Supplementary Material

List of Supplementary Material for the article

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Supplementary Table 1. Phase 3 Clinical Studies of Brexpiprazole in the Adjunctive Treatment of Adults with MDD

Study Name (ClinicalTrials.gov Identifier)	Design	Criteria for Inadequate Response to ADT	Dosing	Number of Patients (Safety Population)	
				ADT + Placebo	ADT + Brexpiprazole
Pyxis (NCT01360645)[1]	8-week, single-blind, prospective phase followed by 6-week, randomized, double-blind, placebo-controlled phase	HAM-D$_{17}$ Total score: <50% reduction from the start to the end of prospective treatment; ≥14 at the end of prospective treatment	2 mg (fixed)	191	188
Polaris (NCT01360632)[2]		CGI-I score: ≥3 at the end of prospective treatment	1 mg, 3 mg (fixed)	220	455
Sirius (NCT02196506)[3]		HAM-D$_{17}$ Total score: <50% reduction from the start to the end of prospective treatment; ≥14 at the end of prospective treatment	2 mg (fixed)	202	192
		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			
Delphinus (NCT01727726)[4]	8- or 10-week, double-blind, prospective phase followed by 6-week, randomized, double-blind, placebo-controlled, active-referenced (quetiapine XR) phase	MADRS Total score: <50% reduction from the start to Weeks 2, 4, 6, and 8[a] of prospective treatment; ≥18 at the end of prospective treatment	2–3 mg (flexible)	206	197
		CGI-I score: ≥3 at Weeks 2, 4, 6, and 8[a] of prospective treatment			
Orion (NCT01360866)[5]	52-week (amended to 26 weeks), open-label extension	Not applicable (enrolled patients who completed Pyxis, Polaris and Delphinus, including those patients who responded to prospective ADT)	0.5–3 mg (flexible)	Not applicable	2,938

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

Abbreviations: ADT=antidepressant treatment; CGI-I=Clinical Global Impressions – Improvement; HAM-D$_{17}$=17-item Hamilton Depression Rating Scale; MADRS=Montgomery–Åsberg Depression Rating Scale; MDD=major depressive disorder; XR=extended release.

References

1. Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a Phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015;76(9):1224–1231.

2. Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a Phase 3, randomized, double-blind study. J Clin Psychiatry. 2015;76(9):1232–1240.

3. Hobart M, Skuban A, Zhang P, et al. A randomized, placebo-controlled study of the efficacy and safety of fixed-dose brexpiprazole 2 mg/d as adjunctive treatment of adults with major depressive disorder. J Clin Psychiatry. 2018;79(4):17m12058.

4. Hobart M, Skuban A, Zhang P, et al. Efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of major depressive disorder: a randomized, active-referenced, placebo-controlled study. Curr Med Res Opin. 2018;34(4):633–642.

5. Hobart M, Zhang P, Skuban A, et al. A long-term, open-label study to evaluate the safety and tolerability of brexpiprazole as adjunctive therapy in adults with major depressive disorder. J Clin Psychopharmacol. 2019;39(3):203–209.

Supplementary Table 2. Incidence of Treatment-Emergent Shifts in Fasting Total Cholesterol[a] from Baseline to Any Post-Baseline Visit in the Short-Term, Fixed-Dose Studies[b]

n/N (%)	ADT + Placebo	ADT + Brexpiprazole		
		1 mg	2 mg	3 mg
High to normal	7/110 (6.4)	3/41 (7.3)	2/80 (2.5)	8/49 (16.3)
Borderline to normal	68/204 (33.3)	25/83 (30.1)	25/101 (24.8)	21/57 (36.8)
High to borderline	40/110 (36.4)	19/41 (46.3)	25/80 (31.3)	25/49 (51.0)
Normal to borderline	68/230 (29.6)	20/80 (25.0)	41/145 (28.3)	29/101 (28.7)
Borderline to high	47/204 (23.0)	31/83 (37.3)	24/101 (23.8)	19/57 (33.3)
Normal to high	7/230 (3.0)	3/80 (3.8)	3/145 (2.1)	2/101 (2.0)

[a]Normal: <200 mg/dL; borderline: ≥200 to <240 mg/dL; high: ≥240 mg/dL.

