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Effects of Brexpiprazole Across Symptom Domains in Patients With Schizophrenia: *Post Hoc* Analysis of Short- and Long-Term Studies

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The successful treatment of schizophrenia entails improvement across a spectrum of symptoms. The aim of this *post hoc* analysis was to characterize the short- and long-term effects of brexpiprazole on Positive and Negative Syndrome Scale (PANSS) 'Marder factors.' Data were included from three 6-week, randomized, double-blind, placebo-controlled studies; a 52-week, randomized, double-blind, placebo-controlled maintenance treatment study; and two 52-week open-label extension (OLEx) studies—all in schizophrenia (DSM-IV-TR criteria). Patients receiving oral brexpiprazole were dosed at 2–4 mg/day (short-term studies) or 1–4 mg/day (long-term studies). At Week 6, least squares mean differences (LSMDs, with 95% confidence limits [CLs]) for brexpiprazole (n = 868) vs placebo (n = 517) were: Positive symptoms: −1.55 (−2.30, −0.80), P < .0001, Cohen's d effect size (ES) = 0.27; Negative symptoms: −1.12 (−1.63, −0.61), P < .0001, ES = 0.29; Disorganized thought: −1.26 (−1.78, −0.74), P < .0001, ES = 0.32; Uncontrolled hostility/excitement: −0.76 (−1.15, −0.37), P = .0002, ES = 0.26; Anxiety/depression: −0.56 (−0.91, −0.22), P = .0014, ES = 0.22. At last visit of the maintenance study, LSMDs (95% CLs) for brexpiprazole (n = 96) vs placebo (n = 104) were: Positive symptoms: −3.44 (−4.99, −1.89), P < .0001, ES = 0.62; Negative symptoms: −1.23 (−2.52, 0.07), P = .063, ES = 0.27; Disorganized thought: −1.69 (−2.81, −0.56), P = .0035, ES = 0.42; Uncontrolled hostility/excitement: −1.26 (−2.12, −0.39), P = .0046, ES = 0.41; Anxiety/depression: −0.72 (−1.47, 0.03), P = .061, ES = 0.27. In the OLEx studies, improvements were maintained over 58 (6 + 52) weeks of brexpiprazole treatment. In conclusion, these data suggest that brexpiprazole treats the continuum of schizophrenia symptoms, in the short- and long-term. Trial Registration: Data used in this *post hoc* analysis came from ClinicalTrials.gov identifiers: NCT01396421, NCT01393613, NCT01810380, NCT01668797, NCT01397786, NCT01810783.

Key words: antipsychotic/clinical trial/Marder factors/Positive and Negative Syndrome Scale

Introduction

Patients with schizophrenia present with a wide spectrum of clinical manifestations. The core features are positive symptoms (delusions and hallucinations), negative symptoms (such as diminished emotional expression and social withdrawal), and cognitive symptoms (such as disorganized thought or speech).[1,2] Each of these domains is associated with considerable deficits in patient functioning.[3,4] In addition, mood symptoms such as depression and anxiety are common in schizophrenia, and some patients experience hostility and aggression.[1] Depressive symptoms in schizophrenia are associated with poor long-term outcomes, including worse functioning and quality of life, and greater use of mental health services.[5]

Based on clinical trial data, atypical antipsychotics are efficacious for treating the overall symptoms of schizophrenia, as measured by the 30-item Positive and Negative Syndrome Scale (PANSS) or similar scales.[6,7] However, given the heterogeneity of schizophrenia, PANSS subscales may better characterize the efficacy of antipsychotics across the spectrum of schizophrenia symptoms. Factor analyses of the 30 PANSS items consistently identify 5 subscales (such as the 5 PANSS 'Marder factors'), albeit with some variation in items between different 5-factor models.[8–11]

Brexpiprazole 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 affinity.[12] In acute schizophrenia, the efficacy and tolerability of brexpiprazole have been demonstrated in 2 pivotal 6-week, fixed-dose, placebo-controlled studies,[13,14] supported by a 6-week, flexible-dose, placebo-controlled, active-referenced study.[15,16] Over the long-term, the efficacy and tolerability of brexpiprazole as maintenance treatment in stabilized patients have been demonstrated in a randomized, placebo-controlled study,[17] and brexpiprazole was generally well tolerated for up to 52 weeks in open-label extension (OLEx) studies, with continued improvement in efficacy measures.[18]

The aim of this *post hoc* analysis was to characterize the short- and long-term effects of brexpiprazole across a spectrum of schizophrenia symptoms, using PANSS Marder factor and item scores. For this analysis, data were included from 3 short-term studies, a maintenance study, and 2 OLEx studies.

Methods

Study Design and Patients

The studies were conducted in compliance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline and the World Medical Association Declaration of Helsinki. The protocols were approved by independent ethics committees or institutional review boards at each site/country, and all patients provided written informed consent to participate after procedures and possible side effects were explained to them.

Short-Term Studies. Data from 3 randomized, double-blind, placebo-controlled studies of brexpiprazole in patients with acute schizophrenia—'Vector' (ClinicalTrials.gov identifier: NCT01396421),[13] 'Beacon' (NCT01393613),[14] and 'Lighthouse' (NCT01810380)[15,16]—were included in the present short-term analyses. Descriptions of the designs and selection criteria for these 3 studies have been published.[13,14,16]

In brief, the studies enrolled patients aged 18–65 years experiencing an acute exacerbation of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR] criteria),[19] and who would benefit from hospitalization or continued hospitalization. Exclusion criteria included having a first episode of schizophrenia, treatment-resistant schizophrenia, a DSM-IV-TR Axis I diagnosis other than schizophrenia, clinically significant tardive dyskinesia, or substance abuse or dependence in the previous 180 days. The studies had similar designs, comprising a ≤14-day screening phase, a 6-week double-blind treatment phase (in which patients were hospitalized), and a 30-day follow-up phase.

