BL-1020, a New γ-Aminobutyric Acid–Enhanced Antipsychotic: Results of 6-Week, Randomized, Double-Blind, Controlled, Efficacy and Safety Study

Yona Geffen, PhD; Richard Keefe, PhD; Jonathan Rabinowitz, PhD; Ravi Anand, MD; and Michael Davidson, MD

ABSTRACT

Objective: BL-1020 is a γ-aminobutyric acid (GABA)–enhanced antipsychotic that combines dopamine antagonism with GABA agonist activity. On the basis of animal models, we tested the hypotheses that BL-1020 would be effective in ameliorating both psychotic symptoms and cognitive impairments, with a favorable safety profile in acutely ill schizophrenia patients.

Method: 363 hospital-based psychiatric patients in India, Romania, and United States aged 18 to 65 years and meeting criteria for *DSM-IV-TR* diagnosis of chronic schizophrenia were randomized double-blind to receive BL-1020 10 mg/d, BL-1020 20–30 mg/d, placebo, or risperidone (2–8 mg/d) for 6 weeks. The main outcome measures were the Positive and Negative Syndrome Scale (PANSS), Brief Assessment of Cognition in Schizophrenia, Readiness for Discharge Questionnaire, Clinical Global Impressions Scale (CGI) , and Extrapyramidal Symptom Rating Scale. The study ran from July 2008 to June 2009.

Results: BL-1020 20–30 mg was significantly better than placebo on PANSS ($P = .02$) and CGI ($P < .001$) measurements, with no significant differences noted between BL-1020 20–30 mg and risperidone. There were no significant differences in the maximum change on Extrapyramidal Symptom Rating Scale between risperidone and BL-1020 20–30 mg, and both were significantly worse ($P < .001$) than placebo. BL-1020 20–30 mg was associated with significantly greater improvements on cognitive functioning as measured by the Brief Assessment of Cognition in Schizophrenia composite score when compared to placebo (effect size = 0.50, $P = .009$), risperidone (effect size = 0.43, $P = .019$), and BL-1020 10 mg (effect size = 0.42, $P = .013$) after 6 weeks.

Conclusions: BL-1020 appears to be an effective antipsychotic with possible procognitive effects that will need to be further tested for short- and long-term effects. A further randomized controlled trial using the US Food and Drug Administration–recommended Measurement and Treatment Research to Improve Cognition in Schizophrenia cognitive battery is ongoing.

Trial Registration: ClinicalTrials.gov identifier: NCT00567710

J Clin Psychiatry 2012;73(9):e1168–e1174

Submitted: *January 9, 2012; accepted: May 1, 2012 (doi:10.4088/JCP.12m07642).*
Corresponding author: *Yona Geffen, PhD, Avraham Pharmaceuticals, 42 Hayarkon St, Industrial Zone, Yavneh, 81227, Israel (yg@avphar.com).*

Antipsychotics have not been effective for core cognitive impairments in schizophrenia.[1–4] In fact, there is evidence that conventional antipsychotics may be neurotoxic and induce neuronal loss and gliosis in the striatum, hypothalamus, brainstem, limbic system, and cortex as well as apoptosis (for a review, see Vernon et al[5]). Cognitive impairments[6] are important targets for intervention, as they affect vocational and social functioning and independent living.[7] Second-generation antipsychotics are, at best, only slightly better at reducing some cognitive impairments than first-generation antipsychotics.[8–10] Two recent landmark studies, European First-Episode Schizophrenia Trial[2] in first-episode patients and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)[4] in chronically ill patients, did not find first- or second-generation antipsychotics to be significantly effective in ameliorating cognitive impairment. The small effects observed in these studies could even be practice effects.[3] Thus, there is little evidence that antipsychotics ameliorate cognitive impairments in schizophrenia.

BL-1020 is an orally administered antipsychotic that is a γ-aminobutyric acid (GABA) ester of perphenazine.[11,12] On the basis of animal and preclinical data, we hypothesized that BL-1020 would provide antipsychotic efficacy with minimal extrapyramidal symptoms and could improve cognition. In novel object recognition and reversal learning in rats, it was able to reverse cognitive impairment induced by phencyclidine, perphenazine alone did not have this effect, and there was an increase in GABA in the rat brain.[12,13] BL-1020 combines dopamine receptor blockade (high affinity for D_{2L} and D_{2S}) with high affinity for serotonin 5-HT_{2A} and histamine H_1 receptors. Unlike other antipsychotics, it has agonist activity at $GABA_A$ receptor but no activity at metabotropic $GABA_B$ receptor.[12] Hypoactivity of GABA is implicated in schizophrenia.[14–19] Preclinically, BL-1020 showed a favorable safety profile, while retaining efficacy. In animals, it was devoid of cataleptic extrapyramidal symptoms at doses associated with efficacy.[12] The current study is the first controlled study to examine BL-1020.

METHOD

Study Setting and Design

This was a 6-week, randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 2 study to determine safety, efficacy, and tolerability of low (10 mg/d)- and flexible high (20–30 mg/d)-dose ranges of BL-1020. Risperidone 2 to 8 mg (based on a previous study[20]) was an active control. Acutely exacerbated schizophrenia patients were randomized and titrated to target dose based on tolerability during first treatment week. The study was powered at 90% to find a 15 (SD = 25)-point difference in change on Positive and Negative Syndrome Scale total score between BL-1020 20–30 mg and placebo. This difference required 60 patients per arm. To compensate for dropout, we aimed to enroll 360 patients.

The study was conducted according to Good Clinical Practice[21] and after local institutional review board approval was obtained. Safety was monitored by an independent data and safety monitoring board. Between July 2008 and April 2009, subjects were screened in India (15 sites), Romania (17 sites), and the United States (2 sites), and the last patient completed the study in June 2009. Adherence to inclusion and exclusion criteria was monitored by an independent psychiatrist. The study was registered at ClinicalTrials.gov (identifier: NCT00567710).

Clinical Points

- Cognitive deficits in schizophrenia may be ameliorated with BL-1020.
- Further research is needed to examine the short- and long-term possible procognitive effects.

Participants

Inclusion criteria were as follows: (1) male and female subjects (excluding those of childbearing potential); (2) subjects who were aged 18 to 65 years (inclusive); (3) *DSM-IV-TR* diagnosis of chronic schizophrenia (excluding residual type), as confirmed by the Mini-International Neuropsychiatric Interview[22]; (4) acute exacerbation within 30 days; (5) Positive and Negative Syndrome Scale (PANSS)[23] total score ≥ 70 and score ≥ 4 on 2 key PANSS items (delusions, hallucinatory behaviors, conceptual disorganization, or suspiciousness/persecution); (6) Clinical Global Impressions-Severity of illness scale (CGI-S) rating of ≥ 4 (moderately ill); (7) subjects who were currently hospitalized for less than a month, with a willingness to be hospitalized for at least 20 days; and (8) willingness to have a caregiver to assist with treatment compliance.

Exclusion criteria included the following: (1) a score greater than 9 on the modified InterSePT Scale for Suicidal Thinking,[24] (2) risk of harming others, (3) treatment-refractory psychosis following 2 years of exposure to a therapeutic dose of antipsychotics, (4) substance abuse, (5) a primary psychiatric diagnosis other than schizophrenia, (6) tardive dyskinesia (past or present as in the CATIE study[25]), (7) inability to stop benzodiazepine treatment, (8) use of mood stabilizers within 30 days, unless plasma concentration was below limit of quantification, (9) clozapine use within 3 years, (10) being within a treatment cycle of a depot antipsychotic (depot risperidone, 2 treatment cycles) plus 1 week; (11) presence of likely allergy or sensitivity to BL-1020 or perphenazine, and (12) history of blood cell disorder. All participants provided written informed consent in their spoken language.

Randomization

Randomization was performed using an interactive voice response system. One randomization scheme was generated across all sites (ie, a central randomization scheme). On the study day, when the drug was dispensed, the investigator called the interactive voice response system to assign the treatment code number. This medication code number was used to identify the medication kit to be dispensed to the patient. The investigator then recorded the patient number on the label in the space provided.