[b]Pooled data from Pyxis, Polaris, and Sirius.

Abbreviations: ADT=antidepressant treatment; n/N=number of patients with metabolic shift/total number of patients in category at baseline who had a post-baseline result for the given test.

Supplementary Table 3. Incidence of Treatment-Emergent Shifts in Fasting LDL Cholesterol[a] from Baseline to Any Post-Baseline Visit in the Short-Term, Fixed-Dose Studies[b]

n/N (%)	ADT + Placebo	ADT + Brexpiprazole		
		1 mg	2 mg	3 mg
High to normal	0/74 (0.0)	1/33 (3.0)	1/53 (1.9)	1/39 (2.6)
Borderline to normal	65/311 (20.9)	28/120 (23.3)	33/171 (19.3)	26/98 (26.5)
High to borderline	21/74 (28.4)	18/33 (54.5)	20/53 (37.7)	26/39 (66.7)
Normal to borderline	59/144 (41.0)	19/44 (43.2)	27/93 (29.0)	28/69 (40.6)
Borderline to high	44/311 (14.1)	19/120 (15.8)	21/171 (12.3)	22/98 (22.4)
Normal to high	0/144 (0.0)	0/44 (0.0)	0/93 (0.0)	0/69 (0.0)

[a]Normal: <100 mg/dL; borderline: ≥100 to <160 mg/dL; high: ≥160 mg/dL.

[b]Pooled data from Pyxis, Polaris, and Sirius.

Abbreviations: ADT=antidepressant treatment; LDL=low-density lipoprotein; n/N=number of patients with metabolic shift/total number of patients in category at baseline who had a post-baseline result for the given test.

Supplementary Table 4. Incidence of Treatment-Emergent Shifts in Fasting HDL Cholesterol[a] from Baseline to Any Post-Baseline Visit in the Short-Term, Fixed-Dose Studies[b]

n/N (%)	ADT + Placebo	ADT + Brexpiprazole		
		1 mg	2 mg	3 mg
Low to normal	27/53 (50.9)	6/20 (30.0)	15/31 (48.4)	11/24 (45.8)
Normal to low	32/490 (6.5)	13/184 (7.1)	9/292 (3.1)	12/183 (6.6)

[a]Normal: ≥40 mg/dL; low: <40 mg/dL.

[b]Pooled data from Pyxis, Polaris, and Sirius.

Abbreviations: ADT=antidepressant treatment; HDL=high-density lipoprotein; n/N=number of patients with metabolic shift/total number of patients in category at baseline who had a post-baseline result for the given test.

Supplementary Table 5. Incidence of Treatment-Emergent Shifts in Fasting Triglycerides[a] from Baseline to Any Post-Baseline Visit in the Short-Term, Fixed-Dose Studies[b]

n/N (%)	ADT + Placebo	ADT + Brexpiprazole		
		1 mg	2 mg	3 mg
High/very high to normal	15/84 (17.9)	8/28 (28.6)	10/51 (19.6)	10/27 (37.0)
Borderline to normal	40/75 (53.3)	17/31 (54.8)	26/49 (53.1)	18/29 (62.1)
High/very high to borderline	39/84 (46.4)	8/28 (28.6)	11/51 (21.6)	13/27 (48.1)
Normal to borderline	46/385 (11.9)	30/145 (20.7)	31/226 (13.7)	34/150 (22.7)
Borderline to high/very high	24/75 (32.0)	11/31 (35.5)	20/49 (40.8)	12/29 (41.4)
Normal to high/very high	17/385 (4.4)	7/145 (4.8)	19/226 (8.4)	13/150 (8.7)

[a]Normal: <150 mg/dL; borderline: ≥150 to <200 mg/dL; high/very high: ≥200 mg/dL.

[b]Pooled data from Pyxis, Polaris, and Sirius.

Abbreviations: ADT=antidepressant treatment; n/N=number of patients with metabolic shift/total number of patients in category at baseline who had a post-baseline result for the given test.