In Vector and Beacon, eligible patients were randomized to placebo or fixed-dose brexpiprazole (0.25/1, 2, or 4 mg/day, depending on the study). In the 2 mg and 4 mg groups, brexpiprazole was titrated as follows: first 4 days, 1 mg/day; days 5–7, 2 mg/day; eighth day onwards, allocated dose. In Lighthouse, eligible patients were randomized to placebo, flexible-dose brexpiprazole 2–4 mg/day, or flexible-dose quetiapine extended-release (XR) 400–800 mg/day (an active reference). Brexpiprazole titration was as follows: first day, 1 mg; second day, 2 mg; third day, 3 mg; fourth day onwards, 2–4 mg/day. Brexpiprazole was administered as an oral tablet.

Long-Term Maintenance Study. 'Equator' (Clinical Trials.gov identifier: NCT01668797)[17] was a 52-week, randomized, double-blind, placebo-controlled maintenance treatment study. Full descriptions of the study design and selection criteria have been published.[17]

In brief, the study enrolled inpatients and outpatients aged 18–65 years experiencing an acute exacerbation of schizophrenia (DSM-IV-TR), and with a history of relapse and/or symptom exacerbation in the absence of antipsychotic treatment. Exclusion criteria included having a first episode of schizophrenia, treatment-resistant schizophrenia, a DSM-IV-TR Axis I diagnosis other than schizophrenia, clinically significant tardive dyskinesia, or substance abuse or dependence in the previous 180 days.

The study comprised an as-needed conversion and washout phase, a 12–36 week single-blind stabilization phase, a 52-week double-blind maintenance phase, and a safety follow-up phase. In the stabilization phase, all patients received brexpiprazole 1–4 mg/day, adjusted to a dose that would maintain stability of psychotic symptoms while minimizing tolerability issues, according to the investigator's judgment. Patients who met stabilization criteria for 12 consecutive weeks entered the maintenance phase and were randomized to continue receiving brexpiprazole 1–4 mg/day (at their stabilization dose) or to switch to placebo.

Long-term OLEx studies. Data from 2 OLEx studies in schizophrenia—'Zenith' (ClinicalTrials.gov identifier: NCT01397786)[18] and 'Study 14644B' (NCT01810783)—were included in the long-term analysis. Full descriptions of the study design and selection criteria in Zenith have been published,[18] whereas Study 14644B design and selection criteria are available online (https://clinicaltrials.gov/show/NCT01810783).

In brief, outpatients who completed Vector or Beacon were eligible to roll over into Zenith, and inpatients and outpatients who completed Lighthouse were eligible to roll over into Study 14644B. Zenith also enrolled *de novo* patients and those who completed Equator; these patients are not included in the present *post hoc* analyses.

Patients in the long-term studies received flexibly dosed brexpiprazole 1–4 mg/day for up to 52 weeks (Zenith was amended to 26 weeks towards the end; this amendment only applied to the 11.2% of patients who enrolled after the date of the amendment). Open-label brexpiprazole was initiated at 2 mg/day and could be adjusted in 1 mg increments for reasons of efficacy or tolerability, according to the investigator's judgment.

Throughout the short-term, maintenance, and OLEx studies, all psychotropic agents (including antipsychotics, antidepressants, mood stabilizers, and benzodiazepines) were prohibited, except for specific oral benzodiazepines (lorazepam, oxazepam, diazepam, and clonazepam) when used as rescue therapy for the control of agitation and/or insomnia. Non-benzodiazepine sleep aids (zolpidem, zaleplon, zopiclone, and eszopiclone) were permitted for the treatment of insomnia, but not on the same day that a benzodiazepine was administered.

Assessments

In the short-term studies, the primary outcome was mean change in PANSS Total score from randomization to Week 6, which has been previously reported for the individual studies and the pooled sample.[13–16] The primary outcome in the maintenance study was time from randomization to impending relapse,[17] and, in the OLEx studies, was safety and tolerability.[18] Mean change in PANSS Total score was a secondary or exploratory outcome in the maintenance and OLEx studies.

The present analysis encompasses PANSS Marder factors and items. Marder factors comprise the following 5 domains of schizophrenia: positive symptoms (8 items), negative symptoms (7 items), disorganized thought (7 items), uncontrolled hostility/excitement (4 items), and anxiety/depression (4 items).[8] Each PANSS item is scored from 1 (absent) to 7 (extreme).[7] Five-factor structures generally demonstrate good internal consistency and reliability in both acute/relapsed and chronic/stable patients.[20]

In the short-term studies, the PANSS was administered at baseline and at Weeks 1, 2, 3, 4, 5, and 6. In the maintenance study, the PANSS was administered at baseline and at 2-weekly visits to Week 36 of the stabilization phase; and at Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52 of the maintenance phase. In the OLEx studies, the PANSS was administered at baseline and at Weeks 1, 2, 4, 8, 14, 20, 26, 32, 38, 44 and 52 of the treatment phase. PANSS raters were qualified and experienced clinicians who were trained and certified in PANSS administration for these studies.

