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Enclosure:

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Effects of adjunctive brexpiprazole on depression and life engagement in patients with noradrenaline-mediated symptoms

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Introduction

- Noradrenaline (norepinephrine) hypoactivity may drive aspects of major depressive disorder (MDD) such as poor concentration, decreased energy, and cognitive slowing.[1]
- These symptoms overlap with the patient life engagement framework. Patient life engagement is a broad term describing positive aspects relating to cognition, vitality, motivation and reward, and the ability to feel pleasure, and the framework comprises emotional, physical, social, and cognitive domains.[2,3] Thus, noradrenaline could be implicated in patient life engagement.
- Brexpiprazole is an atypical antipsychotic with high affinity for serotonin, dopamine, and noradrenaline receptors, including antagonism at α_{1B} and α_{2C} adrenoceptors, which may modulate symptoms caused by noradrenaline system dysregulation.[4,5]
- In clinical trials and post hoc analyses, brexpiprazole adjunct to antidepressant treatment (ADT) improved depressive symptoms, patient life engagement (measured using the 10-item Inventory of Depressive Symptomatology Self-Report [IDS-SR$_{10}$] Life Engagement subscale), and functioning, and was generally well tolerated.[6-10]
- This post hoc analysis aimed to determine the effects of adjunctive brexpiprazole on depressive symptoms, patient life engagement, and functioning in patients with noradrenaline-mediated symptoms.

Methods

Trial designs and participants

- Data were pooled from three Phase 3 randomized, double-blind, fixed-dose, placebo-controlled studies of adjunctive brexpiprazole in MDD: Pyxis (ClinicalTrials.gov identifier: NCT01360645),[6] Polaris (NCT01360632),[7] and Sirius (NCT02196506).[8]
- The trials enrolled adults with MDD, a current depressive episode of ≥8 weeks in duration, a 17-item Hamilton Depression Rating Scale (HAM-D$_{17}$) Total score of ≥18, and inadequate response to 1-3 prior ADTs during the current episode.[6-8]
- After screening, participants received 8 weeks of prospective treatment with a different open-label ADT + single-blind placebo.[6-8] Participants with inadequate response to open-label ADT were randomly allocated to adjunctive brexpiprazole (fixed-dose 1, 2, or 3 mg/day, depending on the trial) or adjunctive placebo for 6 weeks.[6-8]
- The primary endpoint of each trial was change from baseline (randomization) to Week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) Total score.[6-8]

Selection of noradrenaline-mediated symptoms

- For this post hoc analysis, the authors identified items from the IDS-SR$_{10}$ that are primarily driven by noradrenaline pathways. The selection was guided by outputs from a consensus panel on the role of noradrenaline dysregulation in different disorders, including MDD.[1]
- Four items were selected: “concentration/decision making”, “general interest”, “energy level”, and “feeling slowed down” (Table 1).
- The remaining six IDS-SR$_{10}$ items may have some level of noradrenaline involvement, but were thought to be primarily driven by other neurotransmitters.

Table 1: IDS-SR$_{10}$ items primarily driven by the noradrenaline pathway

IDS-SR$_{10}$ item	Item score descriptors[11] (0 / 1 / 2 / 3)				Link to noradrenaline
Concentration/ decision making	There is no change in my usual capacity to concentrate or make decisions	I occasionally feel indecisive or find that my attention wanders	Most of the time, I struggle to focus my attention or to make decisions	I cannot concentrate well enough to read or cannot make even minor decisions	• Hypoactive noradrenaline signaling may lead to poor concentration[1] • α_2-adrenergic receptor agonism can increase decisiveness[12]
General interest	There is no change from usual in how interested I am in other people or activities	I notice that I am less interested in people or activities	I find I have interest in only one or two of my formerly pursued activities	I have virtually no interest in formerly pursued activities	• Hypoactive noradrenaline signaling may lead to apathy[1] • Noradrenaline is linked to motivational salience[13]
Energy level	There is no change in my usual level of energy	I get tired more easily than usual	I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work)	I really cannot carry out most of my usual daily activities because I just don’t have the energy	• Hypoactive noradrenaline signaling may lead to fatigue, lassitude, and decreased energy[1]
Feeling slowed down	I think, speak, and move at my usual rate of speed	I find that my thinking is slowed down or my voice sounds dull or flat	It takes me several seconds to respond to most questions and I’m sure my thinking is slowed	I am often unable to respond to questions without extreme effort	• Hypoactive noradrenaline signaling may lead to cognitive slowing[1]

