are subtherapeutic doses. Four pooled groups were created to assess different aspects of brexpiprazole dosing: (1) fixed-dose studies (Pyxis, Polaris, Sirius), 2 and 3 mg/d; (2) flexible-dose studies (Delphinus, 211, 222), 1–3 mg/d; (3) phase 3 studies (Pyxis, Polaris, Sirius, Delphinus), 2–3 mg/d; and (4) all studies (Pyxis, Polaris, Sirius, Delphinus, 211, 222), 1–3 mg/d.

The analysis was performed in the target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase (Table 1). This

Table 1. Brexpiprazole Short-Term Clinical Study Designs for the Adjunctive Treatment of MDD

Study name (ClinicalTrials.gov identifier)	Design	Main inclusion criteria for prospective phase	Criteria for consistent inadequate response throughout the prospective treatment phase[a]	Dosing	Treatment groups (efficacy population[b])
Phase 3					
Pyxis (NCT01360645) (Thase et al., 2015a)	8-week, single-blind, prospective phase followed by 6-week, randomized, double-blind, placebo-controlled phase	DSM-IV-TR diagnosis of single or recurrent nonpsychotic MDD, current episode ≥8 weeks in duration, history of inadequate response to ADT,[c] and HAM-D_{17} total score ≥18 at screening and at the start of prospective treatment	HAM-D_{17} total score: <50% reduction from the start to the end of prospective treatment; ≥14 at the end of prospective treatment CGI-I score: ≥3 at weeks 2, 4, 6, and 8 of prospective treatment MADRS total score: <50% reduction from the start to weeks 2, 4, 6, and 8 of prospective treatment	Fixed	**ADT +** brexpiprazole 2 mg/d (n = 175) placebo (n = 178)
Polaris (NCT01360632) (Thase et al., 2015b)				Fixed	**ADT +** brexpiprazole 1 mg/d (n = 211) brexpiprazole 3 mg/d (n = 213) placebo (n = 203)
Sirius (NCT02196506) (Hobart et al., 2018a)				Fixed	**ADT +** brexpiprazole 2 mg/d (n = 191) placebo (n = 202)
Delphinus (NCT01727726) (Hobart et al., 2018b)	8- or 10-week, double-blind, prospective phase followed by 6-week, randomized, double-blind, placebo-controlled phase	DSM-IV-TR diagnosis of single or recurrent nonpsychotic MDD, current episode ≥8 weeks in duration, history of inadequate response to ADT,[c] and MADRS total score ≥26 at screening and at the start of prospective treatment	CGI-I score: ≥3 at weeks 2, 4, 6, and 8[d] of prospective treatment MADRS total score: <50% reduction from the start to weeks 2, 4, 6, and 8[d] of prospective treatment; ≥18 at the end of prospective treatment	Flexible	**ADT +** brexpiprazole 2–3 mg/d (n = 191) quetiapine XR 150–300 mg/d (n = 99) placebo (n = 205)
Phase 2					
Study 211 (NCT00797966) (Thase et al., 2011, 2016)	As for Pyxis, Polaris, and Sirius	As for Pyxis, Polaris, and Sirius, except HAM-D_{17} total score ≥18 at the start of prospective treatment only (not at screening)	As for Pyxis, Polaris, and Sirius (retrospectively applied for the pooled analysis)	Flexible	**ADT +** brexpiprazole 0.15 mg/d (fixed) (n = 45) brexpiprazole 0.5 ± 0.25 mg/d (n = 94) brexpiprazole 1.5 ± 0.5 mg/d (n = 90) placebo (n = 89)
Study 222 (NCT01052077) (Thase et al., 2016)				Flexible	**ADT +** brexpiprazole 1–3 mg/d (n = 158) placebo (n = 147)

Abbreviations: ADT, antidepressant treatment; CGI-I, Clinical Global Impressions – Improvement; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; HAM-D_{17}, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; XR, extended-release.

[a]Following an amendment to Pyxis and Polaris.

[b]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222.