Statistical Analyses

Short-Term Studies. Data from the short-term studies were pooled for all patients allocated to placebo, and for all patients allocated to a brexpiprazole dose in the recommended dose range of 2–4 mg/day (ie, 2 mg, 4 mg, and 2–4 mg), as stated in the Rexulti (brexpiprazole) prescribing information (https://www.otsuka-us.com/media/static/Rexulti-PI.pdf). The brexpiprazole 0.25 mg/day and 1 mg/day groups, intended to evaluate the lower dose range (and which did not demonstrate efficacy on the primary endpoints[13,14]), were not included in this analysis. The quetiapine XR group from Lighthouse was also excluded because quetiapine XR was used as an active reference for assay sensitivity rather than as an active comparator, and because the objective of the present analysis was to present pooled brexpiprazole data on Marder factors and not to compare directly with other treatments. Within these pooled subgroups, efficacy analyses were performed in the sample of patients who received at least one dose of study medication and had a baseline and at least one post-baseline PANSS Total score assessment. Baseline was defined as the randomization visit (prior to the first dose of study drug).

Changes from baseline in each PANSS Marder factor score and each item score were analyzed using a mixed model for repeated measures (MMRM) analysis, with fixed effect of protocol, trial center within protocol, treatment, visit, treatment–visit interaction, baseline value, and baseline–visit interaction as covariates. Marder factor analyses used an unstructured/Toeplitz/heterogeneous Toeplitz/heterogeneous autoregressive variance–covariance matrix structure, depending on the analysis. Least squares mean differences (LSMDs) were calculated between brexpiprazole and placebo groups, with 95% confidence limits (CLs), *P*-values, and Cohen's *d* effect sizes (ESs).[21]

Maintenance Study. Maintenance study analyses were performed in the sample of patients who entered the randomized phase of the study. Baseline was defined as the first visit of the conversion/stabilization phase; the term 'randomization' was used to describe the first visit of the maintenance phase.

In the stabilization phase, mean changes in PANSS Marder factor and item scores were calculated relative to baseline, using observed cases.

In the maintenance phase, mean changes in PANSS Marder factor and item scores were calculated relative to randomization, using an ANCOVA model with treatment and trial center as factors and baseline value as covariate. A last observation carried forward (LOCF) approach was used, rather than MMRM; MMRM analyses were underpowered at Week 52 because the trial was terminated early based on the positive result of an interim analysis, resulting in a low completion rate.[17] LSMDs were calculated between brexpiprazole and placebo groups, with 95% CLs, *P*-values, and Cohen's *d* ESs.

OLEx Studies. For analyses of the OLEx studies, data were combined from the 6-week short-term studies and

the 52-week OLEx studies, so that a total of up to 58 weeks of brexpiprazole treatment could be investigated. With this treatment duration in mind, the analyses included only the 408 patients in the long-term studies who had previously received brexpiprazole 2–4 mg/day in the short-term studies (ie, patients who previously received placebo or low doses of brexpiprazole were not analyzed).

Baseline was defined as the randomization visit of the short-term studies. Mean changes from baseline in PANSS Marder factor and item scores were summarized using descriptive statistics with observed cases.

Results

Patients

Short-Term Studies. In the short-term studies, 1414 patients were randomized to placebo (n = 531) or brexpiprazole 2–4 mg (n = 883) (figure 1A). Of these patients, 335 (63.1%) in the placebo group and 617 (69.9%) in the brexpiprazole group completed the studies. The most common reasons for discontinuation (≥1% in either treatment group) were adverse events, lack of efficacy, and patient withdrew consent (figure 1A).

Baseline demographic and clinical characteristics were similar between the treatment groups (table 1).

During the short-term studies, concomitant psychotropics were taken by 299/529 patients (56.5%) in the placebo group, and 552/882 (62.6%) in the brexpiprazole group. The most common concomitant psychotropics (taken by >10% of patients) were lorazepam (211 [39.9%], 394 [44.7%]) and zolpidem (48 [9.1%], 110 [12.5%]).

Maintenance Study. In the maintenance study, 202 patients met stability criteria in the stabilization phase and were randomized to placebo (n = 105) or brexpiprazole (n = 97) (figure 1B). The maintenance study was terminated early based on the positive result of an interim analysis. Due primarily to this early termination, only 40 patients (38.1%) in the placebo group and 50 patients (51.5%) in the brexpiprazole group were treated during Week 24 of the maintenance phase. Furthermore, only 9 patients (8.6%) in the placebo group and 14 patients (14.4%) in the brexpiprazole group completed the study; the most common reasons for discontinuation (≥10% in either treatment group) were early termination of the trial by the sponsor and lack of efficacy (impending relapse) (figure 1B).

At randomization, demographic and clinical characteristics were similar between treatment groups (table 1). The clinical characteristics reflect that these patients were stabilized.