Presence of noradrenaline-mediated symptoms at baseline was defined as a score ≥1 on all four of the selected IDS-SR$_{10}$ items; “noradrenaline-mediated symptoms” refers to a post hoc grouping of IDS-SR$_{10}$ items, not a validated diagnostic construct. IDS-SR$_{10}$, 10-item Inventory of Depressive Symptomatology Self-Report Life Engagement subscale

Data analysis

- Participants with noradrenaline-mediated symptoms at baseline, defined as a score ≥1 on all four of the selected IDS-SR$_{10}$ items, were analyzed.
- The following efficacy outcomes were evaluated for ADT + brexpiprazole 2-3 mg/day (recommended-to-maximum dose for MDD in the United States)[14] versus ADT + placebo using a mixed model for repeated measures approach: MADRS Total score (depressive symptoms); IDS-SR$_{10}$ score (patient life engagement); Sheehan Disability Scale (SDS) Mean score (functioning); IDS-SR Total score (depressive symptoms); “Concentration/decision making”, “general interest”, “energy level”, and “feeling slowed down” item scores.
- Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs).

Results

Participants

- Of 1162 trial participants, 839 (72.2%) had baseline scores ≥1 for all four noradrenaline-mediated items and were analyzed (ADT + brexpiprazole, n=414; ADT + placebo, n=425).
- Trial completion rates were 392 of 414 (94.7%) for ADT + brexpiprazole, and 406 of 425 (95.5%) for ADT + placebo.
- Baseline characteristics were similar between treatment groups (Table 2).

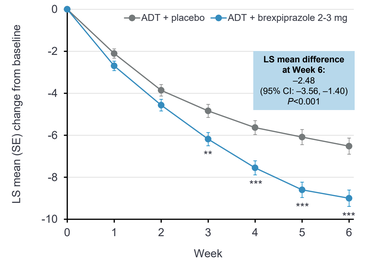
Efficacy

- ADT + brexpiprazole showed greater improvement (P<0.05) than ADT + placebo in:
  - MADRS Total score (depressive symptoms) from Week 3 onwards (Figure 1)
  - IDS-SR$_{10}$ score (patient life engagement) from Week 1 onwards (Figure 2)
  - SDS score (functioning) from Week 3 (first post-baseline measurement) onwards (Figure 3)
  - IDS-SR Total score (depressive symptoms) from Week 4 onwards
- The four noradrenaline-mediated symptoms showed numerically greater improvement with ADT + brexpiprazole versus ADT + placebo at Week 6.

Safety

- The overall incidence of TEAEs was 250 of 414 (60.4%) in the brexpiprazole 2-3 mg/day group, and 202 of 425 (47.5%) in the placebo group.
- TEAEs reported by ≥5% of participants in either treatment group were akathisia (ADT + brexpiprazole, 10.1%; ADT + placebo, 3.8%), weight increase (6.3%, 1.6%), restlessness (5.8%, 0.7%), somnolence (5.6%, 1.4%), and headache (4.1%, 7.3%).