[c]An inadequate response to 1 to 3 prior ADTs during the current episode (including any ADT being taken at screening), defined as <50% improved on a therapeutic dose for an adequate duration (≥6 weeks) according to the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

[d]And Week 10, if applicable (in this study, to blind the timing of randomization, patients were randomly assigned to an 8- or 10-week prospective treatment phase).

definition was per final protocol for the phase 3 studies and was retrospectively applied to the phase 2 studies, for which the protocols had required that inadequate response criteria were met only at the end of prospective treatment. Within the target population, the randomized population comprised all patients who were randomized to double-blind medication, and the efficacy population was defined as all patients who took at least one dose of double-blind medication and who had a baseline and at least one post-baseline MADRS total evaluation in the randomized treatment phase.

Least squares (LS) mean changes from baseline (randomization) to week 6 of the randomized treatment phase, differences from placebo, and *P* values (2-sided tests at the 5% level) were calculated for the SDS mean and individual items. Cohen's *d* effect sizes were calculated for between-group differences. A mixed model for repeated measures (MMRM) was applied to the individual phase 3 studies, with model terms of treatment, site, visit, treatment-by-visit, and baseline-by-visit interaction as covariates. For the individual phase 2 studies, which had only one post-baseline SDS measurement, an ANCOVA model was used, with terms of treatment and site as main effects and baseline value as covariate. For the pooled analyses, MMRM was used but with the model term of site replaced by site nested within trial.

Finally, to investigate if the duration of MDD episode could influence the degree of functional change, Pearson correlation coefficients (*r*) were calculated between duration of current episode and change from baseline to week 6 in SDS mean/item scores.

Results

Patients

A total of 2066 patients were randomized to ADT + brexpiprazole at the doses of interest (n = 1034) or to ADT + placebo (n = 1032). Completion rates were high (≥90%) in both treatment groups (Table 2). The main reason for discontinuation in the ADT + brexpiprazole group was adverse events (2.8%) and in the ADT + placebo group was that the patient withdrew consent (2.8%).

Baseline demographic and clinical characteristics were similar between the treatment groups (Table 3). The mean age was 44 years, and two-thirds of patients were female. Mean (SD) SDS mean scores at baseline were 5.7 (2.1) in the ADT + brexpiprazole group and 5.8 (2.1) in the ADT + placebo group, indicating moderate impairment.

Change in Functioning

In all 4 pooled analyses (fixed-dose studies, flexible-dose studies, phase 3 studies, and all studies), ADT + brexpiprazole showed a greater improvement in SDS mean score from baseline to week 6 than ADT + placebo (all $P < .01$), with a treatment effect (between-group difference) of –0.4 points in each analysis (Figure 1; Table 4). The Cohen's *d* between-group effect size in the pooled analysis of all 6 studies was 0.22.

In each of the 6 individual studies, ADT + brexpiprazole showed a greater numerical improvement in SDS mean score from baseline to week 6 than ADT + placebo (Figure 1). In 3 of the studies (Pyxis, Polaris, and Study 211), the benefit of ADT + brexpiprazole over ADT + placebo met the threshold of $P < .05$.

Considering individual SDS items, in the pooled analysis of all 6 studies, ADT + brexpiprazole showed a greater benefit than ADT + placebo on the social life (LS mean difference: –0.45; 95% CI: –0.63, –0.27; $P < .001$) and family life (–0.50; –0.70, –0.31; $P < .001$) items, but not on the work/studies item (–0.16; –0.38, 0.06; $P = .16$) (Figure 2; Table 4). Cohen's *d* between-group effect sizes were 0.08 for work/studies, 0.23 for social life, and 0.23 for family life. The same pattern of benefits was observed in the other 3 pooled analyses (fixed-dose studies, flexible-dose studies, phase 3 studies), with benefits for ADT + brexpiprazole on the social life and family life items (all $P < .01$) but not on the work/studies item (Table 4).