The mean daily dose of brexpiprazole during the stabilization phase was 3.4 mg (n = 202), and the mean

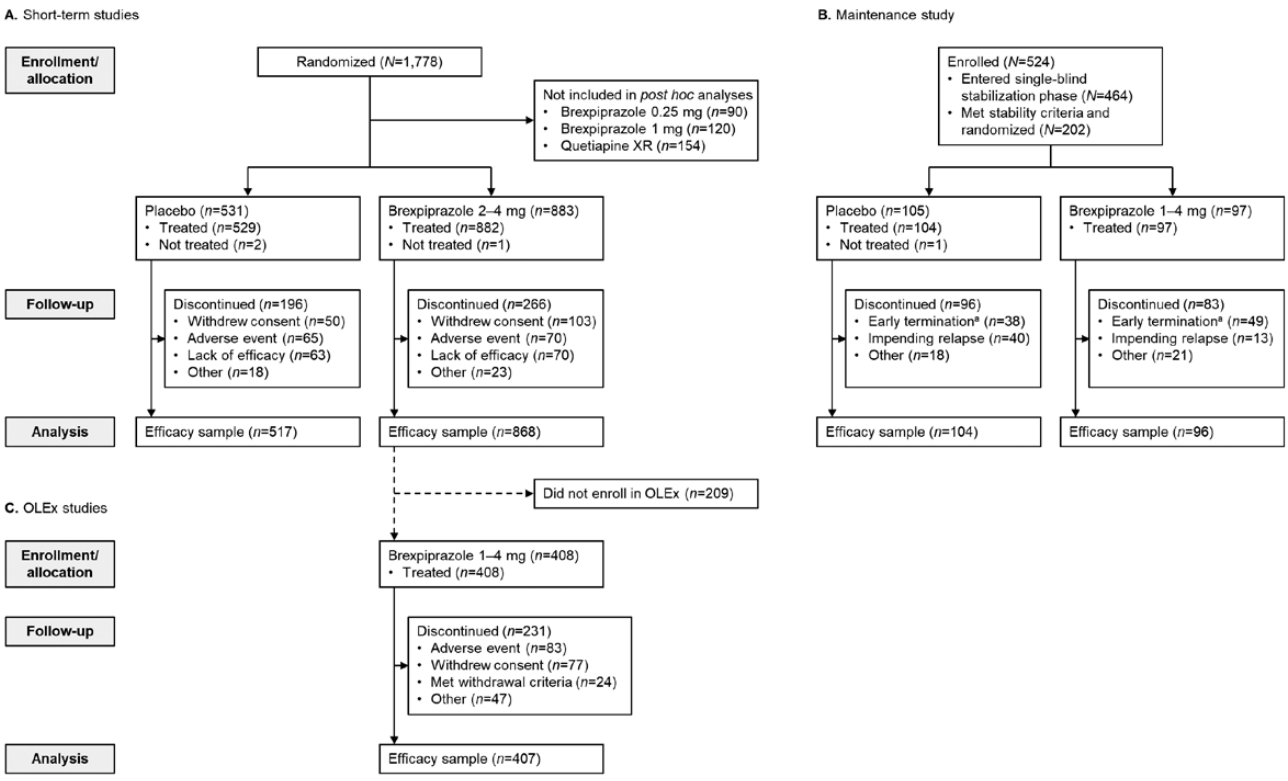

Fig. 1. Patient disposition. [a]Sponsor terminated trial early due to interim analysis. *Note:* Efficacy sample, patients who received at least one dose of study medication and had a baseline and at least one post-baseline PANSS Total score assessment.

Table 1. Baseline Demographic and Clinical Characteristics

	Short-Term Studies (6 wk)		Maintenance Study[a]			OLEx Studies (58 wk)[b]
			Stabilization Phase (12–36 wk)	Maintenance Phase (52 wk)		
	Placebo (n = 531)	Brexpiprazole 2–4 mg (n = 883)	Brexpiprazole 1–4 mg (n = 202)	Placebo (n = 105)	Brexpiprazole 1–4 mg (n = 97)	Brexpiprazole 1–4 mg (n = 408)
Demographic characteristics						
Age (y), mean (SD)	39.8 (10.8)	39.1 (10.9)	40.2 (10.7)	41.6 (10.6)	38.8 (10.7)	38.7 (10.5)
BMI (kg/m^2), mean (SD)	26.5 (5.5)	26.9 (6.1)	28.1 (6.7)	29.1 (6.9) (n = 104)	28.2 (6.7)	26.9 (5.9)
Female, n (%)	209 (39.4)	342 (38.7)	79 (39.1)	40 (38.1)	39 (40.2)	175 (42.9)
White, n (%)	354 (66.7)	575 (65.1)	127 (62.9)	65 (61.9)	62 (63.9)	290 (71.1)
Clinical characteristics						
Age at first diagnosis (y), mean (SD)	26.5 (9.1)	26.4 (8.5)	27.2 (8.2)	27.9 (8.3)	26.5 (8.2)	27.4 (8.6)
Duration of current episode (wk), mean (SD)	2.7 (2.7) (n = 368)	2.5 (2.3) (n = 732)	N/A	N/A	N/A	2.7 (2.7) (n = 344)
PANSS Total score, mean (SD)	96.2 (11.8) (n = 527)	95.9 (12.4) (n = 878)	81.5 (11.9)	58.1 (8.1) (n = 104)	56.5 (8.7)	96.8 (13.2) (n = 407)
Positive symptoms MF	29.6 (4.5)	29.6 (4.5)	24.1 (4.7)	15.8 (3.2)	15.8 (4.0)	29.7 (4.4)
Negative symptoms MF	23.0 (4.9)	22.8 (4.9)	21.0 (4.8)	16.1 (3.7)	15.0 (3.6)	23.2 (5.1)
Disorganized thought MF	22.3 (4.3)	22.2 (4.6)	19.6 (3.7)	14.3 (3.1)	14.5 (3.0)	22.6 (4.6)
Uncontrolled hostility/ excitement MF	9.7 (3.3)	9.7 (3.4)	8.2 (3.0)	5.7 (2.2)	5.6 (1.8)	9.7 (3.3)
Anxiety/depression MF	11.6 (3.0)	11.6 (3.0)	8.6 (3.1)	6.2 (2.5)	5.6 (1.8)	11.5 (3.0)
CGI-S score, mean (SD)	4.9 (0.6) (n = 529)	4.9 (0.6) (n = 882)	4.2 (0.8)	3.1 (0.6) (n = 104)	3.0 (0.6)	4.9 (0.6)

