Request for Copy of Published Material

Enclosure:

- POSTER: Correll C, Pflug B, Zhang Z et al. Presented at 33rd European Congress of Psychiatry (EPA), April 5-8, 2025, Madrid, Spain

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

Christoph U. Correll,[1-3] Brian Pflug,[4] Zhen Zhang,[4] Anton M. Palma,[4] Pedro Such[5]

1. The Zucker Hillside Hospital, Department of Psychiatry, Glen Oaks, NY, USA; 2. The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine, Hempstead, NY, USA;
3. Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Child and Adolescent Psychiatry, Berlin, Germany;
4. Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA; 5. H. Lundbeck A/S, Valby, Copenhagen, Denmark

EPV1766

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 D_2 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.**

[a]Brexpiprazole 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

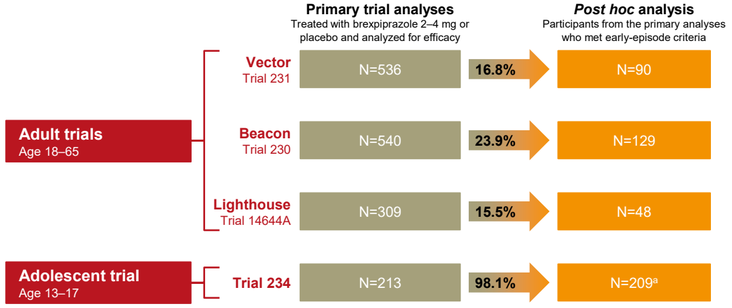
- Early-episode schizophrenia was defined as age 13–35, and ≤5 years' duration of illness. Each element of the definition has been used previously to reflect early schizophrenia (age ≥13;[12-14] age ≤35;[15-17] ≤5 years' duration of illness[15,18]).
- Data from the four trials were pooled and compared 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.

Figure 1: Analysis sample



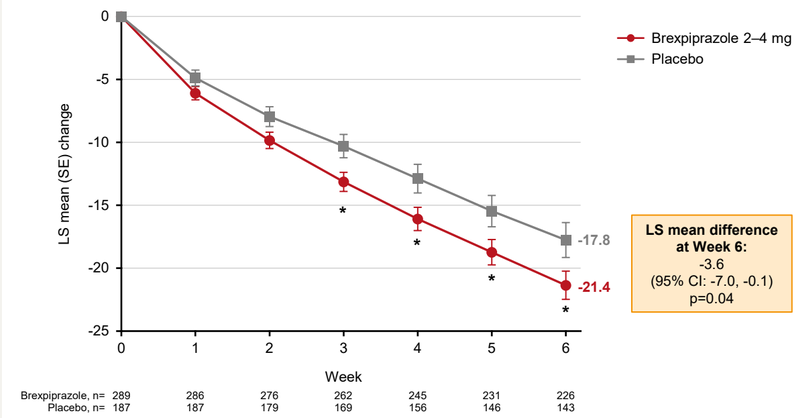
Efficacy samples; [a]four participants from adolescent Trial 234 had >5 years' duration of illness, and are therefore not included in the present *post hoc* analysis

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; [a]n=288
BMI=body mass index; CGI-S=Clinical Global Impression – Severity; PANSS=Positive and Negative Syndrome Scale; SD=standard deviation

Figure 2: Change from baseline in PANSS Total score



[a]p<0.05 versus placebo; MMRM
CI=confidence interval; LS=least squares; MMRM=mixed model for repeated measures; PANSS=Positive and Negative Syndrome Scale; SE=standard error

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 ≥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: ≥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

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.

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.**

References

1. Perkins et al. Am J Psychiatry 2005; 162 (10): 1785–1804.
2. Robinson et al. Arch Gen Psychiatry 1999; 56 (3): 241–247.
3. Salimi et al. CNS Drugs 2009; 23 (10): 837–855.
4. Rexulti® (brexpiprazole). Prescribing information. Otsuka Pharmaceutical Co. Ltd., May 2024.
5. Rxulti® (brexpiprazole). Summary of product characteristics. Otsuka Pharmaceutical Netherlands B.V., June 2023.
6. Maeda et al. J Pharmacol Exp Ther 2014; 350 (3): 589–604.
7. Jain et al. J Clin Psychiatry 2024; 85 (4): plunaro2417ah.
8. Correll et al. Am J Psychiatry 2015; 172 (9): 870–880.
9. Kane et al. Schizophr Res 2015; 164 (1–3): 127–135.
10. Marder et al. Acta Neuropsychiatr 2017; 29 (5): 278–290.
11. Ward et al. Oral presentation at the Schizophrenia International Research Society (SIRS) Annual Meeting; 3–7 April 2024; Italy.
12. Findling et al. J Child Adolesc Psychopharmacol 2012; 22 (5): 327–342.
13. Findling et al. J Child Adolesc Psychopharmacol 2013; 23 (8): 531–544.
14. Kryzhanovskaya et al. J Am Acad Child Adolesc Psychiatry 2009; 48 (1): 60–70.
15. Malla et al. Int Clin Psychopharmacol 2016; 31 (6): 307–314.
16. Naber et al. Schizophr Res 2015; 168 (1–2): 498–504.
17. Ferrara et al. Psychiatry Res 2024; 339: 116034.
18. Newton et al. NPJ Schizophr 2018; 4 (1): 21.

The abstract for this poster reports: "The TEAE with the highest incidence in the brexpiprazole group was akathisia (6.5%; placebo, 2.1%)." The sentence contains an inaccuracy, and is corrected as follows: "The TEAE with the highest incidence in the brexpiprazole group, and with a higher incidence than placebo, was akathisia (6.5%; placebo, 2.1%)."

Acknowledgements

This work was supported by Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Copenhagen, Denmark).

Medical writing support was provided by Liz Kelly, BSc, and colleagues of Cambridge (a division of Prime, Knutsford, UK), funded by Otsuka Pharmaceutical Development & Commercialization Inc. (Princeton, NJ, USA) and H. Lundbeck A/S (Valby, Copenhagen, Denmark).

Disclosures

Christoph U. Correll: shareholder: Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, and Quantic, Terran; grant/research support: Boehringer-Ingelheim, Janssen, Takeda; consultant: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Tolmar, Vertex, Viatris, and Xenon Pharmaceuticals; Speakers bureau: AbbVie, Angelini, Aristo, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cerevel, Darnitsa, Gedeon Richter, Hikma, IntraCellular Therapies, Janssen/J&J, Karuna, Lundbeck, Mitsubishi Tanabe Pharma, Mylan, Otsuka, Recordati, Seqirus, Sunovion, Tabuk, Takeda, Viatris.
Brian Pflug, Zhen Zhang and Anton M. Palma are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc.
Pedro Such is a full-time employee of H. Lundbeck A/S.