In the pooled analysis of all 6 studies, Pearson's *r* between duration of MDD episode and change in SDS mean score was 0.00 in the ADT + brexpiprazole group and 0.07 in the ADT +

Table 2. Patient Disposition and Reasons for Discontinuation for All Studies Pooled (Randomized Population[a])

n (%)	ADT + placebo (n = 1032)	ADT + brexpiprazole[b] (n = 1034)
Completed	958 (92.8)	931 (90.0)
Discontinued	74 (7.2)	103 (10.0)
Adverse event	8 (0.8)	29 (2.8)
Patient withdrew consent	29 (2.8)	27 (2.6)
Met withdrawal criteria	7 (0.7)	19 (1.8)
Protocol deviation	12 (1.2)	11 (1.1)
Lost to follow-up	5 (0.5)	9 (0.9)
Withdrawn by investigator	3 (0.3)	5 (0.5)
Lack of efficacy	10 (1.0)	3 (0.3)
Efficacy population[a]	1024 (99.2)	1018 (98.5)

Abbreviation: ADT, antidepressant treatment.
[a]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222.
[b]The following brexpiprazole dose groups were included in the pooled analysis: Pyxis and Sirius, 2 mg/d; Polaris, 3 mg/d; Delphinus, 2–3 mg/d; study 211, 1.5 ± 0.5 mg/d; study 222, 1– 3 mg/d.

Table 3. Baseline Demographic and Clinical Characteristics for All Studies Pooled (Efficacy Population[a])

	ADT + placebo (n = 1024)	ADT + brexpiprazole[b] (n = 1018)
Demographic characteristics		
Age (y), mean (SD)	43.6 (11.8)	44.1 (11.7)
Female, n (%)	707 (69.0)	694 (68.2)
White, n (%)[c]	855 (83.5)	865 (85.0)
BMI (kg/m^2), mean (SD)	29.7 (7.3)	29.6 (6.9)
Clinical characteristics		
Duration of current depressive episode (months), mean (SD)	18.8 (36.4)	18.0 (29.0)
MADRS total score, mean (SD)	26.5 (5.8)	26.5 (5.5)
SDS mean score, mean (SD)	5.8 (2.1) (n = 993)	5.7 (2.1) (n = 981)
SDS work/studies	5.4 (2.4) (n = 713)	5.3 (2.6) (n = 690)
SDS social life	6.0 (2.3) (n = 993)	6.0 (2.3) (n = 982)
SDS family life	5.7 (2.3) (n = 993)	5.7 (2.3) (n = 981)

Abbreviations: ADT, antidepressant treatment; BMI, body mass index; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation; SDS, Sheehan Disability Scale.
[a]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222.
[b]The following brexpiprazole dose groups were included in the pooled analysis: Pyxis and Sirius, 2 mg/d; Polaris, 3 mg/d; Delphinus, 2–3 mg/d; study 211, 1.5 ± 0.5 mg/d; study 222, 1–3 mg/d.
[c]Race was not recorded for 1 patient in the ADT + brexpiprazole group and 1 patient in the ADT + placebo group.

