

Supplementary information

Supplementary Table 1. Phase 3 clinical studies with brexpiprazole in the treatment of adults with acute exacerbation of schizophrenia included in the analysis

Study/Reference	Study Design and Daily Dose	Number of patients (safety population ^a)	
		Brexpiprazole	Placebo
BEACON			
NCT01393613 Kane et al, 2015	6-week, double-blind, placebo controlled 1 mg, 2 mg and 4 mg fixed dose	490	184
VECTOR			
NCT01396421 Correll et al, 2015	6-week, double-blind, placebo controlled 0.25 mg, 2 mg and 4 mg fixed dose	452	184
ZENITH			
NCT01397786	52-week, open-label extension Flexible doses (1 – 4 mg)	788	N/A

^a All randomized patients who received ≥ 1 dose of study medication

Supplementary Table 2. Definitions of fasting metabolic parameters levels measured

Parameter	Low (mg/dL)	Normal (mg/dL)	Borderline^a (mg/dL)	High (mg/dL)
Cholesterol	-	<200	200–<240	≥240
LDL	-	<100	100–<160	≥160
HDL	<40	≥40	-	-
Triglycerides	-	<150	150–<200	≥200
Glucose	-	<100	100–<126	≥126

^aBorderline level defined as impaired for glucose parameter

LDL: low density lipoprotein; HDL: high density lipoprotein

Supplementary Table 3. Mean changes from baseline to Weeks 26 and 58 in fasting metabolic parameters during long-term treatment

	LT brexpiprazole
Cholesterol, mg/dL	
Baseline, mean (SD), [n]	187.58 (41.74) [658]
Change at Week 26, mean (SD), [n]	-0.69 (35.53) [175]
Change at Week 58, mean (SD), [n]	6.09 (39.95) [130]
LDL, mg/dL	
Baseline, mean (SD), [n]	109.98 (36.53) [654]
Change at Week 26, mean (SD), [n]	-1.28 (28.23) [171]
Change at Week 58, mean (SD), [n]	3.86 (33.99) [125]
HDL, mg/dL	
Baseline, mean (SD), [n]	51.51 (16.53) [658]
Change at Week 26, mean (SD), [n]	-0.61 (9.95) [175]
Change at Week 58, mean (SD), [n]	1.67 (13.30) [129]
Triglycerides, mg/dL	
Baseline, mean (SD), [n]	132.74 (74.44) [658]
Change at Week 26, mean (SD), [n]	9.13 (83.92) [175]
Change at Week 58, mean (SD), [n]	7.35 (81.83) [130]
Glucose, mg/dL	
Baseline, mean (SD), [n]	94.15 (18.20) [657]
Change at Week 26, mean (SD), [n]	2.90 (37.37) [175]
Change at Week 58, mean (SD), [n]	2.12 (15.89) [130]

SD: standard deviation; LDL: low density lipoprotein; HDL: high density lipoprotein

Supplementary Table 4. Incidences of treatment-emergent shifts in fasting cholesterol from baseline to any time post-baseline during the first 6 weeks, first 6 months (baseline to Week 26), and last 6 months (Weeks 27 to 58)

Cholesterol shift, n/ne (%)	Placebo (N=368)	Short-term brexpiprazole					LT brexpiprazole 1-4 mg (N=696)	
		0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	2 and 4 mg (N=732)	First 6 months	Last 6 months
High-normal	5/38 (13.2)	0/10 (0.0)	1/12 (8.3)	6/39 (15.4)	6/40 (15.0)	12/79 (15.2)	19/72 (26.4)	9/45 (20.0)
Borderline-normal	36/76 (47.4)	6/18 (33.3)	14/30 (46.7)	28/70 (40.0)	38/75 (50.7)	66/145 (45.5)	93/146 (63.7)	41/79 (51.9)
High-borderline	17/38 (44.7)	3/10 (30.0)	5/12 (41.7)	17/39 (43.6)	18/40 (45.0)	35/79 (44.3)	54/72 (75.0)	22/45 (48.9)
Normal-borderline	27/211 (12.8)	8/47 (17.0)	11/68 (16.2)	49/226 (21.7)	59/215 (27.4)	10/441 (24.5)	131/438 (29.9)	71/250 (28.4)
Borderline-high	21/76 (27.6)	3/18 (16.7)	6/30 (20.0)	22/70 (31.4)	13/75 (17.3)	35/145 (24.1)	53/146 (36.3)	23/79 (29.1)
Normal-high	5/211 (2.4)	0/47 (0.0)	2/68 (2.9)	5/226 (2.2)	5/215 (2.3)	10/441 (2.3)	21/438 (4.8)	15/250 (6.0)