Interventions

For 5 to 14 days, patients were weaned off antipsychotics and other prohibited medications. Study medications were packaged identically. Patients were randomized to BL-1020 low dose (10 mg/d), BL-1020 high dose (20–30 mg/d), risperidone (2–8 mg/d), or placebo. Every 2 days during first study week, patients randomized to BL-1020 high dose and risperidone had doses titrated toward target dose with BL-1020 high-dose patients starting at 10 mg/d and risperidone patients starting at 2 mg/d. BL-1020 high-dose patients were increased to 20 mg/d on day 3 and then to 30 mg/d on day 7, based on tolerability. In the risperidone group, patients started at a dose of 2 mg/d, with escalation to 4, 6, and 8 mg/d on days 3, 5, and 7, respectively. In case of intolerance, dosing could be maintained, decreased, or interrupted for up to 2 days. Increases were allowed only at regularly scheduled visits. Vital signs, electrocardiogram, and blood samples were obtained on day 14 up to 5 hours after first dose.

Patients were evaluated at screening, day 0 (baseline), weekly, or at early discontinuation. Patients were required to remain as inpatients for the first 14 days of treatment. If they responded to treatment, as judged by Readiness for Discharge Questionnaire,[26] they could be discharged.

Outcomes

The PANSS[23] was the primary efficacy measure. Secondary measures were the Calgary Depression Scale for schizophrenia,[27] CGI-S,[28] and the Clinical Global Impressions-Improvement scale (CGI-I),[28] administered at all study visits (the CGI-I was not administered until week 1 of treatment); the Strauss-Carpenter Level of Functioning Scale,[29] administered at day 0 and 42 or at early discontinuation; the Readiness for Discharge Questionnaire,[26] administered at all visits from day 7; and the Medication Satisfaction Questionnaire,[30] administered every 2 weeks or at end of study.

The Brief Assessment of Cognition in Schizophrenia[31] was administered at day 0 and at the primary end point (6 weeks, day 42). For patients who terminated prior to day 42 and who had at least 28 days of treatment, an early discontinuation assessment was done. The Brief Assessment of Cognition in Schizophrenia takes about 35 minutes to administer. It assesses processing speed, reasoning and problem-solving, working memory, and verbal memory. It was translated and back translated to the major languages in India and to Romanian. A composite score is obtained by summing the normalized *z* scores for each measure (obtained by comparing each measure with a healthy control sample) and dividing by standard deviation of mean *z* scores in healthy controls. The composite score has a high test-retest reliability in patients

© Copyright 2012 Physicians Postgraduate Press, Inc.

with schizophrenia and healthy controls (intraclass correlation coefficient > 0.80).[31,32]

Tolerability and safety were assessed based on incidence of adverse events, dropouts due to adverse events, weekly ratings on the Extrapyramidal Symptom Rating Scale (ESRS),[33,34] vital signs, electrocardiogram, laboratory test results (including prolactin), and physical examination.

Experienced raters who successfully completed a 3-day, sponsor-approved certification program were used. This program included training in using the Brief Assessment of Cognition in Schizophrenia by R.K., who developed the scale, and training in using the ESRS by the scale developer. Multicenter rater-training meetings were also held. Whenever possible, the same raters were used to assess the same patients.

Statistical Analyses

The planned primary end point was the difference in the mean change in the PANSS total score from day 0 to day 42 between high-dose BL-1020 (target dose 30 mg/d) and placebo. The safety and efficacy population consisted of all patients with at least 1 dose of study medication. The primary analysis of the PANSS was a mixed-effect model for repeated measures (with treatment, site, week, treatment-by-week as factors and baseline value as covariate with an unstructured covariance matrix) and the composite approach.[35] The composite approach combines the *P* values of yes/no completion and change to week 42 among completers, thereby making no assumptions regarding the nature of missing data due to discontinuation. Additional planned analyses included examining change in cognition and the other efficacy measures by using analysis of covariance (ANCOVA) of change in score to end point (last observation carried forward), adjusting for baseline. In the case of the cognitive assessment, baseline observation carried forward and day 42 end point were similarly examined. The proportion of patients in each group with a clinical response, defined as a 20% decline on the PANSS, was compared to placebo by using χ^2. The planned comparison was of BL-1020 (20–30 mg) and placebo; thus, there was no adjustment for multiple comparisons.

RESULTS

A total of 363 patients from India (n = 252; 15 investigators), Romania (n = 88; 17 investigators), and the United States (n = 23; 2 investigators) were randomized and included in the safety and intent-to-treat analysis populations. There were no statistically significant differences among treatment groups on background characteristics (largest difference, $P < .27$). The mean (SD) age was 34.0 (10.2) years; 67.5% were male, 69.7% were Asian, 27.0% were white, and 3.3% were black/African American or other; 80% had 8 or more years of education; and the majority (57.9%) were unmarried. Patients' mean (SD) height was 163.4 (9.52) cm and weight was 61.7 (14.93) kg, with mean (SD) body mass index (BMI [kg/m^2]) of 22.96 (4.70). Mean duration of illness was 8.6 years. Only 5 were already inpatients at the time of enrollment; the rest were recruited upon admission for exacerbation, 27.8% were current smokers, and 47.9% drank less than 1 cup of coffee per day (supplementary eFigure 1 and eTable 1).

There were no statistically significant differences among treatment groups on schizophrenia symptoms, psychosocial and cognitive functioning, and extrapyramidal symptoms at baseline (all *P* values < .22). PANSS, Strauss-Carpenter Level of Functioning Scale, Brief Assessment of Cognition in Schizophrenia, and ESRS total mean scores at baseline were as follows: 98, 13.6, 15.5, and 3.25 (supplementary eTable 2). The highest completion rate, 78%, was for risperidone, and the lowest, 60.2%, was for placebo ($P = .076$). The most common reason for discontinuing was "lack of efficacy" or "withdrawal of consent" in all groups except the risperidone group, where adverse events was the most commonly reported reason (supplementary eTable 3).

All patients tolerated the starting dose. A similar proportion of patients in each arm had their doses escalated during the first week of treatment. The proportion of patients reaching highest dose level on day 7 was similar for BL-1020 10 mg, risperidone, and placebo (approximately 72%) but slightly lower for BL-1020 20–30 mg (64.7%). Most patients tolerated the maximum dose. At their last study visit, about 83% of the risperidone group were on the maximum dose (8 mg, n = 59; 6 mg, n = 16; 4 mg, n = 10; 2 mg, n = 6), as were the BL-1020 20–30 mg group (30 mg, n = 60; 20 mg, n = 26; 10 mg, n = 3).

Efficacy

Mixed-effect model for repeated measures and composite approach found significantly greater improvement on the PANSS for both BL-1020 20–30 mg (mixed effect, $P = .02$; composite, $P = .02$) and risperidone (mixed effect, $P = .001$; composite, $P < .01$) compared to placebo but not for BL-1020 10 mg (mixed effect, $P = .81$, composite, $P = .13$). Analysis of covariance showed trends for a difference versus placebo for both BL-1020 20–30 mg ($P = .09$) and risperidone ($P = .07$) (Table 1).

On PANSS total during the first 2 weeks of treatment, the 3 treatment groups separated from placebo, and, after that, 10 mg did not do better than placebo and, at week 5, did worse (Figure 1). After week 1, placebo had the highest dropout rate. At week 6, BL-1020 10 and 20–30 mg had the same dropout rate, and risperidone had the lowest rate (Figure 1B). The higher dropout rate of BL-1020, as compared to risperidone, was due to more "lack of efficacy" and "withdrawal of consent" dropout.

At days 14, 35, and 42, there was a significant difference ($P < .009$) between the arms in the number of patients who had a decline of at least 20% on PANSS total score. The most pronounced difference was at day 14 (placebo: 45%, n = 36/80; BL-1020 10 mg: 52.4%, n = 43/82; risperidone: 62.4%, n = 53/85; BL-1020 20–30 mg: 69.9%, n = 58/83, $P < .007$), with similar differences at days 35 and 42 (both $P < .009$).

