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Efficacy and safety of brexpiprazole in early-episode schizophrenia: post hoc analysis of clinical trials in adults and adolescents

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Introduction

- For patients with schizophrenia, effective treatment of early episodes may improve long-term outcomes, reduce the risk of relapse, and limit functional impairment.¹⁻³
- Brexpiprazole is approved for the treatment of schizophrenia in adults (US, Europe, and other regions) and adolescents (US and other regions).^{a,4,5}
- Therapeutic effects of brexpiprazole in schizophrenia may result from modulation of monoamine systems, including antagonism at noradrenaline $\alpha_{1/2}$ and serotonin 5-HT_{2A} receptors, and partial agonism at serotonin 5-HT_{1A} and dopamine D₂ receptors.^{6,7}

- The aim of this analysis was to evaluate the efficacy and safety of brexpiprazole versus placebo in adults and adolescents with early-episode schizophrenia (age 13-35, and ≤ 5 years' duration of illness), based on data from 6-week trials.

^aBrexpiprazole is approved for the treatment of schizophrenia in adults in Argentina, Australia, Brazil, Canada, Chile, China, the European Union, Guatemala, Hong Kong, Indonesia, Israel, Japan, Kazakhstan, Kuwait, Lebanon, Malaysia, Mexico, Morocco, Myanmar, Nicaragua, the Philippines, Russia, Saudi Arabia, Singapore, South Africa, Switzerland, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates, the United Kingdom, and the United States of America. Brexpiprazole is approved for the treatment of schizophrenia in adolescents in Brazil, the European Union, Israel, Mexico, Singapore, Thailand, United Arab Emirates, and the United States of America.

Methods

Trials

- Data were analyzed from four Phase 3, 6-week trials:
 - Three trials in adults (ClinicalTrials.gov: NCT01396421 [Vector; Trial 231],⁸ NCT01393613 [Beacon; Trial 230],⁹ NCT01810380 [Lighthouse; Trial 14644A]).¹⁰ Participants aged 18-65 were randomized to placebo, brexpiprazole, or quetiapine extended-release (active reference in one trial).
 - One trial in adolescents (NCT03198078 [Trial 234]).¹¹ Participants aged 13-17 were randomized to placebo, brexpiprazole, or aripiprazole (active reference).
- In all trials, the primary efficacy endpoint was change from baseline in Positive and Negative Syndrome Scale (PANSS) Total score.⁸⁻¹¹

Post hoc analyses

- Early-episode schizophrenia was defined as age 13-35, and ≤ 5 years' duration of illness. Each element of the definition has been used previously to reflect early schizophrenia (age ≥ 13 ;¹²⁻¹⁴ age ≤ 35 ;¹⁵⁻¹⁷ ≤ 5 years' duration of illness^{15,18}).
- Data from the four trials were pooled and compared between brexpiprazole 2-4 mg/day (recommended dose range in adults and adolescents)^{4,5} and placebo. Active-reference arms were not analyzed.
- PANSS Total score and Clinical Global Impression – Severity (CGI-S) score were analyzed using least squares (LS) mean change from baseline (mixed model for repeated measures). Clinical Global Impression – Improvement (CGI-I) score was analyzed as LS mean score.
- Safety was evaluated by the incidence of treatment-emergent adverse events (TEAEs), changes in body weight and body mass index (BMI), and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Results

Participants

- In the primary trials, mean baseline PANSS Total scores suggested that the adult and adolescent samples had similar disease severity,⁸⁻¹¹ which supported pooling the trials.
- Figure 1 illustrates the composition of the post hoc analysis sample.
- Table 1 summarizes baseline characteristics of the post hoc sample.