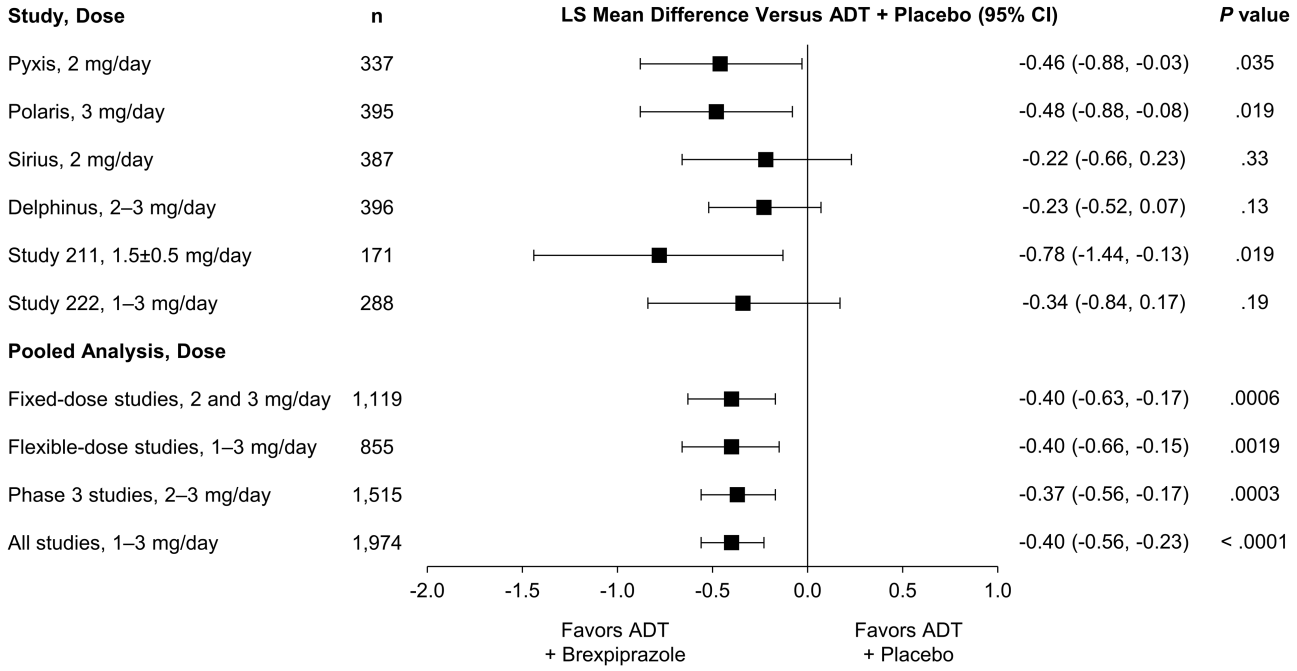

Figure 1. Estimated treatment effect for antidepressant treatment (ADT) + brexpiprazole: mean change in Sheehan Disability Scale (SDS) mean score from baseline to week 6 (efficacy population[a]). Abbreviations: CI, confidence interval; LS, least squares; MMRM, mixed model for repeated measures. MMRM for Pyxis, Polaris, Sirius, and Delphinus; ANCOVA for Study 211 and Study 222; MMRM for pooled analyses. [a]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222.

Table 4. Mean Change in SDS Mean and Item Scores from Baseline to Week 6 (Efficacy Population[a])

	SDS Mean		SDS work/studies		SDS social life		SDS family life	
	ADT + placebo	ADT + brexpiprazole	ADT + placebo	ADT + brexpiprazole	ADT + placebo	ADT + brexpiprazole	ADT + placebo	ADT + brexpiprazole
Fixed-dose studies, 2 and 3 mg/d	(n = 564)	(n = 555)	(n = 421)	(n = 400)	(n = 564)	(n = 555)	(n = 564)	(n = 555)
Mean (SD) at baseline	5.83 (2.10)	5.81 (2.20)	5.35 (2.42)	5.42 (2.64)	6.07 (2.32)	6.07 (2.42)	5.80 (2.31)	5.77 (2.39)
LS mean (SE) change to week 6	−1.03 (0.09)	−1.43 (0.09)***	−1.04 (0.13)	−1.14 (0.13)	−1.10 (0.10)	−1.58 (0.11)***	−0.97 (0.10)	−1.46 (0.10)***
Flexible-dose studies, 1–3 mg/d	(n = 429)	(n = 426)	(n = 292)	(n = 290)	(n = 429)	(n = 427)	(n = 429)	(n = 426)
Mean (SD) at baseline	5.72 (2.05)	5.62 (2.01)	5.54 (2.34)	5.24 (2.47)	5.87 (2.22)	5.80 (2.16)	5.66 (2.23)	5.65 (2.22)
LS mean (SE) change to week 6	−0.56 (0.11)	−0.97 (0.10)**	−0.57 (0.13)	−0.82 (0.13)	−0.57 (0.12)	−0.99 (0.11)**	−0.36 (0.12)	−0.88 (0.12)***
Phase 3 studies, 2–3 mg/d	(n = 769)	(n = 746)	(n = 557)	(n = 525)	(n = 769)	(n = 746)	(n = 769)	(n = 746)
Mean (SD) at baseline	5.80 (2.06)	5.75 (2.09)	5.41 (2.34)	5.39 (2.47)	5.99 (2.25)	5.98 (2.28)	5.77 (2.24)	5.70 (2.29)
LS mean (SE) change to week 6	−0.95 (0.08)	−1.31 (0.08)***	−0.99 (0.10)	−1.04 (0.11)	−0.98 (0.08)	−1.42 (0.08)***	−0.87 (0.08)	−1.34 (0.09)***
All studies, 1–3 mg/d	(n = 993)	(n = 981)	(n = 713)	(n = 690)	(n = 993)	(n = 982)	(n = 993)	(n = 981)
Mean (SD) at baseline	5.78 (2.08)	5.73 (2.12)	5.43 (2.39)	5.34 (2.57)	5.98 (2.28)	5.95 (2.31)	5.74 (2.27)	5.72 (2.32)
LS mean (SE) change to week 6	−0.80 (0.07)	−1.20 (0.07)***	−0.81 (0.09)	−0.97 (0.09)	−0.84 (0.07)	−1.30 (0.07)***	−0.67 (0.08)	−1.18 (0.08)***