Note: Short-term studies and maintenance study: randomized samples. OLEx studies: sample comprises only those patients in the long-term studies who had previously received brexpiprazole 2–4 mg in the short-term studies (ie, patients who previously received placebo or low doses of brexpiprazole were not analyzed). BMI, body mass index; CGI-S, Clinical Global Impressions – Severity of illness; MF, Marder factor; N/A, not available; OLEx, open-label extension; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.
[a]Stabilization phase values are for baseline of the conversion/stabilization phase; maintenance phase values are for randomization (except age).
[b]Baseline was defined as the randomization visit of the parent study.

average daily dose of brexpiprazole in the maintenance phase was 3.6 mg at patients' last visit (n = 97). During the stabilization phase, 48 patients (23.8%) took a concomitant psychotropic, most commonly, lorazepam (33 [16.3%]). During the maintenance phase, 23 patients (21.9%) in the placebo group and 11 patients (11.3%) in the brexpiprazole group took a concomitant psychotropic, most commonly, lorazepam (15 [14.3%], 5 [5.2%]).

OLEx Studies. The long-term sample comprised 408 patients who rolled over from the short-term studies (figure 1C). Of these patients, 177 (43.4%) completed the studies. The most common reasons for discontinuation (≥10%) were adverse events and that the patient withdrew consent (figure 1C).

Baseline demographic and clinical characteristics are presented in table 1.

Across the duration of the studies, the mean (SD) brexpiprazole dose was 3.0 (0.8) mg/day. Concomitant psychotropics were taken by 168 patients (41.2%); the most common psychotropic was lorazepam (78 [19.1%]).

Efficacy

Short-Term Studies. Brexpiprazole was associated with greater improvement than placebo in each Marder factor score from baseline to Week 6 (figure 2). Least squares (LS) mean differences (95% CLs) vs placebo at Week 6 were: Positive symptoms: −1.55 (−2.30, −0.80), $P < .0001$, ES = 0.27; Negative symptoms: −1.12 (−1.63, −0.61), $P < .0001$, ES = 0.29; Disorganized thought: −1.26 (−1.78, −0.74), $P < .0001$, ES = 0.32; Uncontrolled hostility/excitement: −0.76 (−1.15, −0.37), $P = .0002$, ES = 0.26; and Anxiety/depression: −0.56 (−0.91, −0.22), $P = .0014$, ES = 0.22.

Brexpiprazole was also associated with greater improvement than placebo ($P < .05$) from baseline to Week 6 on 25 out of 30 individual PANSS items (figure 3; supplementary table S1).