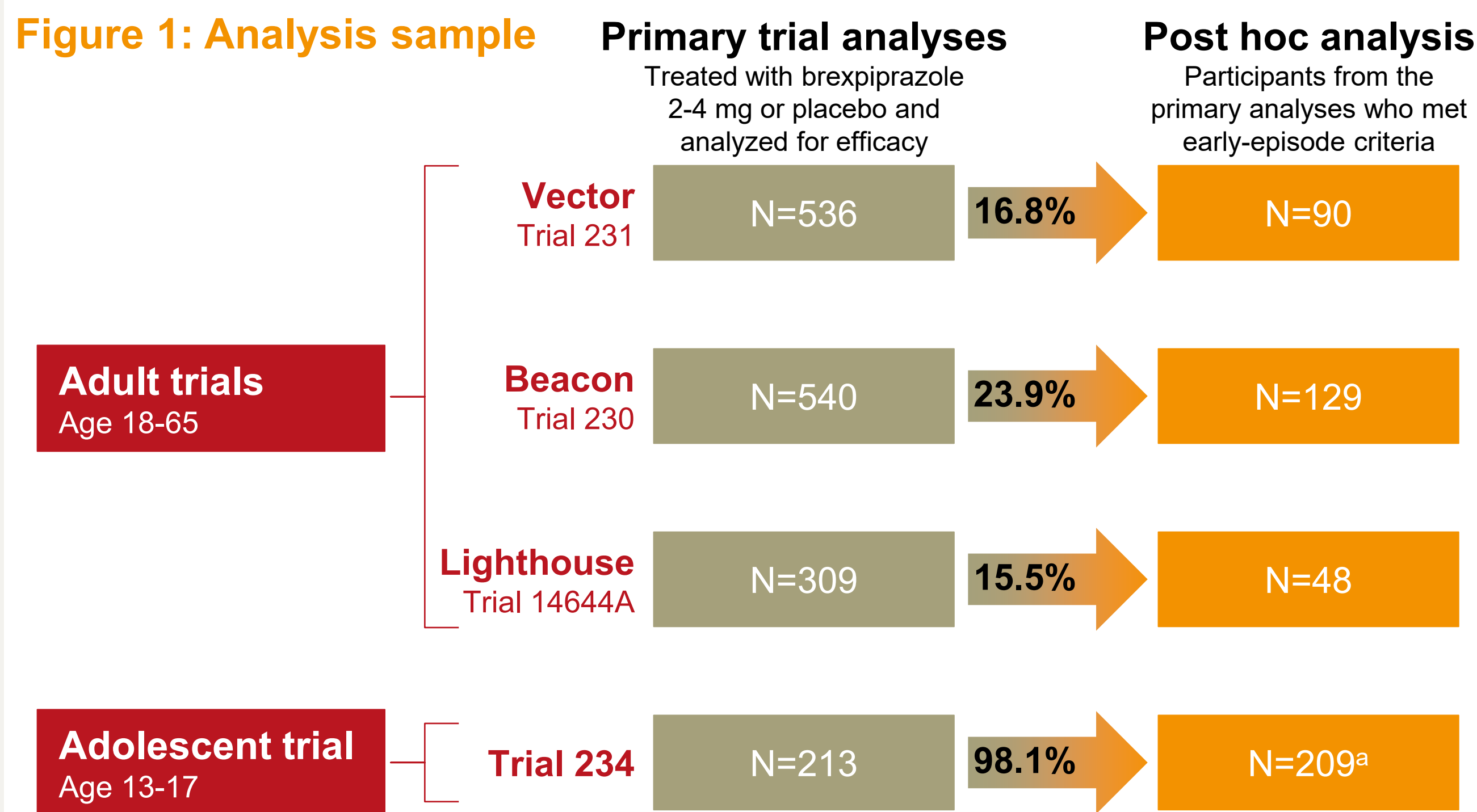


Table 1: Baseline demographic and clinical characteristics

	Brexpiprazole 2-4 mg (n=289)	Placebo (n=187)
Demographic characteristics		
Age (years)	22.4 (6.6)	20.5 (6.6)
BMI (kg/m ²)	24.3 (5.0)	24.3 (5.3)
Sex, n (%)		
Female	110 (38.1)	71 (38.0)
Male	179 (61.9)	116 (62.0)
Race, n (%)		
Alaska Native or Pacific Islander	4 (1.4)	4 (2.1)
Asian	13 (4.5)	8 (4.3)
Black or African American	34 (11.8)	21 (11.2)
White	194 (67.1)	123 (65.8)
Other	44 (15.2)	30 (16.0)
Data not available	0 (0.0)	1 (0.5)
Clinical characteristics		
Age at first diagnosis (years)	20.2 (6.0)	18.6 (5.9)
Duration of current episode (weeks)	21.0 (36.4)	25.7 (36.7)
PANSS Total score	97.9 (13.5)	100.4 (14.2)
CGI-S score	4.8 (0.6) ^a	4.8 (0.7)

Efficacy sample; data are mean (SD), unless otherwise stated; ^an=288
BMI=body mass index; CGI-S=Clinical Global Impression – Severity; PANSS=Positive and Negative Syndrome Scale; SD=standard deviation

Efficacy

- PANSS Total**: change from baseline is shown in Figure 2.
- CGI-S**: LS mean (standard error [SE]) change from baseline to Week 6:
 - Brexpiprazole: –1.08 (0.06)
 - Placebo: –0.92 (0.07)
 - LS mean difference: –0.16; $P=0.09$
- CGI-I**: LS mean (SE) score at Week 6:
 - Brexpiprazole: 2.64 (0.06)
 - Placebo: 2.85 (0.07)
 - LS mean difference: –0.21; $P=0.02$

Safety

- A summary of safety outcomes is shown in Table 2.