Supplementary Table 6. Incidence of Treatment-Emergent Shifts in Fasting Glucose[a] from Baseline to Any Post-Baseline Visit in the Short-Term, Fixed-Dose Studies[b]
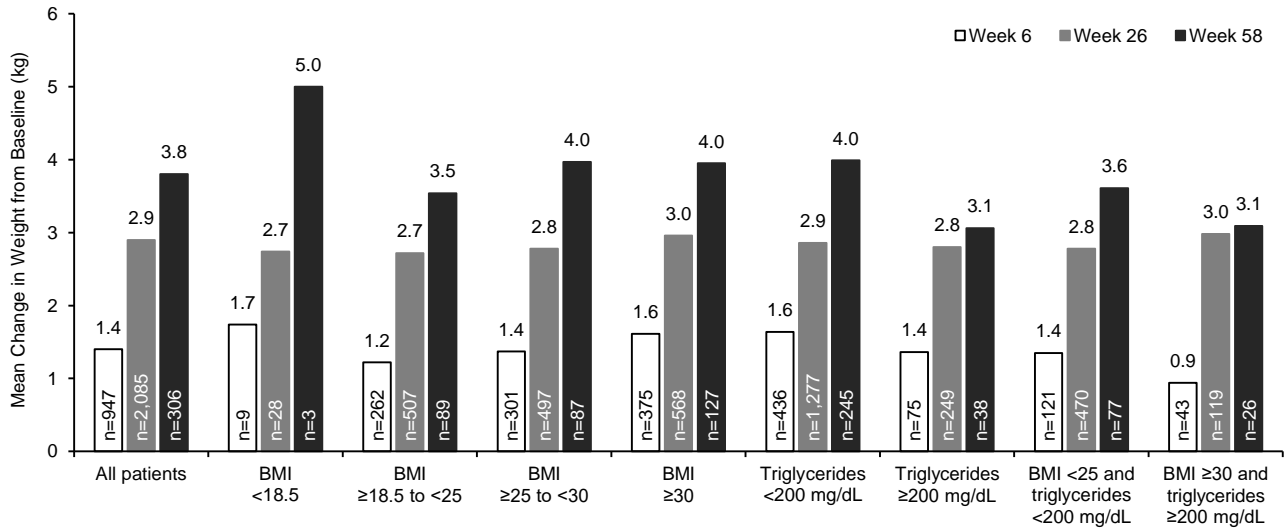
n/N (%)	ADT + Placebo	ADT + Brexpiprazole		
		1 mg	2 mg	3 mg
High to normal	1/15 (6.7)	0/3 (0.0)	3/11 (27.3)	2/4 (50.0)
Impaired to normal	61/110 (55.5)	35/52 (67.3)	41/71 (57.7)	27/46 (58.7)
High to impaired	9/15 (60.0)	3/3 (100.0)	9/11 (81.8)	2/4 (50.0)
Normal to impaired	94/415 (22.7)	38/149 (25.5)	45/244 (18.4)	39/154 (25.3)
Impaired to high	11/110 (10.0)	9/52 (17.3)	8/71 (11.3)	6/46 (13.0)
Normal to high	10/415 (2.4)	2/149 (1.3)	1/244 (0.4)	4/154 (2.6)

[a]Normal: <100 mg/dL; impaired: ≥100 to <126 mg/dL; high: ≥126 mg/dL.

[b]Pooled data from Pyxis, Polaris, and Sirius.

Abbreviations: ADT=antidepressant treatment; n/N=number of patients with metabolic shift/total number of patients in category at baseline who had a post-baseline result for the given test.

Supplementary Figure 1. Mean Change in Body Weight from Baseline to Week 6 (Short-Term Studies[a]), and to Weeks 26 and 58 (Long-Term Treatment[b]), for Patients Receiving ADT + Brexpiprazole, Stratified by Baseline BMI and Triglyceride Level

[a]Pooled data from Pyxis, Polaris, Sirius, and Delphinus.

[b]Data from Orion, including parent studies for patients previously exposed to brexpiprazole (see Methods for full definition).

Abbreviations: ADT=antidepressant treatment; BMI=body mass index.