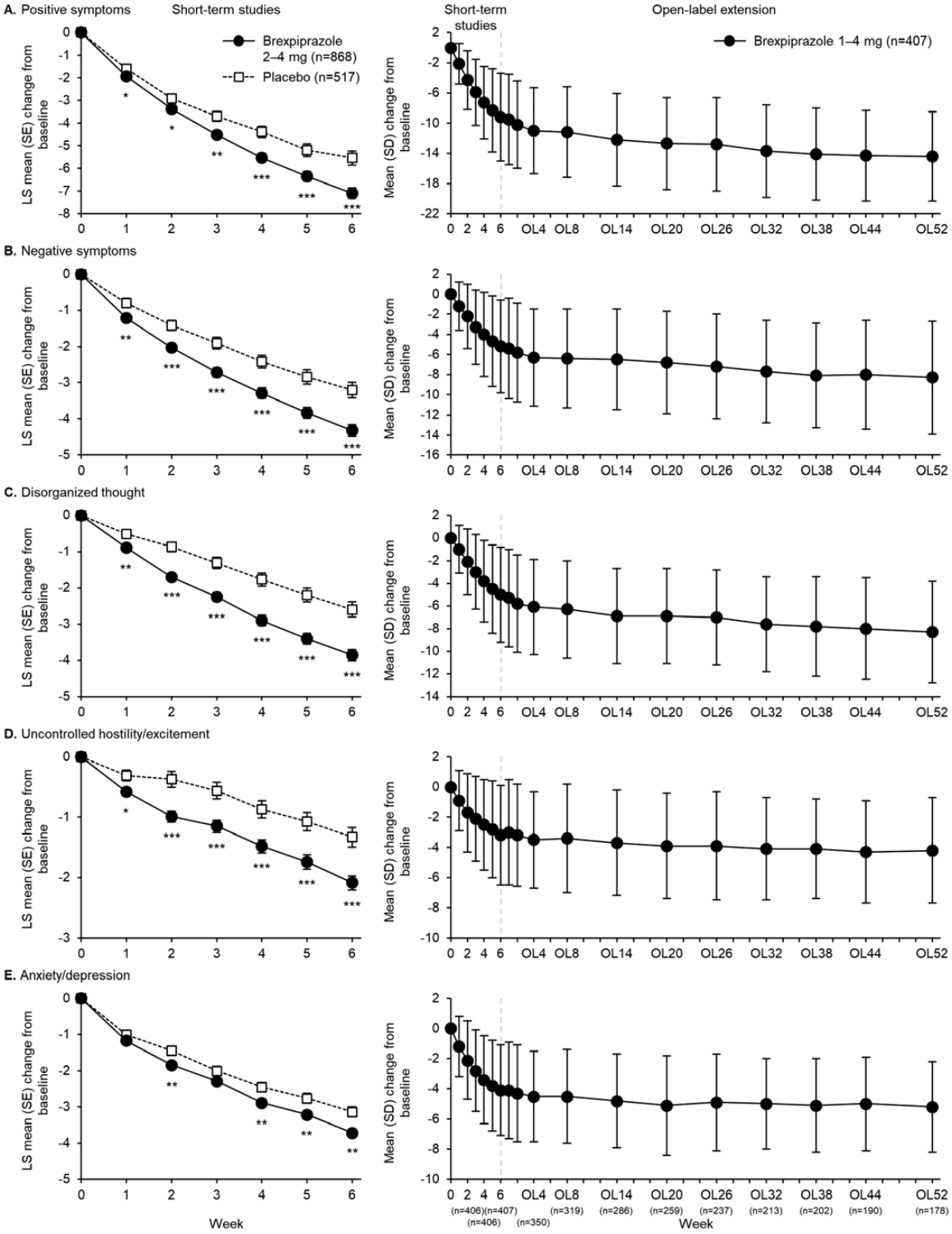

Fig. 2. Short-term and OLEx studies: mean change in PANSS Marder Factor scores from baseline over 6 weeks and over 58 weeks (efficacy sample). *$P < .05$, **$P < .01$, ***$P < .001$ vs placebo, MMRM (short-term); observed cases (long-term). *Note:* LS, least squares; MMRM, mixed model for repeated measures; OL, open-label; OLEx, open-label extension; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SE, standard error.