Abbreviations: ADT, antidepressant treatment; LS, least squares; MMRM, mixed model for repeated measures; SDS, Sheehan Disability Scale.
**P < .01, ***P < .001 vs ADT + placebo; MMRM.
[a]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222.

placebo group. Equivalent Pearson's *r* for the individual SDS items were: work/studies, 0.00 (ADT + brexpiprazole), 0.09 (ADT + placebo); social life, −0.02, 0.05; and family life, 0.00, 0.06.

Discussion

In these pooled analyses of over 2000 patients, adjunctive brexpiprazole improved functioning vs adjunctive placebo in patients with MDD, as measured by change in SDS mean score over 6 weeks of treatment. Each of the pooled analyses had a similar result, showing that the benefit of brexpiprazole over placebo was consistent between studies and not dependent on any one study. To the authors' knowledge, no minimal clinically important difference has been established for the SDS. In the pool of all 6 studies, SDS mean score decreased by 1.2 points with adjunctive brexpiprazole (from 5.7 at baseline), thereby approaching the threshold for functional response, suggested as ≤4 points by Sheehan and Sheehan (2008). The Cohen's *d* between-group effect size indicated a small but clinically meaningful benefit.

Other adjunctive treatments have also been assessed for their effect on functioning among patients with MDD and inadequate response to ADT. In a systematic review of 26 randomized, placebo-controlled studies of adjunctive agents, only aripiprazole, brexpiprazole, edivoxetine, and risperidone improved

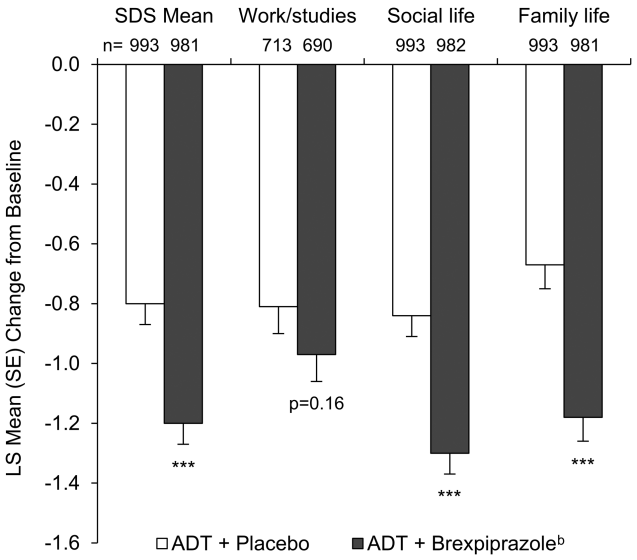

Figure 2. Mean change in Sheehan Disability Scale (SDS) mean and item scores from baseline to week 6, for all studies pooled (efficacy population[a]). Abbreviations: ADT, antidepressant treatment; LS, least squares; MMRM, mixed model for repeated measures. ***P < .001 vs ADT + placebo; MMRM. [a]Per target population, defined as patients who met criteria for consistent inadequate response throughout the prospective treatment phase. This definition was retrospectively applied to study 211 and study 222. [b]The following brexpiprazole dose groups were included in the pooled analysis: Pyxis and Sirius, 2 mg/d; Polaris, 3 mg/d; Delphinus, 2–3 mg/d; study 211, 1.5 ± 0.5 mg/d; study 222, 1–3 mg/d.