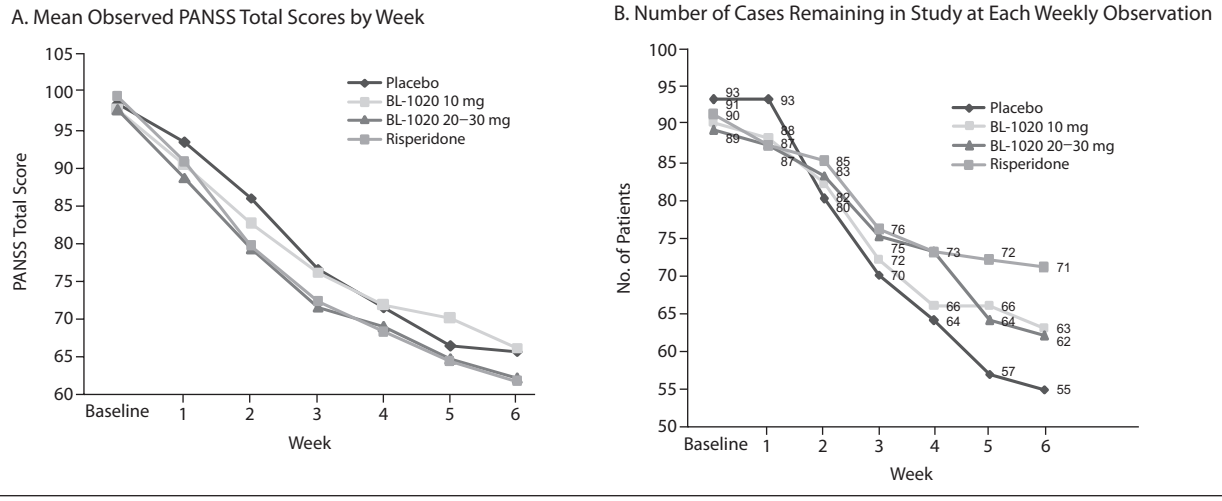
On secondary efficacy measures CGI-S, CGI-I, Readiness for Discharge Questionnaire, and Strauss-Carpenter Level

Table 1. Outcomes of BL-1020 10 mg and 20–30 mg and Risperidone as Compared to Placebo

	BL-1020 10 mg (n = 90)			BL-1020 20–30 mg (n = 89)			Risperidone (n = 91)		
Symptom Measure	Mean	95% CI	*P*	Mean	95% CI	*P*	Mean	95% CI	*P*
Difference in PANSS total LS mean score from placebo,[a] mixed model	−0.7	−6.3 to 5.0	.81	−6.6	−12.2 to −0.9	.02	−9.4	−14.9 to −3.8	.001
Positive symptoms	−0.4	−2.5 to 1.6	.69	−3.7	−5.8 to −1.7	≤ .001	−4.7	−6.7 to −2.6	< .001
Negative symptoms	−0.4	−1.8 to 1.0	.56	−1.3	−2.7 to 0.1	.067	−2.0	−3.4 to −0.6	.004
General psychopathology	−1.3	−4.1 to 1.4	.35	−4.1	−6.9 to −1.4	.003	−5.3	−8.0 to −2.5	< .001
20% Improvement in PANSS total (LOCF) score vs placebo	7.1%		.33	16.4%		.001	18.1%		< .001
Composite difference (yes/no completion and difference in PANSS change for completers)[b]			.13			.02			< .01
PANSS score, ANCOVA model (with treatment, site, and baseline value as factors)	−0.2	−5.2 to 4.8	.95	−4.3	−9.3 to 0.7	.09	−4.6	−9.5 to 0.3	.07
CGI-S score, ANCOVA model (with treatment, site, and baseline value as covariates)	−0.07[c]	−0.42 to 0.27	.67	−0.60[c]	−0.94 to −0.25	< .001	−0.67[c]	−1.02 to −0.33	< .001
CGI-I score, responders ("much improved" or "very much improved" [score of 1 or 2], LOCF)	−0.14	−0.52 to 0.24	.47	−0.77	−1.15 to −0.39	< .001	−0.83	−1.20 to −0.45	< .001
CGI-I score, responders ("much improved" or "very much improved" [score of 1 or 2], observed cases)	0.01	−0.27 to 0.29	.94	−0.37	−0.65 to −0.09	.009	−0.30	−0.57 to 0.03	.031
Readiness for discharge (any time point)	1.27[d]	0.70 to 2.29	.43	2.04[d]	1.10 to 3.79	.023	2.88[d]	1.51 to 5.48	.001
Calgary Depression Scale for Schizophrenia score	0.1	−0.3 to 0.6	.55	−0.2	−0.7 to 0.3	.52	−0.6	−1.0 to −0.1	.02
Strauss-Carpenter Level of Functioning Scale score	1.04[c]	−0.39 to 2.46	.153	1.72[c]	0.31 to 3.14	.017	2.14[c]	0.74 to 3.54	.003

[a]Analysis of covariance, with treatment, site, and baseline values as covariates.
[b]Combined *P* values (1-tail) of χ^2 test of yes/no completion vs placebo (BL1020 10 mg, *P* = .06; BL1020 20–30 mg, *P* = .07; risperidone, *P* = .003) and complete cases ANCOVA at day 42 (BL1020 10 mg, *P* = .47; BL1020 20–30 mg, *P* = .04; risperidone, *P* = .03) using *P* = p(d) × p(e) × (1 − 1n[p(d) × p(e)]), where p(d) is the *P* value of the difference on rates of dropouts and p(e) is the *P* value of the difference in efficacy in complete cases between each treatment group.
[c]Value indicates least squares mean.
[d]Value indicates odds ratio.
Abbreviations: ANCOVA = analysis of covariance, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of illness scale, LOCF = last observation carried forward, LS = least squares, PANSS = Positive and Negative Syndrome Scale.

Figure 1. Mean Observed Positive and Negative Syndrome Scale (PANSS) by Week and Cases Remaining in Study by Week