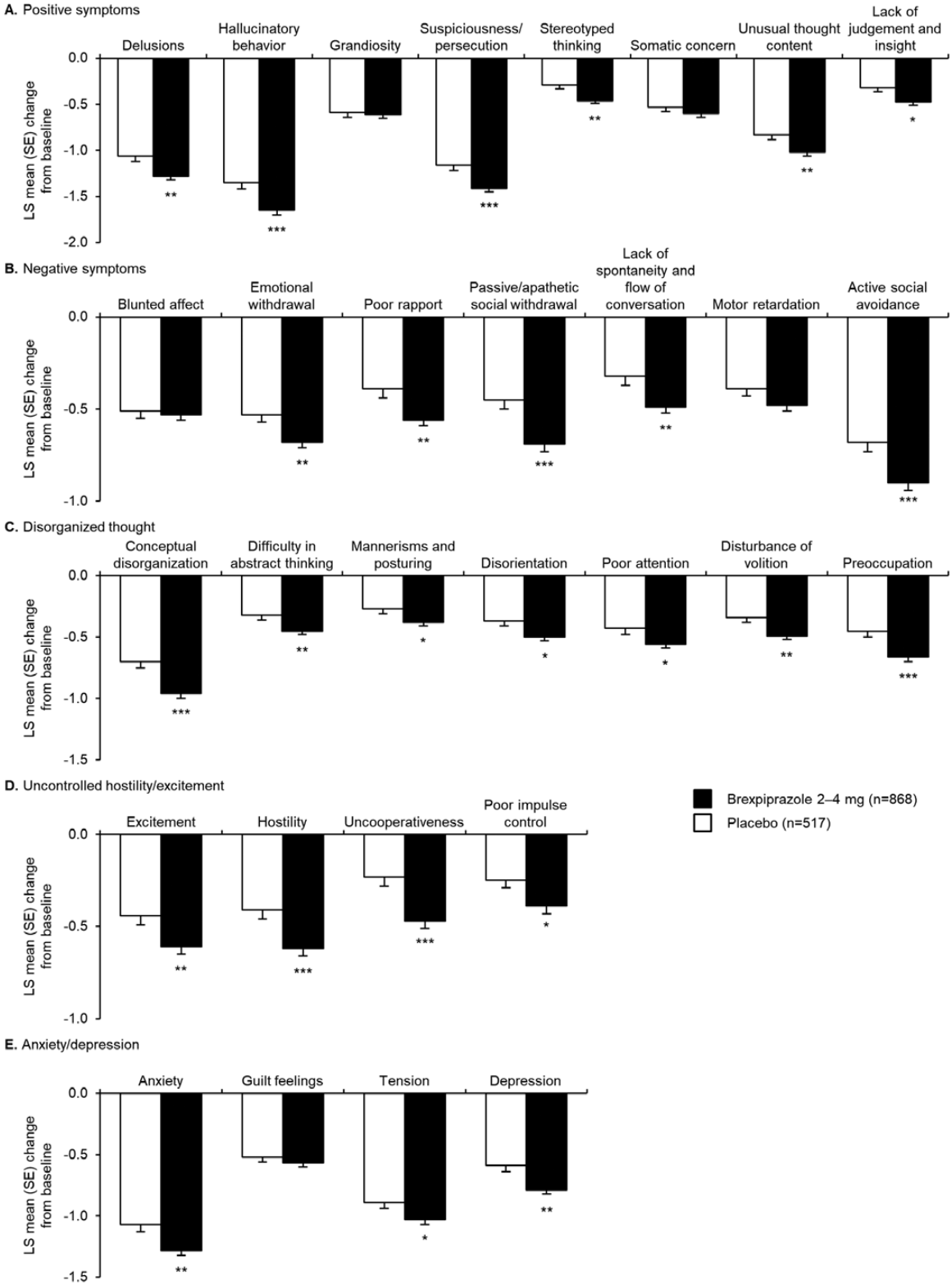

Fig. 3. Short-term studies: mean change in PANSS item scores from baseline to week 6, organized by Marder Factor (efficacy sample). *$P < .05$, **$P < .01$, ***$P < .001$ vs placebo, MMRM. *Note:* LS, least squares; MMRM, mixed model for repeated measures; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

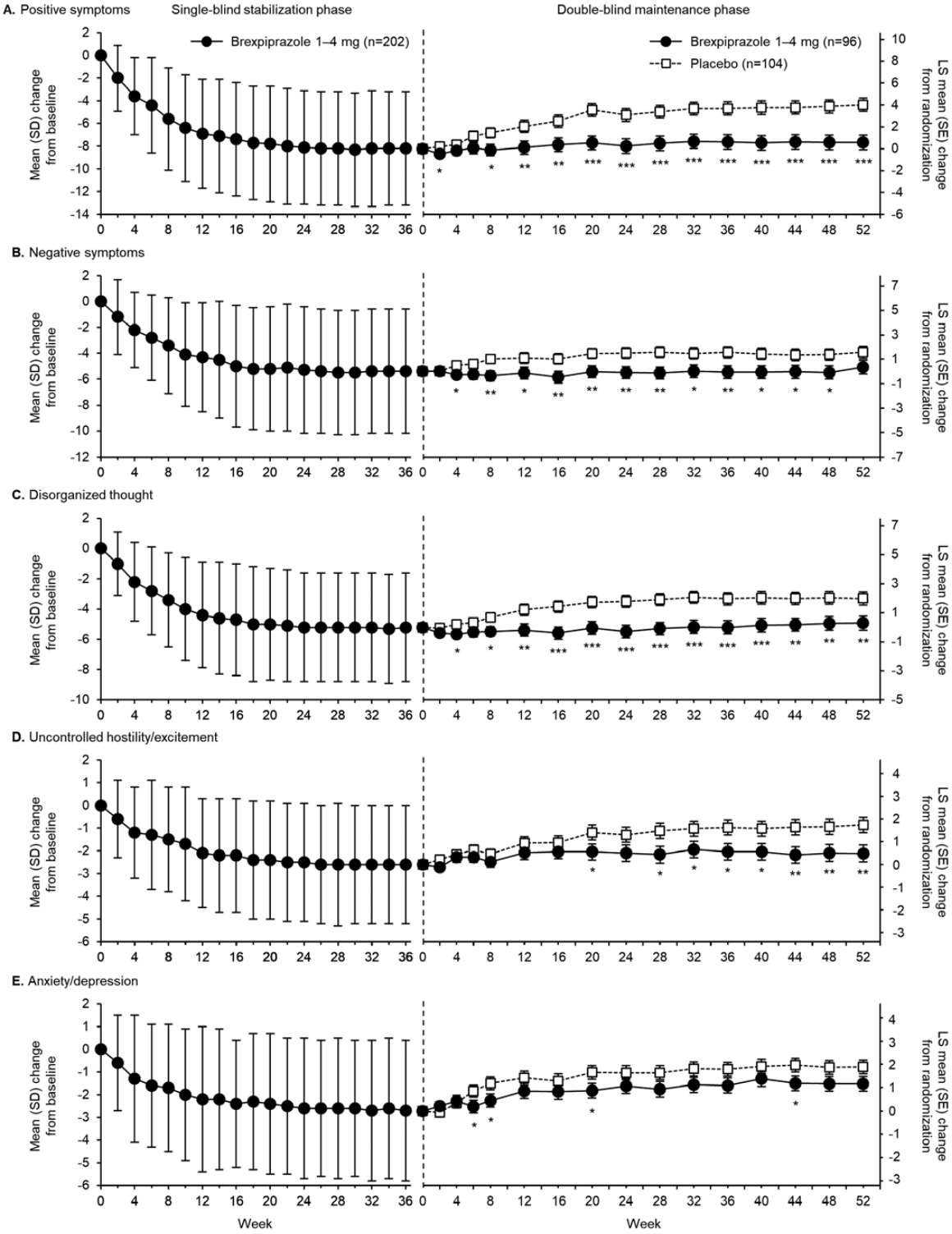

Fig. 4. Maintenance study: mean change in PANSS Marder Factor scores from baseline over 36 weeks in the single-blind stabilization phase and from randomization over 52 weeks in the double-blind maintenance phase (efficacy sample). Observed cases (stabilization phase); *$P < .05$, **$P < .01$, ***$P < .001$ vs placebo, ANCOVA, LOCF (maintenance phase). *Note:* ANCOVA, analysis of covariance; LOCF, last observation carried forward; LS, least squares; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation; SE, standard error.

Maintenance Study. During the stabilization phase, patients receiving brexpiprazole showed improvement in each Marder factor score over the first 20 weeks (approximately), which was maintained to the end of the 36-week phase (figure 4). At the end of the phase, all 30 individual PANSS items had improved from baseline (supplementary table S2).