functioning, as measured by the SDS total or mean score (Weiller et al., 2018). Of these agents, edivoxetine and risperidone are not indicated for the adjunctive treatment of MDD. In the adjunctive aripiprazole studies, SDS mean score decreased by 1.0–1.3 points over 6 weeks among patients taking aripiprazole (Berman et al., 2007, 2009; Marcus et al., 2008; Kamijima et al., 2013), similar to the score change with adjunctive brexpiprazole in the present analysis. However, use of aripiprazole in MDD is associated with a higher rate of akathisia than is seen with brexpiprazole (Nelson et al., 2016; Citrome et al., 2010).

In the present pooled analyses, adjunctive brexpiprazole showed a benefit over adjunctive placebo on the SDS items of social life and family life, but not on the work/studies item. Thus, the observed benefit on SDS mean was driven by the social life and family life items. This observation is in line with the systematic review of adjunctive agents in MDD (described above), which showed that the SDS work/studies item is generally unable to distinguish active treatment from placebo in short-term studies of patients with inadequate response to ADT (Weiller et al., 2018). In the systematic review, one posited explanation for this lack of sensitivity in MDD inadequate responders was that patients who were not working did not complete the work/studies item, meaning that the power to detect a treatment effect was reduced for this item. In the present study, only 71.1% of patients rated the work/studies item compared with other items at baseline, and thus we can assume that the other 28.9% of patients were not working, as might be expected in this population of persistent inadequate responders with a mean depressive episode duration of 1.5 years. However, due to the large population in this pooled analysis, loss of power is unlikely to explain the lack of effect on the work/studies item over 6 weeks. A more likely explanation is that the included studies were of insufficient duration to show a benefit. Patients with inadequate response to an initial ADT are prone to persistent impairment in occupational productivity, even after achieving remission of symptoms (Trivedi et al., 2013). Thus, studies longer than 6 weeks may be needed for adjunctive brexpiprazole to show a benefit on the work/studies item. This hypothesis is supported by the results of a long-term, open-label study of adjunctive brexpiprazole in MDD, in which, over 6 to 12 months of treatment, patients improved by a similar amount on the work/studies item as on the social and family life items (Hobart et al., 2018c).

There was negligible correlation (Pearson's $r < 0.1$) between duration of current depressive episode and change from baseline to week 6 in SDS mean or item scores. Thus, episode duration did not affect the degree of functional improvement during this 6-week study. Furthermore, while they are clearly related, functional impairment cannot be fully explained by depressive symptom severity (Zimmerman et al., 2006). Studies examining the relationship between functioning and symptomatic rating scale outcomes have found moderate, but highly variable correlations (McKnight and Kashdan, 2009). Individual depressive symptoms also vary in their effect on functional impairment (Fried and Nesse, 2014; Jha et al., 2016). Thus, the benefits of brexpiprazole augmentation on overall depression severity (Thase et al., 2011, 2015a, 2015b, 2016; Hobart et al., 2018a, 2018b) are unlikely to fully account for the benefit in functioning observed in the present analysis.

Although the present analysis was limited by its post hoc nature, this allowed for a large sample size. In addition, as is the nature of randomized, controlled trials, the studied population may not be representative of patients in clinical practice due to the inclusion/exclusion criteria of the primary studies.

In conclusion, brexpiprazole, as adjunct to ADT, improves functioning in patients with MDD and inadequate response to ADTs. Specifically, benefits were observed for brexpiprazole over placebo in the domains of social and family life.

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Statement of Interest

Mary Hobart, Peter Zhang, and Catherine Weiss are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. Stine Rasmussen Meehan and Hans Eriksson are full-time employees of H. Lundbeck A/S; Hans Eriksson also holds H. Lundbeck A/S stock.

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