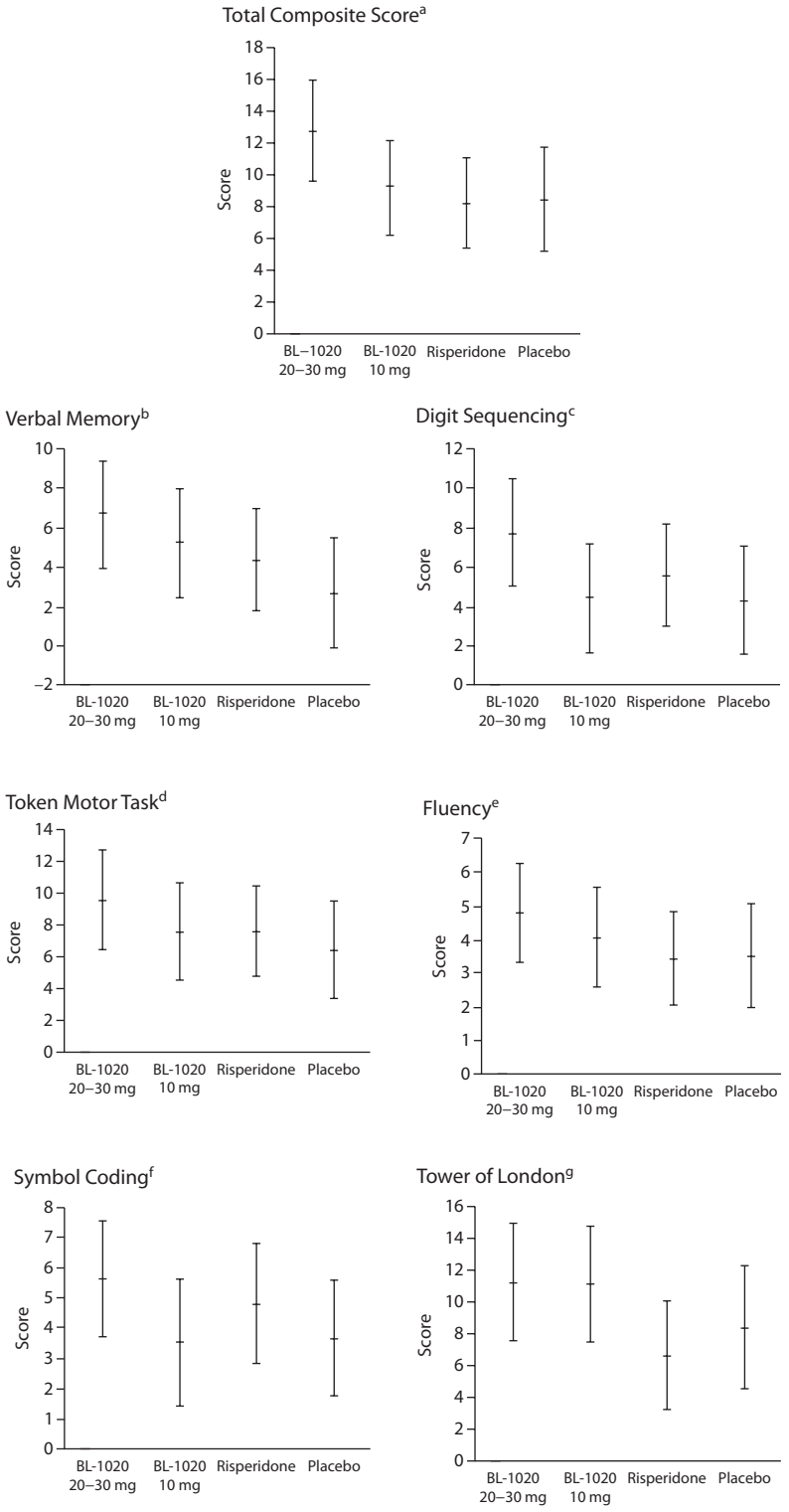


of Functioning Scale, BL-1020 20–30 mg and risperidone improved significantly more than placebo, with no significant differences between BL-1020 20–30 mg and risperidone. On the Calgary Depression Scale for schizophrenia, BL-1020 20–30 mg was not significantly different on change from placebo, whereas risperidone was. BL-1020 10 mg was not significantly different from placebo on change from baseline on these measures; the largest difference was on the Strauss-Carpenter Level of Functioning Scale (*P* = .15) (Table 1).

Cognitive Functioning

BL-1020 20–30 mg achieved significantly more improvement than placebo, BL-1020 10 mg, and risperidone on the Brief Assessment of Cognition in Schizophrenia composite score change (mean [95% CI]) from baseline to end point (9.27 [6.94–11.59] vs 6.01 [3.64–8.38], *P* = .027; 6.43 [4.17–8.69] *P* = .04; and 6.20 [4.06–8.34], *P* = .027), at day 42 (ie, persons who had 42 days of treatment) (10.13 [7.82–12.44] vs 6.21 [3.82–8.60], *P* = .009; 6.84 [4.57–9.12], *P* = .019; and 6.73

Figure 2. Changes in Score on Brief Assessment of Cognition in Schizophrenia Subscales From Baseline to End of Study (adjusted for age and sex; least squares mean and 95% CI)



[a]20–30 mg vs placebo, $P = .03$; 10 mg vs placebo, $P = .68$; risperidone vs placebo, $P = .92$.
[b]20–30 mg vs placebo, $P = .02$; 10 mg vs placebo, $P = .13$; risperidone vs placebo, $P = .32$.
[c]20–30 mg vs placebo, $P = .04$; 10 mg vs placebo, $P = .94$; risperidone vs placebo, $P = .44$.
[d]20–30 mg vs placebo, $P = .10$; 10 mg vs placebo, $P = .54$; risperidone vs placebo, $P = .51$.
[e]20–30 mg vs placebo, $P = .17$; 10 mg vs placebo, $P = .55$; risperidone vs placebo, $P = .90$.
[f]20–30 mg vs placebo, $P = .12$; 10 mg vs placebo, $P = .43$; risperidone vs placebo, $P = .87$.
[g]20–30 mg vs placebo, $P = .22$; 10 mg vs placebo, $P = .23$; risperidone vs placebo, $P = .45$.

[4.63–8.84], $P = .013$), and after baseline observation carried forward analysis (5.96 [4.14–7.78] vs 3.64 [1.90–5.38], $P = .041$; 3.76 [2.03–5.48], $P = .049$; and 3.86 [2.16–5.57], $P = .061$). The effect size difference on Cohen d[36] at day 42 (completers) between BL-1020 20–30 mg as compared to placebo, BL-1020 10 mg, and risperidone were as follows: 0.50, 0.42, and 0.43. At end point, these differences were 0.40, 0.35, 0.38, and, when using baseline observation carried forward analysis, the differences were 0.29, 0.27, and 0.26. Superiority of BL-1020 20–30 mg adjusted for age and gender are illustrated by subscale in Figure 2. Change in cognition by patients in Romania and India separately showed the same pattern of group differences (data not presented).

Safety and Tolerability

The proportion of patients with any event, drug-related event, and event leading to discontinuation was highest for risperidone (supplementary eTable 4). Serious adverse events were rare. Nervous system disorders were most prevalent for BL-1020 20–30 mg (62.5%), followed by risperidone (51.6%), BL-1020 10 mg (31.1%), and placebo (22.6%). Prevalence of extrapyramidal symptoms was comparable for BL-1020 20–30 mg and risperidone and substantially higher than BL-1020 10 mg and placebo. One risperidone patient died of suicide.

Maximum changes on ESRS parkinsonism, dystonia, and dyskinesia subscale scores were not significantly different between BL-1020 10 mg and placebo. Both BL-1020 20–30 mg and risperidone had significantly more increases of a similar magnitude (both P values $< .001$) on the total score and parkinsonism subscale score than placebo and BL-1020 10 mg. On the dystonia subscale, compared to placebo, BL-1020 20–30 mg had significantly more score increase ($P = .02$), whereas this difference did not reach significance for risperidone ($P = .14$). Both risperidone and BL-1020 20–30 mg had significantly higher akathisia maximum scores on the ESRS than placebo and BL-1020 10 mg. However, the BL-1020 20–30 mg and risperidone did not differ significantly on the akathisia subscale ($P = .42$) (supplementary eTable 5).

There were no clinically meaningful changes in vital signs, metabolic variables, liver function tests, hematology profile, and urinanalysis. Change from baseline to end point on prolactin levels was dramatically ($P < .0001$) higher for risperidone (mean = 45.74, SD = 44.96, n = 77) than for BL-1020 20–30 mg (mean = 8.43, SD = 38.89, n = 78), BL-1020 10 mg (mean = 3.69 SD = 26.84, n = 75), and placebo (mean = −3.39, SD = 22.31, n = 80). BL-1020 20–30 mg showed significantly greater increase in prolactin levels than placebo ($P = .02$) but not BL-1020 10 mg ($P = .20$) (supplementary eTable 5).

The notable differences in use of concomitant medications were higher use of benzodiazepine-related drugs with BL-1020 10 mg (38.9%) and placebo (35.5%) as compared to risperidone (28.6%) and BL-1020 20–30 mg (19.1%). Anticholinergics were used more frequently for patients getting BL-1020 20–30 mg (48.3%) and risperidone (40.7%) than BL-1020 10 mg (15.6%) and placebo (17.2%). Use of concomitant medications for extrapyramidal symptoms was similar for BL-1020 20–30 mg and risperidone (22.7%, n = 20/89; 23.1%, n = 21/91) and considerably lower for BL-1020 10 mg and placebo (5.6%, n = 5/90; 2.2%, n = 21/91) (supplementary eTable 6).

DISCUSSION

BL-1020 20–30 mg showed significantly greater improvement on the PANSS and readiness for discharge than placebo. There were no significant differences on these measures between BL-1020 20–30 mg and risperidone. BL-1020 (both arms) had a numerically (but not statistically) higher dropout rate, which was due to "lack of efficacy" and "uncooperativeness," than risperidone. This outcome may be due, at least in part, to a starting dose of 10 mg in the high-dose group, which was too low and was the same dose as the low-dose group. BL-1020 20–30 mg and risperidone had similarly higher maximum ESRS scores than placebo.