Across the 52-week double-blind maintenance phase, improvement was generally maintained in the brexpiprazole group, whereas the placebo group worsened (figure 4). LS mean differences (95% CLs) vs placebo at last visit of the 52-week double-blind maintenance phase were: Positive symptoms: −3.44 (−4.99, −1.89), $P < .0001$, ES = 0.62; Negative symptoms: −1.23 (−2.52, 0.07), $P = .063$, ES = 0.27; Disorganized thought: −1.69 (−2.81, −0.56), $P = .0035$, ES = 0.42; Uncontrolled hostility/excitement: −1.26 (−2.12, −0.39), $P = .0046$, ES = 0.41; and Anxiety/depression: −0.72 (−1.47, 0.03), $P = .061$, ES = 0.27.

Brexpiprazole was also associated with a benefit over placebo ($P < .05$) on 17 out of 30 individual PANSS items, in terms of change from randomization to last visit of the 52-week double-blind maintenance phase (supplementary table S2).

OLEx Studies. The change in Marder factor scores over 58 weeks of brexpiprazole treatment is shown in figure 2. Brexpiprazole treatment was associated with improvement on each Marder factor, with the majority of the improvement occurring over the first 10 weeks (approximately).

All 30 individual PANSS items improved from baseline over 58 weeks (supplementary table S3).

Discussion

The successful treatment of schizophrenia entails improvement across a spectrum of symptoms. In this *post hoc* analysis, over 6 weeks, brexpiprazole 2–4 mg showed broad efficacy in acute schizophrenia across all 5 Marder factors: positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression, with small benefits (ES = 0.22–0.32) over placebo. Brexpiprazole also demonstrated efficacy on most individual PANSS items.

In the long-term maintenance study, brexpiprazole showed medium benefits (ES = 0.41–0.62) over placebo at last visit on positive symptoms, disorganized thought, and uncontrolled hostility/excitement. However, only 11.4% of patients completed the 52-week maintenance study (due primarily to early termination by the study sponsor), which limits the interpretation of these data. In contrast, 43.4% of patients completed the 52-week OLEx studies, which is comparable to the completion rates in other 1-year studies of atypical antipsychotics in schizophrenia.[22,23] In the OLEx analysis, the benefits of brexpiprazole on all 5 Marder factors and all individual items were maintained for up to 58 weeks of treatment. Overall, the present analyses suggest that brexpiprazole treats the continuum of schizophrenia symptoms, in the short-term and the long-term.

In other pooled *post hoc* analyses of short-term studies, the atypical antipsychotics aripiprazole, cariprazine, iloperidone, lurasidone and risperidone have shown a benefit vs placebo on all 5 Marder factors (or related 5-factor approaches),[8,24–27] and olanzapine has shown a benefit vs placebo on all factors except for anxiety/depression.[28] Over 6 months, oral cariprazine, risperidone, paliperidone extended-release (ER) and olanzapine have shown improvements on all 5 Marder (or related) factors,[29–32] and, over 1 year, oral asenapine and olanzapine have shown improvements on 3 Marder factors (only 3 were studied).[33] Thus, based on brexpiprazole's OLEx study data, and in the absence of comprehensive long-term data for other agents, brexpiprazole is the only oral antipsychotic that has shown a benefit on all 5 Marder factors over 1 year.

Despite their similar efficacies, atypical antipsychotics differ markedly in terms of their side-effect profiles, which can include akathisia, sedation, weight gain, prolactin elevation, and QTc prolongation.[6] The majority of patients (around 4 out of every 5 in a US nationwide survey) experience at least one bothersome antipsychotic side effect.[34] If not addressed, antipsychotic side effects can have a substantial impact on daily functioning and quality of life.[35] Brexpiprazole is well tolerated in the short- and long-term, with low rates of akathisia, sedation, weight gain, hyperprolactinemia and QTc prolongation.[36]

Strengths of this analysis include the large dataset, the comprehensive approach that considered each individual PANSS item, and that patients were followed for up to 58 weeks in the OLEx studies. The analysis is limited by its *post hoc* nature; the patient selection criteria and restrictions regarding concomitant medications, meaning that the results may not be generalizable to a broader patient population (as with all clinical trials conducted for the purpose of regulatory approval); the fact that only a small number of patients completed the 52-week maintenance study; and that there was no correction for multiple comparisons. Additionally, from this analysis, it is not possible to determine if brexpiprazole has a specific effect on non-positive symptoms, or whether improvement in psychosis during acute treatment leads to secondary improvement in other symptom domains. Further studies should include an active comparator to potentially address this point.

In conclusion, treatment with brexpiprazole in the recommended dose range was associated with clinically relevant improvement in all 5 Marder factors among adults with acute schizophrenia, and with maintenance of this improvement in stabilized schizophrenia, suggesting that brexpiprazole treats the continuum of schizophrenia symptoms in the short- and long-term.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Conflict of Interest

Dr. Marder has received consulting fees from Boehringer-Ingelheim, H. Lundbeck A/S, Otsuka, Takeda, Teva, Roche, Genentech, Targacept, Forum, Abbvie, Allergan, Neurocrine. He has received research support from Boehringer-Ingelheim, Takeda, Neurocrine; Drs. Weiss, Chen and Hobart are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc.; Dr. Meehan and Mr. Hefting are full-time employees of H. Lundbeck A/S.

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