Supplementary material

Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial

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Table S1. Number of patients with fasting metabolic parameters or prolactin measurements within the normal range at baseline and outside the normal range during the study (safety population)*

	Number of patients: Outside normal range during study[a]/normal at baseline			
		Brexpiprazole		
	Placebo (n=184)	0.25 mg (n=90)	2 mg (n=182)	4 mg (n=180)
Fasting metabolic parameters[b] (baseline to last visit)				
Cholesterol; normal to high	1/100	2/45	3/92	3/95
HDL cholesterol; normal to low	4/102	1/56	0/106	4/119
LDL cholesterol; normal to high	3/96	0/47	4/94	2/102
Triglycerides; normal to high	3/103	2/56	6/112	8/117
Fasting glucose[c]				
Normal to high at last visit	21/89	9/42	14/91	15/100
Normal to high at any visit	4/127	2/57	6/120	4/126
Borderline to high at any visit	3/33	3/21	3/39	3/30
Prolactin[d] (baseline to last visit)				
Female; normal to high	2/28	1/16	5/36	7/37
Male; normal to high	2/53	1/31	5/51	9/57

[a]Baseline to last visit for fasting metabolic parameters and prolactin; baseline to any visit for glucose.
[b]Normal ranges: cholesterol 162–280 mg/dL; HDL cholesterol 27–67 mg/dL; LDL cholesterol 81–189 mg/dL; triglycerides 55–327 mg/dL.
[c]Glucose measurements: normal <100 mg/dL; borderline 100 to <126 mg/dL; high ≥126 mg/dL.
[d]Normal ranges: female 2.74–26.72 ng/mL; male 2.64–13.13 ng/mL.
*The Fisher's exact test was used to test treatment difference for all parameters. There were no statistically significant differences between treatment groups.

Table S2. Mean change from baseline to the last visit in laboratory measurements (safety population)*