BL-1020 20–30 mg was associated with a significantly greater improvement in cognitive functioning on the Brief Assessment of Cognition in Schizophrenia as compared to risperidone, placebo, and BL-1020 10 mg. In results that were different from both recent landmark studies that compared a first-generation antipsychotic to second-generation antipsychotics, European First-Episode Schizophrenia Trial[2] in first-episode patients and CATIE[4] in chronically ill patients, we found a significant effect for BL-1020 in ameliorating cognitive impairments. Superiority of BL-1020 on cognition was consistent with observations made in animal models of cognition that demonstrated that BL-1020, but not perphenazine, was able to reverse cognitive impairment induced by phencyclidine.[12] We hypothesize that the addition of GABA contributes to the procognitive outcome of BL-1020, which is supported by data[12,13] suggesting that administration of a GABA type A antagonist (picrotoxin and bicuculline) in conjunction with BL-1020 reversed the ability of BL-1020 to repair cognitive impairments induced by phencyclidine in animal models. Perphenazine alone in the animal models was not sufficient to effect cognitive changes. Data from CATIE suggest, however, that perphenazine may have some precognitive effect relative to other drugs, as a post hoc 18-month assessment in CATIE found that perphenazine was slightly better at improving cognition than risperidone and olanzapine.[4]

Limitations of this study include a relatively high dose of risperidone, which may have negatively impacted cognition. Patients may not be representative of typical clinical samples; they had relatively low rates of smoking and low BMI. We excluded treatment-refractory psychosis and clozapine-treated patients, other diagnoses, patients with tardive dyskinesia, and depot treatments, thereby enriching this sample with patients who may have been more likely to do better when receiving treatment. Comparisons with risperidone were not planned. Improvements observed early in all groups might be clinical trials effect. Motor side effects did not differ between clinically effective dose of BL-1020 and risperidone; thus, anticipated motor effect was not found. Benzodiazepines may have interfered with GABAergic moiety to a greater extent than other prohibited drugs. A perphenazine arm would have allowed examining the utility of the GABA conjugate.

Cognitive improvement may have been due to pseudospecificity. However, whereas BL-1020 was not significantly different than risperidone on improvement of psychotic symptoms, it was significantly superior to risperidone on change in cognition. Furthermore, we reran the planned ANCOVA of cognitive change, controlling for PANSS change. The statistically significant superiority of BL-1020 20–30 mg on cognition over the other groups remained. A claim for cognitive enhancement would require a study of stabilized patients to avoid improvement on psychosis affecting cognitive testing results. It is possible that, at lower dosages, risperidone would have shown more favorable results on cognition.

Future studies should control for possible effects of concomitant medications on cognitive test performance. In this study, we reran protocol-specified ANCOVA cognitive analysis after removing all patients who were taking benzodiazepines, β-blockers, antipsychotics, benztropine, hypnotics and sedatives, psychostimulants and nootropics, and tertiary amines at time of either cognitive testing. Among these patients, the BL-1020 20–30 mg group (n = 29) showed significantly ($P = .04$) greater cognitive improvement than placebo (n = 32) and a numeric superiority ($P = .14$) over risperidone (n = 39), findings that suggest that using these medications did not change study results. In addition, future studies should examine long-term outcomes and whether, for some patients, lower doses of BL-1020 may prove as effective with fewer adverse effects. An ongoing randomized controlled trial of BL-1020 is using the US Food and Drug Administration–recommended Measurement and Treatment Research to Improve Cognition in Schizophrenia cognitive battery.[37]

Drug names: benztropine (Cogentin and others), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa and others), risperidone (Risperdal and others).

Author affiliations: BioLineRx, Ltd, Jerusalem (Dr Geffen); Tel Aviv University, Tel Aviv (Dr Davidson); Bar Ilan University, Ramat Gan (Dr Rabinowitz), Israel; Duke University Medical Center, Durham, North Carolina (Dr Keefe); and APC AG, St Moritz, Switzerland (Dr Anand).

Author contributions: Dr Rabinowitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Potential conflicts of interest: **Dr Geffen** was an employee of BioLineRx at the time this study was conducted. **Dr Keefe** reports that he has received research funding support from US Department of Veterans Affairs, GlaxoSmithKline, National Institute of Mental Health, Novartis, PsychoGenics, Research Foundation for Mental Hygiene, and Singapore Medical Research Council; has been a consultant to Abbott Amgen, Astellas, Asubio, BiolineRx, Cypress Bioscience, Eli Lilly, EnVivo, Helicon, Lundbeck, Merck, Pfizer, Roche, Shire, Sunovion, and Takeda; has been a shareholder in NeuroCog Trials; and has received royalties from the Brief Assessment of Cognition in Schizophrenia (BACS) testing battery and the MATRICS Battery (BACS Symbol Coding). **Dr Rabinowitz** has been a consultant to BiolineRx, Janssen, Avraham, Roche, and Amgen; has received grant/research support from Eli Lilly, and has received honoraria from Pfizer. **Dr Anand** has participated in advisory boards and received honoraria from Abbott, Cephalon, Forest, Janssen, Newron, Pfizer, Roche, Schering-Plough, Takeda, and Teva and has served as a consultant to BiolineRx. **Dr Davidson** has received research grant support, travel support, speaker fees, and/or consultancy fees from Johnson & Johnson, Pfizer, Lundbeck, Teva, BioLineRx, Eli Lilly, Sanofi-Aventis, Roche, GlaxoSmithKline, Servier, Takeda, Envivo, and Cypress and holds stocks in Tangent Data and BioLineRx.
Funding/support: This study was sponsored by BioLineRx.
Role of sponsor: The study sponsor was involved in design and conduct of the study; collection, management, analysis, and interpretation of the data; and review of the manuscript.
Previous presentation: Cognition in Schizophrenia: A Satellite Meeting of the Schizophrenia International Research Society; April 15, 2010; Florence, Italy ▪ 6th International Society for CNS Clinical Trials and Methodology (ISCTM) Conference; February 21–23, 2011; Baltimore, Maryland.
Supplementary material: See accompanying pages.