n, number of patients with metabolic shift; ne, total number of randomized patients who met baseline criteria and had a post-baseline result for given lab test

Normal, <200 mg/dL; borderline, 200–<240 mg.dL; high, ≥240 mg/dL

Supplementary Table 5. Incidences of treatment-emergent shifts in fasting LDL from baseline to any time post-baseline during the first 6 weeks, first 6 months (baseline to Week 26), and last 6 months (Weeks 27 to 58)

LDL shift, n/ne (%)	Placebo (N=368)	Short-term brexpiprazole					LT brexpiprazole 1-4 mg (N=696)	
		0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	2 and 4 mg (N=732)	First 6 months	Last 6 months
High-normal	1/32 (3.1)	0/7 (0.0)	0/7 (0.0)	1/37 (2.7)	1/26 (3.8)	2/63 (3.2)	6/53 (11.3)	3/30 (10.0)
Borderline-normal	44/157 (28.0)	10/41 (24.4)	17/55 (30.9)	44/163 (27.0)	40/163 (24.5)	84/326 (25.8)	142/329 (43.2)	53/184 (28.8)
High-borderline	16/32 (50.0)	2/7 (28.6)	2/7 (28.6)	24/37 (64.9)	14/26 (53.8)	38/63 (60.3)	41/53 (77.4)	18/30 (60.0)
Normal-borderline	35/136 (25.7)	10/26 (38.5)	15/48 (31.3)	41/132 (31.1)	45/138 (32.6)	86/270 (31.9)	101/270 (37.4)	56/153 (36.6)
Borderline-high	24/157 (15.3)	2/41 (4.9)	5/55 (9.1)	14/163 (8.6)	16/163 (9.8)	30/326 (9.2)	49/329 (14.9)	24/184 (13.0)
Normal-high	0/136 (0.0)	0/26 (0.0)	1/48 (2.1)	1/132 (0.8)	1/138 (0.7)	2/270 (0.7)	7/270 (2.6)	4/153 (2.6)

n, number of patients with metabolic shift; ne, total number of randomized patients who met baseline criteria and had a post-baseline result for given lab test

Normal, <100 mg/dL; borderline, 100–<160 mg.dL; high, ≥160 mg/dL

Supplementary Table 6. Incidences of treatment-emergent shifts in fasting HDL from baseline to any time post-baseline during the first 6 weeks, first 6 months (baseline to Week 26), and last 6 months (Week 27 to 58)

HDL shift, n/ne (%)	Short-term brexpiprazole						LT brexpiprazole 1-4 mg (N=696)	
	Placebo (N=368)	0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	2 and 4 mg (N=732)	First 6 months	Last 6 months
Low-normal	32/67 (47.8)	3/13 (23.1)	9/24 (37.5)	45/91 (49.5)	35/72 (48.6)	80/163 (49.1)	93/143 (65.0)	48/82 (58.5)
Normal-low	30/258 (11.6)	5/62 (8.1)	11/86 (12.8)	19/244 (7.8)	28/258 (10.9)	47/502 (9.4)	86/513 (16.8)	48/292 (16.4)

n, number of patients with metabolic shift; ne, total number of randomized patients who met baseline criteria and had a post-baseline result for given lab test