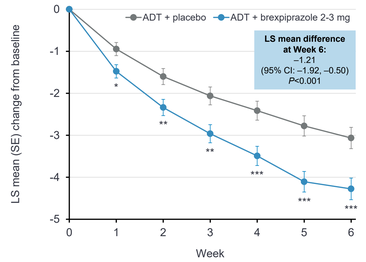
Figure 1: Change in MADRS Total score (depressive symptoms)



ADT + placebo, n=	425	419	415	414	410	405	404
ADT + brexpiprazole, n=	414	407	409	403	399	390	392

**P<0.01, ***P<0.001 versus ADT + placebo
Mean (SD) MADRS Total score at baseline: ADT + placebo, 27.3 (5.7); ADT + brexpiprazole, 27.2 (5.7)
ADT, antidepressant treatment; LS, least squares; MADRS, Montgomery–Asberg Depression Rating Scale; SD, standard deviation; SE, standard error

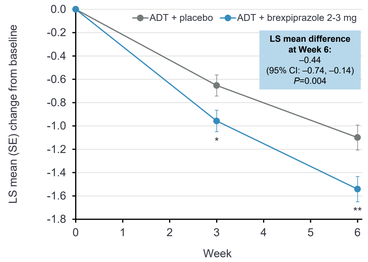
Figure 2: Change in IDS-SR$_{10}$ Life Engagement score (patient life engagement)



ADT + placebo, n=	425	419	415	413	409	405	404
ADT + brexpiprazole, n=	414	406	409	402	399	389	392

*P<0.05, **P<0.01, ***P<0.001 versus ADT + placebo
Mean (SD) IDS-SR$_{10}$ score at baseline: ADT + placebo, 16.8 (4.7); ADT + brexpiprazole, 17.1 (4.6)
ADT, antidepressant treatment; IDS-SR$_{10}$, 10-item Inventory of Depressive Symptomatology Self-Report Life Engagement subscale; LS, least squares; SD, standard deviation; SE, standard error

Figure 3: Change in SDS Mean score (functioning)



ADT + placebo, n=	413					405	397
ADT + brexpiprazole, n=	401					394	387

*P<0.05, **P<0.01 versus ADT + placebo
Mean (SD) SDS score at baseline: ADT + placebo, 6.2 (2.0); ADT + brexpiprazole, 6.3 (2.0)
ADT, antidepressant treatment; LS, least squares; SD, standard deviation; SDS, Sheehan Disability Scale; SE, standard error

Table 2: Baseline demographic and clinical characteristics

	ADT + brexpiprazole 2-3 mg (n=414)	ADT + placebo (n=425)
Demographic characteristics		
Age, years	44.4 (11.3)	45.1 (11.7)
Female, n (%)	291 (70.3)	291 (68.5)
White, n (%)	358 (86.5)	365 (85.9)
BMI, kg/m^2	29.4 (6.8)	29.3 (6.9)

	ADT + brexpiprazole 2-3 mg (n=414)	ADT + placebo (n=425)
Clinical characteristics		
Duration of current episode, months	13.9 (17.8)	15.4 (33.6)
Number of lifetime episodes	1.9 (0.3)	1.8 (0.4)
MADRS Total score	27.2 (5.7)	27.3 (5.7)
IDS-SR$_{10}$ Life Engagement score	17.1 (4.6)	16.8 (4.7)
SDS Mean score	6.3 (2.0) [n=410]	6.2 (2.0) [n=420]
IDS-SR Total score	39.1 (10.0)	38.1 (9.8)

Data are mean (SD), unless otherwise stated. ADT, antidepressant treatment; BMI, body mass index; IDS-SR, Inventory of Depressive Symptomatology Self-Report; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation; SDS, Sheehan Disability Scale

Conclusions

- **In patients with MDD with noradrenaline-mediated symptoms, adjunctive brexpiprazole 2-3 mg/day was associated with greater improvement in depressive symptoms, patient life engagement, and functioning versus adjunctive placebo.**
- **Improvements in patient life engagement with adjunctive brexpiprazole versus adjunctive placebo were observed from Week 1 onwards.**
- **The safety profile of brexpiprazole in patients with MDD with noradrenaline-mediated symptoms was consistent with that observed in the Phase 3 trials.[6-8]**

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Key contributors

Roger S. McIntyre, Ahmad Abdrabboh, and Ferhat Ardic developed the concept for this analysis. Zhen Zhang analyzed the data. All authors were involved in data interpretation, and reviewed and approved the content for poster presentation.

Study registration number

ClinicalTrials.gov identifier: NCT01360645, NCT01360632, NCT02196506.

Disclosures

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