REFERENCES

1. Goldberg TE, Gomar JJ. Targeting cognition in schizophrenia research: from etiology to treatment. *Am J Psychiatry*. 2009;166(6):631–634.
2. Davidson M, Galderisi S, Weiser M, et al.. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). *Am J Psychiatry*. 2009; 166(6):675–682.
3. Goldberg TE, Goldman RS, Burdick KE, et al. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? *Arch Gen Psychiatry*. 2007; 64(10):1115–1122.
4. Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch Gen Psychiatry*. 2007;64(6):633–647.
5. Vernon AC, Natesan S, Modo M, et al. Effect of chronic antipsychotic treatment on brain structure: a serial magnetic resonance imaging study with ex vivo and postmortem confirmation. *Biol Psychiatry*. 2011;69(10): 936–944.
6. Buchanan RW, Davis M, Goff D, et al. A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophr Bull*. 2005;31(1):5–19.
7. Bowie CR, Reichenberg A, Patterson TL, et al. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *Am J Psychiatry*. 2006;163(3):418–425.
8. Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *Am J Psychiatry*. 2004;161(6):985–995.
9. Harvey PD, Rabinowitz J, Eerdekens M, et al. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. *Am J Psychiatry*. 2005;162(10): 1888–1895.
10. Lee MA, Thompson PA, Meltzer HY. Effects of clozapine on cognitive function in schizophrenia. *J Clin Psychiatry*. 1994;55(suppl B):82–87.
11. Nudelman A, Gil-Ad I, Shpaisman N, et al. A mutual prodrug ester of GABA and perphenazine exhibits antischizophrenic efficacy with diminished extrapyramidal effects. *J Med Chem*. 2008;51(9):2858–2862.
12. Geffen Y, Nudelman A, Gil-Ad I, et al. BL-1020: a novel antipsychotic drug with GABAergic activity and low catalepsy, is efficacious in a rat model of schizophrenia. *Eur Neuropsychopharmacol*. 2009;19(1):1–13.
13. Neill J, Grayson B, Idris N, et al. BL1020 Improves a Subchronic Phencyclidine-Induced Deficit in Object Recognition Memory in the Rat: potentially via enhanced dopamine release in the pre-frontal cortex. Society of Biological Psychiatry (SOBP) 64th Annual Scientific Convention and Meeting; May 14–16, 2009; Vancouver, Canada.
14. Akbarian S, Huntsman MM, Kim JJ, et al. GABAA receptor subunit gene expression in human prefrontal cortex: comparison of schizophrenics and controls. *Cereb Cortex*. 1995;5(6):550–560.
15. Beasley CL, Reynolds GP. Parvalbumin-immunoreactive neurons are reduced in the prefrontal cortex of schizophrenics. *Schizophr Res*. 1997;24(3):349–355.
16. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Brain Res Rev*. 2000;31(2–3):251–269.
17. Harrison PJ. The neuropathology of schizophrenia: a critical review of the data and their interpretation. *Brain*. 1999;122(pt 4):593–624.
18. Simpson MD, Slater P, Deakin JF, et al. Reduced GABA uptake sites in the temporal lobe in schizophrenia. *Neurosci Lett*. 1989;107(1–3):211–215.
19. Wassef A, Baker J, Kochan LD. GABA and schizophrenia: a review of basic science and clinical studies. *J Clin Psychopharmacol*. 2003;23(6):601–640.
20. Potkin SG, Gharabawi GM, Greenspan AJ, et al. A double-blind comparison of risperidone, quetiapine and placebo in patients with schizophrenia experiencing an acute exacerbation requiring hospitalization. *Schizophr Res*. 2006;85(1–3):254–265.
21. FDA regulations relating to Good Clinical Practice and clinical trials. US Food and Drug Administration Web site. http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#FDARegulations. Updated April 30, 2012. Accessed July 30, 2012.
22. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33;quiz 4–57.
23. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
24. Lindenmayer JP, Czobor P, Alphs L, et al. The InterSePT scale for suicidal thinking reliability and validity. *Schizophr Res*. 2003;63(1–2):161–170.
25. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophr Bull*. 2003;29(1):15–31.
26. Potkin SG, Gharabawi GM, Greenspan AJ, et al. Psychometric evaluation of the Readiness for Discharge Questionnaire. *Schizophr Res*. 2005; 80(2–3):203–212.
27. Addington D, Addington J, Maticka-Tyndale E. Specificity of the Calgary Depression Scale for schizophrenics. *Schizophr Res*. 1994;11(3):239–244.
28. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
29. Strauss JS, Carpenter WT Jr. The prediction of outcome in schizophrenia, 2: relationships between predictor and outcome variables: a report from the WHO international pilot study of schizophrenia. *Arch Gen Psychiatry*. 1974;31(1):37–42.
30. Gharabawi GM, Greenspan A, Rupnow MF, et al. Reduction in psychotic symptoms as a predictor of patient satisfaction with antipsychotic medication in schizophrenia: data from a randomized double-blind trial. *BMC Psychiatry*. 2006;6:45.
31. Keefe RS, Goldberg TE, Harvey PD, et al. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res*. 2004;68(2–3):283–297.
32. Keefe RS, Poe M, Walker TM, et al. The Schizophrenia Cognition Rating Scale: an interview-based assessment and its relationship to cognition, real-world functioning, and functional capacity. *Am J Psychiatry*. 2006; 163(3):426-432.
33. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res*. 2005;76(2–3):247–265.
34. Chouinard G, Ross-Chouinard A, Annable L, et al. Extrapyramidal Symptom Rating Scale. *Can J Neurol Sci*. 1980;7:233–239.
35. Rabinowitz J, Davidov O. A composite approach that includes dropout rates when analyzing efficacy data in clinical trials of antipsychotic medications. *Schizophr Bull*. 2008;34(6):1145–1150.
36. Cohen J. *Statistical Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.
37. Buchanan RW, Keefe RSE, Umbricht D, et al. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive-enhancing drugs: what do we know 5 years later? *Schizophr Bull*. 2011;37(6):1209–1217.

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: BL-1020, a New γ-Aminobutyric Acid–Enhanced Antipsychotic: Results of 6-Week, Randomized, Double-Blind, Controlled, Efficacy and Safety Study

Author(s): Yona Geffen, PhD; Richard Keefe, PhD; Jonathan Rabinowitz, PhD; Ravi Anand, MD; and Michael Davidson, MD

DOI Number: 10.4088/JCP.12m07642

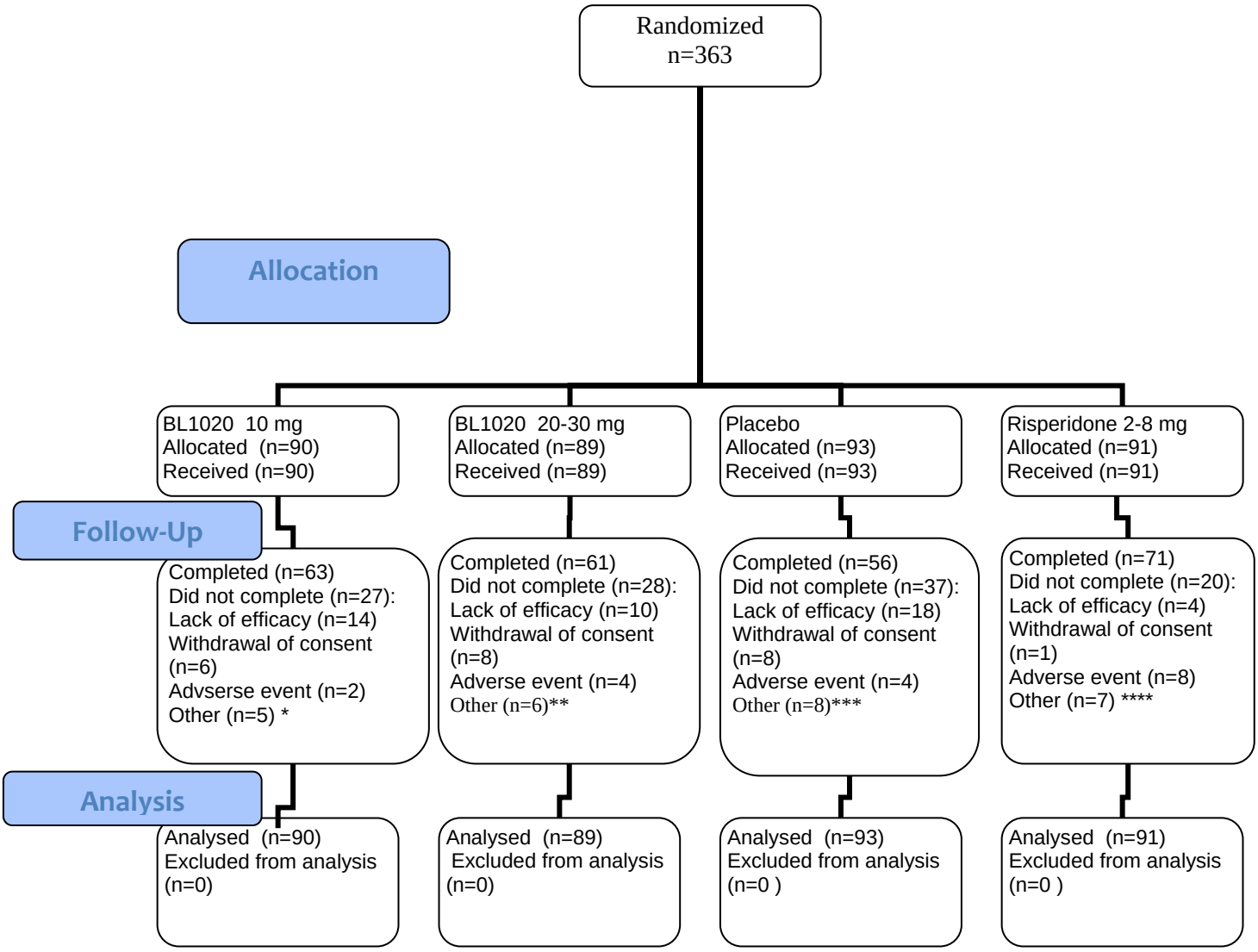
List of Supplementary Material for the article

1. eFigure 1 — Summary of Participant Flow in the Randomized Clinical Trial
2. eTable 1 — Baseline Characteristics
3. eTable 2 — Symptom, Functional, Cognitive and Extrapyramidal Symptoms Measures at Baseline (Means and SD's)
4. eTable 3 — Subject Completion/Discontinuation by Treatment Group and Reason
5. eTable 4 — Incidence of Treatment-Emergent Adverse Events
6. eTable 5 — Safety Data as Compared to Placebo
7. eTable 6 — Concomitant Medications classes and/or individual medications used in >5% of patients in any treatment group

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eFigure 1. Summary of participant flow in the randomized clinical trial (Asterisk indicates consent withdrawal, protocol violation, noncompliance, and loss to follow-up)



.