Low, <40 mg/dL; normal, ≥40 mg/dL

Supplementary Table 7. Incidences of treatment-emergent shifts in fasting triglycerides from baseline to any time post-baseline during the first 6 weeks, first 6 months (baseline to Week 26), and last 6 months (Weeks 27 to 58)

Triglyceride shift, n/ne (%)	Placebo (N=368)	Short-term brexpiprazole					LT brexpiprazole 1-4 mg (N=696)	
		0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	2 and 4 mg (N=732)	First 6 months	Last 6 months
High-normal	9/28 (32.1)	2/11 (18.2)	4/18 (22.2)	15/51 (29.4)	16/50 (32.0)	31/101 (30.7)	48/98 (49.0)	27/61 (44.3)
Borderline-normal	28/48 (58.3)	6/12 (50.0)	13/21 (61.9)	30/51 (58.8)	32/57 (56.1)	62/108 (57.4)	84/108 (77.8)	39/64 (60.9)
High-borderline	16/28 (57.1)	3/11 (27.3)	7/18 (38.9)	14/51 (27.5)	16/50 (32.0)	30/101 (29.7)	52/98 (53.1)	19/61 (31.1)
Normal-borderline	40/247 (16.2)	11/51 (21.6)	12/71 (16.9)	34/229 (14.8)	42/222 (18.9)	76/451 (16.9)	127/449 (28.3)	50/249 (20.1)
Borderline-high	19/48 (39.6)	4/12 (33.3)	6/21 (28.6)	15/51 (29.4)	14/57 (24.6)	29/108 (26.9)	37/108 (34.3)	28/64 (43.8)
Normal-high	13/247 (5.9)	5/51 (9.8)	7/71 (9.9)	17/229 (7.4)	20/222 (9.0)	37/451 (8.2)	67/449 (14.9)	32/249 (12.9)

n, number of patients with metabolic shift; ne, total number of randomized patients who met baseline criteria and had a post-baseline result for given lab test

Normal, <150 mg/dL; borderline, 150–<200 mg.dL; high, >200 mg/dL

Supplementary Table 8. Incidences of treatment-emergent shifts in fasting glucose from baseline to any time post-baseline during the first 6 weeks, first 6 months (baseline to Week 26), and last 6 months (Weeks 27 to 58)

Glucose shift, n/ne (%)	Placebo (N=368)	Short-term brexpiprazole					LT brexpiprazole 1-4 mg (N=696)	
		0.25 mg (N=90)	1 mg (N=120)	2 mg (N=368)	4 mg (N=364)	2 and 4 mg (N=732)	First 6 months	Last 6 months
High-normal	7/14 (50.0)	0/0 (0)	3/3 (100)	5/9 (55.6)	1/7 (14.3)	6/16 (37.5)	14/22 (63.6)	7/12 (58.3)
Impaired- normal	44/71 (62.0)	12/21 (57.1)	15/26 (57.7)	56/81 (69.1)	38/62 (61.3)	94/143 (65.7)	103/135 (76.3)	54/84 (64.3)
High- impaired	8/14 (57.1)	0/0 (0)	2/3 (66.7)	3/9 (33.3)	3/7 (42.9)	6/16 (37.5)	15/22 (68.2)	9/12 (75.0)
Normal- impaired	58/240 (24.2)	12/54 (22.2)	18/80 (22.5)	64/243 (26.3)	55/260 (21.2)	119/503 (23.7)	209/498 (42.0)	99/277 (35.7)
Impaired-high	8/71 (11.3)	3/21 (14.3)	2/26 (7.7)	5/81 (6.2)	6/62 (9.7)	11/143 (7.7)	29/135 (21.5)	7/84 (8.3)
Normal-high	8/240 (3.3)	2/54 (3.7)	3/80 (3.8)	6/243 (2.5)	8/260 (3.1)	14/503 (2.8)	34/498 (6.8)	11/277 (4.0)

n, number of patients with metabolic shift; ne, total number of randomized patients who met baseline criteria and had a post-baseline result for given lab test

Normal, <100 mg/dL; impaired, 100–<126 mg/dL; high, ≥126 mg/dL