Figure 2: Change from baseline in PANSS Total score

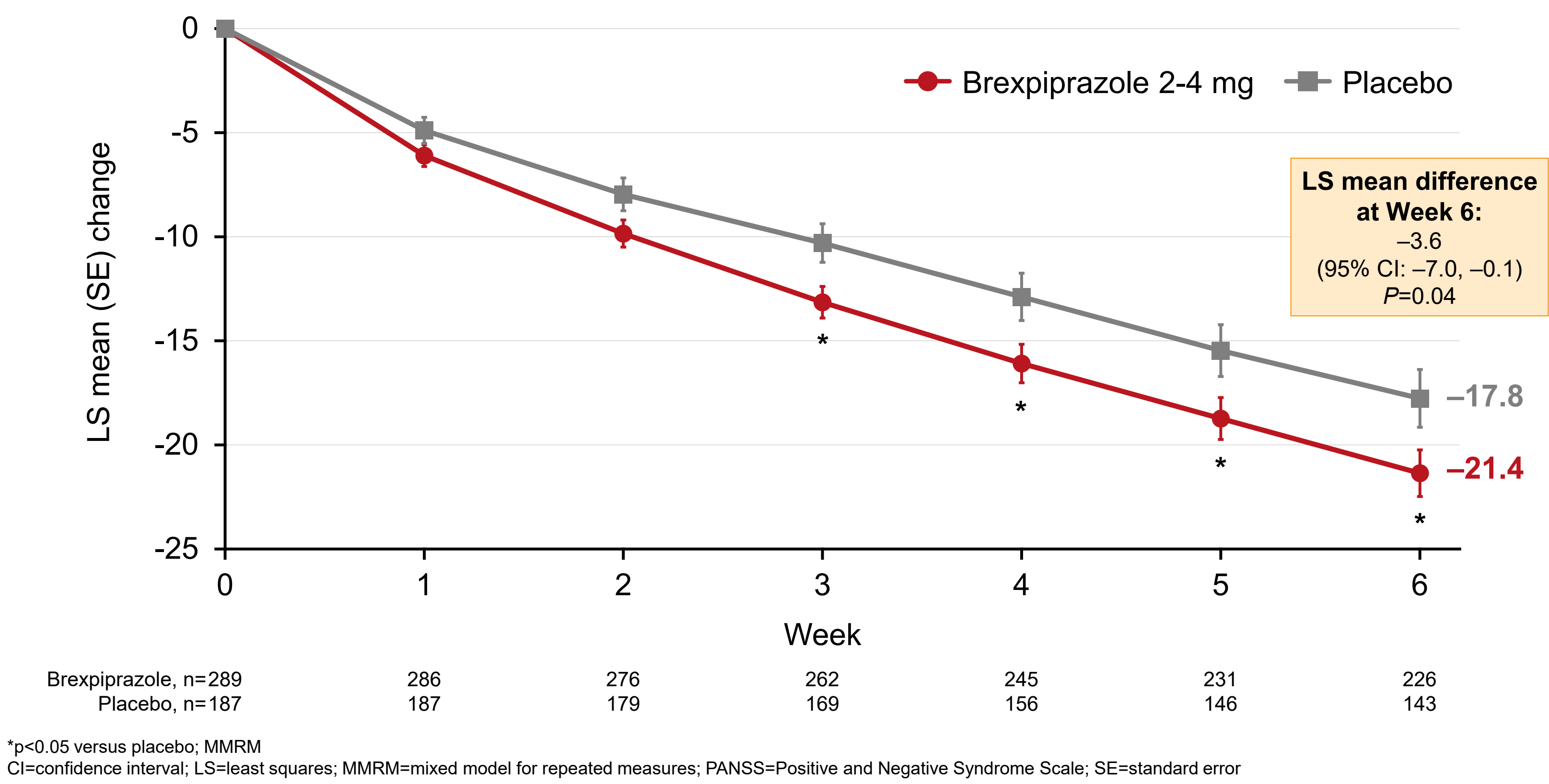


Table 2: Summary of safety outcomes

	Brexpiprazole 2-4 mg (n=292)	Placebo (n=190)
Incidence of TEAEs, n (%)		
At least one TEAE	148 (50.7)	88 (46.3)
Discontinuation due to TEAE	25 (8.6)	14 (7.4)
Most common TEAEs with brexpiprazole (incidence $\geq 2\%$ in the brexpiprazole group and greater than placebo)		
Akathisia	19 (6.5)	4 (2.1)
Somnolence	12 (4.1)	7 (3.7)
Tremor	10 (3.4)	0 (0.0)
Psychotic disorder	7 (2.4)	2 (1.1)
Other safety outcomes		
Body weight: Percentage change from baseline to Week 6, mean (SD)	1.8 (4.3)	0.1 (3.2)
Body weight: $\geq 7\%$ increase from baseline at any time post-baseline, n/N (%)	21/286 (7.3)	7/184 (3.8)
BMI: Change from baseline to Week 6, mean (SD)	0.4 (1.0)	0.0 (0.8)
C-SSRS: Suicidality at any time post-baseline, n (%)	6 (2.1)	7 (3.7)

Safety sample
BMI=body mass index; C-SSRS=Columbia-Suicide Severity Rating Scale; SD=standard deviation; TEAE=treatment-emergent adverse event

Conclusions

- In this post hoc analysis of patients with early-episode schizophrenia, brexpiprazole was associated with greater improvement in schizophrenia symptoms than placebo.
- Safety analyses were consistent with the known safety profile of brexpiprazole.

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