*Uncooperative non-compliant n=3;; SAE n=1; Lost to follow-up n=1

** Uncooperative non-compliant n=4;; Lost to follow-up n=1; Other n=1

*** Uncooperative non-compliant n=3; Withdrawal of consent n=8 ;SAE n=3; Lost to follow-up n=1

**** Death n=1; SAE n=1; Lost to follow-up n=5

eTable 1. Baseline characteristics

Characteristic	BL1020 10 mg (n=90)	BL1020 30 mg (n=89)	Risperidone 8 mg (n=91)	Placebo (n=93)
Age (yr) mean (sd) (a)	33.1 (10.13)	33.6 (10.11)	34.2 (10.34)	35.2 (10.26)
Male sex (%) (b)	68.9% (n=62)	69.7% (n=62)	71.4% (n=65)	60.2% (n=56)
Race or ethnic group (%) (c) Asian	70% (n=63)	70.8% (n=63)	69.2% (n=63)	68.8% (n=64)
White	26.7% (n=24)	25.8% (n=23)	27.5% (n=25)	28.0% (n=26)
Black or other	3.2% (n=3)	3.4% (n=3)	3.3% (n=3)	3.2% (n=3)
Education (%) (d) Illiterate	5.6% (n=5)	6.7% (n=6)	6.6% (n=6)	8.6% (n=8)
1-7 years	11.1% (n=10)	16.9% (n=15)	15.4% (n=14)	12.9% (n=12)
8-15 years	78.9% (n=71)	66.3% (n=59)	74.7% (n=68)	71.0% (n=66)
>=16 years	4.4% (n=4)	10.1% (n=9)	3.3% (n=3)	7.5% (n=7)
Marital status (e) Presently married/ in relationship	36.7% (n=33)	42.7% (n=38)	38.5% (n=35)	50.5% (n=47)
Widowed	2.2% (n=2)	0.0% (n=0)	2.2% (n=2)	2.2% (n=2)
Divorced/Separated	10.0% (n=9)	11.2% (n=10)	8.8% (n=8)	15.1% (n=14)
Never married (Single)	51.1% (n=46)	46.1% (n=41)	50.5% (n=46)	32.3% (n=30)
Height (f)	164.1 (9.34), n=90	163.9 (10.21), n=89	163.9 (9.20), n=91	161.9 (9.32), n=93
Weight (g)	62.07 (14.31), n=90	62.39 (16.28), n=89	60.94 (13.17), n=91	61.38 (15.94), n=93
BMI (h)	22.90 (4.20), n=90	23.00 (4.72), n=89	22.58 (4.02), n=91	23.37 (5.70), n=93
Duration of illness (years) (i)	8.83 (9.01)	7.93 (8.31)	8.26 (8.92)	9.34 (8.88)
Current cigarette smokers (j)	25.6% (n=23)	24.7% (n=22)	34.1% (n=31)	26.59% (n=25)
Caffeine (k) Less than one cup per day	46 51.1%	40 44.9%	44 48.4%	44 47.3%
1-2 cups per day	27 30.0%	30 33.7%	33 34.1%	31 34.1%
3 or more cups per day	17 18.9%	19 21.3%	16 17.6%	16 17.2%

Statistical significance: (a) f=1.04, df=2,360, p=0.35; (b) χ^2=3.16, df=1, p=0.37; (c) χ^2=0.12, df=9, p=0.99; (d) χ^2=7.00, df=9, p=0.64; (e) χ^2=11.00, df=9, p=0.27; (f) f=1.09, df=3, 359, p=.35; (g) f=.17, df=3, 359, p=.91; (h) f=.44, df=3, 359, p=.72 (i) f=.454, df=3, 358, p=.71; *(j) χ^2=2.46, df=3, p=.48;(k) χ^2=1.32, df=6, p=.97*

eTable 2. Symptom, functional, cognitive and extrapyramidal symptoms measures at baseline (Means and SD's)

	BL1020 10 mg (n=90)	BL1020 30 mg (n=89)	Risperidone 8 mg (n=91)	Placebo (n=93)
PANSS Positive	29.0 (3.5) (n=90)	29.1 (3.1) (n=89)	28.9 (3.1) (n=91)	28.9 (3.2) (n=93)
Negative	23.2 (14.2) (n=90)	23.1 (4.2) (n=89)	23.1 (4.2) (n=91)	23.3 (4.5) (n=93)
General psychopathology	45.6 (6.9) (n=90)	45.5 (6.3) (n=89)	46.4 (7.8) (n=91)	46.2 (7.3) (n=93)
Total (a)	97.7 (11.1) (n=90)	97.7 (10.3) (n=89)	99.5 (12.1) (n=91)	98.5 (11.4) (n=93)
Calgary depression scale (b)	1.1 (1.57) (n=90)	1.1 (1.73) (n=89)	1.6 (2.30) (n=91)	1.5 (2.45) (n=93)
CGI-S (c)	4.9 (0.44) (n=90)	5.0 (0.51) (n=89)	5.0 (0.57) (n=91)	5.0 (0.56) (n=93)
Strauss Carpenter Level of Functioning Scale(d)	13.5 (6.00) (n=90)	13.9 (5.16) (n=89)	13.3 (5.10) (n=91)	13.7 (5.99) (n=93)
Brief Assessment of Cognition in Schizophrenia *total (e)*	16.70 (15.5) (n=83)	15.30 (15.5) (n=72)	13.50 (12.3) (n=84)	16.50 (15.4) (n=80)
Verbal memory	29.00 (10.83) (n=85)	28.27 (12.67) (n=82)	28.16 (9.11) (n=87)	29.38 (11.44) (n=85)
Digit Sequencing	25.29 (14.03) (n=84)	23.11 (15.88) (n=78)	22.30 (11.12) (n=86)	24.75 (13.62) (n=85)
Token Motor Task	36.06 (12.16) (n=86)	33.22 (13.08) (n=80)	32.86 (10.50) (n=86)	33.56 (13.75) (n=85)
Fluency	24.24 (8.92) (n=86)	23.49 (8.25) (n=81)	23.75 (7.82) (n=87)	24.66 (9.25) (n=85)
Symbol Coding	24.12 (11.90) (n=84)	21.85 (9.72) (n=74)	21.90 (9.70) (n=84)	24.28 (9.81) (n=82)
Tower of London	26.92 (17.43) (n=85)	25.36 (16.99) (n=78)	24.20 (16.21) (n=85)	27.48 (16.80) (n=81)
Extrapyramidal Symptom Rating Scale *Total (f)*	2.5 (6.00), n=90	3.7 (8.53), n=89	3.1 (7.79), n=91	3.7 (10.32), n=93
Parkinsonism	1.14 (2.42), n=90	1.92 (4.61), n=89	1.58 (3.98), n=93	1.30 (3.25), n=91
Dystonia	.01 (.10), n=90	.00 (.00), n=89	.07 (.44), n=91	.06 (.38), n=93
Dyskensia	.30 (1.43), n=90	.36 (1.52), n=89	.54 (2.19), n=91	.54 (2.25), n=93
Akathisia				

Statistical significance: (a) f=.52, df=3, 359, p=.67; (b) f=1.49, df=3, 359, p=.22; (c) f=.82, df=3, 359, p=.48; (d) (e) f=0.83, df=3, 315; p=.48; (f) f=.43, df=3,359, p=.73

eTable 3. Subject Completion/Discontinuation by Treatment Group and Reason

	10 mg/daily		30 mg/daily		Risperidone		Placebo		Total	
Completed the 6-week study[1]	N	%	n	%	n	%	n	%	n	%
Yes	63	70.0	61	68.5	71	78.0	56[2]	60.2	251	69.1
No	27	30.0	28	31.5	20	22.0	37	39.8	112	30.9
Vs. placebo	10.9%, p=0.06		10.5%, p=.07		18.9%, p=.003					
Reason for discontinuation										
Adverse event	2	2.2	4	4.5	8	8.8	4	4.3	18	5.0
Lack of efficacy	14	15.6	10	11.2	4	4.4	18	19.4	46	12.7
Uncooperativeness/non-compliance	3	3.3	4	4.5	0	0	3	3.2	10	2.8
Withdrawal of consent	6	6.7	8	9.0	1	1.1	8	8.6	23	6.3
Death	0	0	0	0	1	1.1	0	0	1	0.3
Serious Adverse Event	1	1.1	0	0	1	1.1	3	3.2	5	1.4
Lost to follow-up	1	1.1	1	1.1	5	5.5	1	1.1	8	2.2
Other	0	0	1	1.1	0	0	0	0	1	0.3