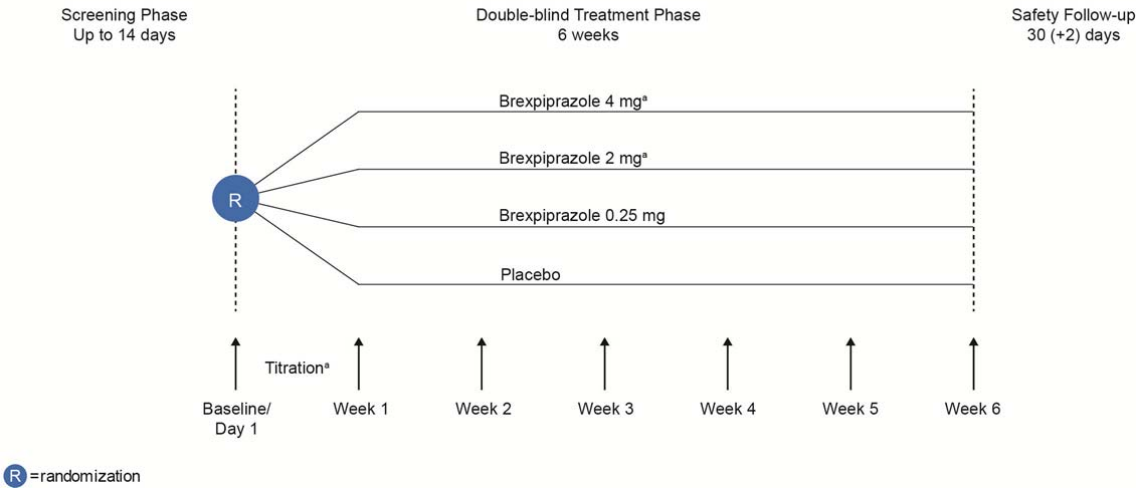
Assessment	Mean (SD) change from baseline to last visit											
				Brexpiprazole								
	Placebo (n=184)			0.25 mg (n=90)			2 mg (n=182)			4 mg (n=180)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Liver enzymes												
ALT, U/L	167	0.08	27.91	84	-1.08	12.80	173	1.93	14.54	167	3.56	19.61
AST, U/L	168	2.65	31.59	83	0.64	9.44	172	2.30	11.38	167	1.63	9.25
Alkaline phosphatase, U/L	168	-0.05	12.61	84	1.10	9.42	173	-0.17	9.80	167	0.75	20.01
Total bilirubin, mg/dL	166	0.04	0.25	80	0.02	0.21	169	0.04	0.21	162	0.00	0.22
Renal parameters												
CPK, U/L	168	177.70	1910.15	84	62.56	300.53	173	83.80	658.22	167	69.72	283.68
Creatinine, mg/dL	168	0.01	0.10	84	0.00	0.10	173	-0.02	0.12	167	-0.01	0.11
Urea nitrogen, mg/dL	168	0.31	3.41	84	-0.32	3.26	173	-0.08	3.63	167	-0.45	3.57
Electrolytes												
Bicarbonate, mEq/L	168	-0.30	2.77	84	0.18	2.25	173	0.04	2.82	167	-0.49	2.91
Chloride, mEq/L	168	0.02	2.75	84	-0.26	2.83	173	-0.12	2.81	167	0.22	2.72
Potassium, mEq/L	168	-0.09	0.47	84	-0.07	0.41	172	-0.12	0.41	167	-0.08	0.39
Sodium, mEq/L	168	-0.24	2.72	84	-0.37	2.78	173	-0.31	2.67	167	0.11	2.57
Hematology												
APTT, sec	148	0.81	6.82	73	1.05	5.87	154	0.91	5.70	151	0.75	4.42
PTT, sec	148	0.22	1.57	75	0.34	1.43	154	-0.02	1.71	151	-0.03	0.86
INR	148	0.03	0.18	75	0.04	0.16	154	-0.00	0.19	151	0.00	0.11
Hematocrit, %	163	-0.34	2.94	81	-0.09	2.95	172	-0.40	2.80	166	-0.43	3.21
Hemoglobin, g/dL	166	-0.01	0.94	82	-0.12	0.86	172	-0.18	0.83	166	-0.16	0.96
HbA1c, %	162	0.01	0.27	79	0.05	0.31	168	0.02	0.30	163	0.03	0.31
Basophils, thousands/µL	166	-0.00	0.04	82	-0.01	0.03	172	0.01	0.04	166	-0.00	0.04
Eosinophils, thousands/µL	166	-0.02	0.11	82	-0.02	0.09	172	-0.01	0.09	166	0.00	0.12
Lymphocytes, thousands/µL	166	-0.03	0.51	82	-0.11	0.48	172	-0.10	0.47	166	-0.07	0.43
Neutrophils, thousands/µL	166	-0.05	1.79	82	0.20	1.52	172	0.32	1.78	166	0.08	1.73
Red blood cells, milllions/µL	166	-0.00	0.31	82	-0.02	0.28	172	-0.04	0.28	166	-0.05	0.31

Mean (SD) change from baseline to last visit												
Assessment				**Brexpiprazole**								
	Placebo (n=184)			**0.25 mg (n=90)**			**2 mg (n=182)**			**4 mg (n=180)**		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
White blood cell, thousands/µL	166	-0.12	1.94	82	0.06	1.77	172	0.22	1.94	166	-0.01	1.84
Platelets, thousands/µL	165	-4.55	49.71	82	-5.82	49.17	172	-6.09	56.02	166	-7.92	48.57

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; HbA1c, hemoglobin A1c; INR, international normalized ratio; PTT, partial thromboplastin time.

*There were no statistically significant differences between treatment groups.

Figure S1. Study design



[a]Titration to assigned dose from baseline to the week 1 visit for patients randomized to brexpiprazole 2 mg or 4 mg. Days 1–4: 1 mg/day; days 5–7: 2 mg/day.

Screening phase included washout from previous antipsychotics (≥7 days) and prohibited concomitant medications. Concomitant medication disallowed during the study included all psychotropic agents (including antipsychotics, antidepressants and mood stabilizers), benzodiazepines (apart from specific use as rescue therapy), non-benzodiazepine sleep medications (apart from limited use for treatment of insomnia), antihistamines (except for loratadine and cetirizine), varenicline, vitamins, nutritional supplements, non-prescription herbal preparations, CYP2D6 inhibitors, and CYP3A4 inhibitors and inducers.

Patients were hospitalized during the screening and double-blind treatment phases, but were allowed day passes during weeks 3–6 if sufficiently stable.

Figure S2. Patient disposition