[1] Chi-Square=6.88, df=3, p=.076
[2] 3 did not complete medication intake.

eTable 4. Incidence of Treatment-Emergent Adverse Events

	BL1020 10 mg (n=90)	BL1020 20-30 mg (n=89)	Risperidone 2-8 mg (n=89)	Placebo (n=93)
At least one AE	68 (75.6%)	72 (80.9%)	**80 (87.9%)**	64 (68.8%)
At least one drug related AE	**50 (55.6%)**	**65 (73.0%)**	**70 (76.9%)**	**47 (50.5%)**
At least one SAE	**4 (4.4%)**	**0 (0.0%)**	3 (3.3%)	**6 (6.5%)**
At least one drug related SAE	**0 (0.0%)**	0 (0.0%)	1 (1.1%)	3 (3.2%)
AE leading to discontinuation	**3 (3.3%)**	**5 (5.6%)**	**10 (11.0%)**	**6 (6.5%)**
Incidence of Treatment-Emergent Adverse Events (≥5% Incidence in Any Treatment Group) or clinically important event*				
Gastrointestinal disorders				
Constipation	3 (3.3)	2 (2.2)	5 (5.5)	2 (2.2)
General disorders				
Pyrexia	5 (5.6)	9 (10.1)	8 (8.8)	7 (7.5)
Laboratory Investigations				
ALT abnormal	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	1 (2.2)	3 (3.4)	1 (1.1)	1 (1.1)
AST increased	3 (3.3)	3 (3.4)	0 (0.0)	0 (0.0)
Blood CPK increased	3 (3.3)	1 (1.1)	1 (1.1)	0 (0.0)
Blood pressure increased	3 (3.3)	1 (1.1)	2 (2.2)	2 (2.2)
ECG abnormal	2 (2.2)	0 (0.0)	4 (4.4)	0 (0.0)
ECG QT prolonged	2 (2.2)	0 (0.0)	4 (4.4)	0 (0.0)
Heart rate decreased	1 (1.1)	3 (3.4)	1 (1.1)	2 (2.2)
Heart rate increased	2 (2.2)	3(3.4)	9 (9.9)	11 (11.8)
Weight increased	5 (5.6)	2 (2.2)	3 (3.3)	2 (2.2)
Nervous system disorders				
Akathisia	1 (1.1)	16 (18.0)	14 (15.4)	1 (1.1)
Bradykinesia	4 (4.4)	10 (11.2)	13 (14.3)	2 (2.2)
Headache	9 (10.0)	9 (10.1)	10 (11)	9 (9.7)
Oromandibular dystonia	2 (2.2)	6 (6.7%)	2 (2.2)	1 (1.1)
Muscle rigidity	5 (5.6)	21 (23.6)	20 (22.0)	4 (4.3)
Parkinsonism	2 (2.2)	5 (5.6)	9 (9.9)	1 (1.1)
Tremor	9 (10.0)	29 (32.6)	19 (20.9)	10 (10.8)
Grand mall seizure			1 (1.1)	
*ischemic stroke	1			
Neuroleptic malignant syndrome				1
Death for suicide	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Psychiatric disorders				
Agitation	16 (17.8)	17 (19.1)	21 (23.1)	25 (26.9)
Insomnia	29 (32.2)	18 (20.2)	23 (25.3)	22 (23.7)
Delirium	0	1 (1.1)	0	0
Restlessness	3 (3.3)	4 (4.5)	5 (5.5)	6 (6.5)
Schizophrenia worsening				

*Values are given as the number (percentage) of patients.

eTable 5. Safety data as compared to placebo (means, 95% Confidence interval, p=)

Safety measures	BL1020 10 mg (n=90)				BL1020 30 mg (n=89)				Risperidone (n=91)			
	Mean	Confidence Interval			Mean	Confidence Interval			Mean	Confidence Interval		
Extrapyramidal Symptom Rating Scale (Maximum change from baseline)	0.9	-2.1	3.9	p=.53	9.3	6.3	12.3	p<.001	9.2	6.3	12.2	p<0.001
Parkinsonism	.43	.47	1.61	p=.68	6.11	4.06	8.15	p<.001	6.35	4.33	-8.37	p<.001
Dystonia	.005	.32	.31	p=.97	.36	.05	.68	p=.02	.23	.07	.32	p=.14
Dyskinesia	-.06	-.14	.26	p=.58	.12	-.08	.33	p=.23	.08	-.12	.28	p=.45
Akathisia	.01	-.29	.32	p=.94	.35	.04	.66	P=.02	.47	.16	.78	p=.003
BMI change to day 35	0.21	-0.04	0.46	p=.10	0.20	-0.03	.43	p=.09	0.16	-0.09	0.41	p=.20
Prolactin to end of study	7.10	-0.68	14.88	p=.07	11.80	1.87	21.73	p=.02	49.10	38.00	60.23	p<.001

eTable 6. Concomitant Medications classes and/or individual medications used in >5% of patients in any treatment group

Chemical Class/ Generic Name	BL-1020		Risperidone	Placebo
	10 mg/day	30 mg/day	8 mg/day	
	n=90	n=89	n=91	n=93
Subjects with at least one concomitant medication [n (%)]	*62 (68.9%)*	*67 (75.3%)*	*72 (79.1%)*	*68 (73.1%)*
Anilides- Paracetamol	6 (6.7%)	5 (5.6%)	8 (8.8%)	9 (9.7%)
Benzodiazepine Derivatives	36 (40.0%)	40 (44.9%)	38 (41.8%)	41 (44.1%)
Lorazepam	33 (36.7%)	36 (40.4%)	36 (39.6%)	38 (40.9%)
Nitrazepam	4 (4.4%)	4 (4.5%)	2 (2.2%)	4 (4.3%)
Benzodiazepine Related Drugs	35 (38.9%)	17 (19.1%)	26 (28.6%)	33 (35.5%)
Zolpidem	33 (36.7%)	16 (18.0%)	24 (26.4%)	33 (35.5%)
Butyrophenone Derivatives- Haloperidol	5 (5.6%)	2 (2.2%)	2 (2.2%)	6 (6.5%)
Diazepines, Oxazepines and Thiazepines	5 (5.6%)	9 (10.1%)	5 (5.5%)	9 (9.7%)
Olanzapine	4 (4.4%)	8 (9.0%)	5 (5.5%)	7 (7.5%)
Hypnotics and Sedatives- Promethazine	2 (2.2%)	7 (7.9%)	4 (4.4%)	2 (2.2%)
Osmotically Active Laxatives- Lacutlose	0 (0.0%)	1 (1.1%)	5 (5.5%)	1 (1.1%)
Other Antipsychotics	7 (7.8%)	8 (9.0%)	5 (5.5%)	5 (5.4%)
Risperidone	6 (6.7%)	8 (9.0%)	5 (5.5%)	3 (3.2%)
Phenothiazines Piperazine Structure- Trifluoperazine	2 (2.2%)	4 (4.5%)	3 (3.3%)	5 (5.4%)
Priopionic Acid Derivatives	9 (10.0%)	9 (10.1%)	8 (8.8%)	6 (6.5%)
Galenic/Ibuprofen/Paracetamol	6 (6.7%)	7 (7.9%)	6 (6.6%)	5 (5.4%)
Tertiary Amines-anticholinergics	14 (15.6%)	43 (48.3%)	37 (40.7%)	16 (17.2%)
Trihexyphenidyl	13 (14.4%)	40 (44.9%)	34 (37.4%)	14 (15.1%)