



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

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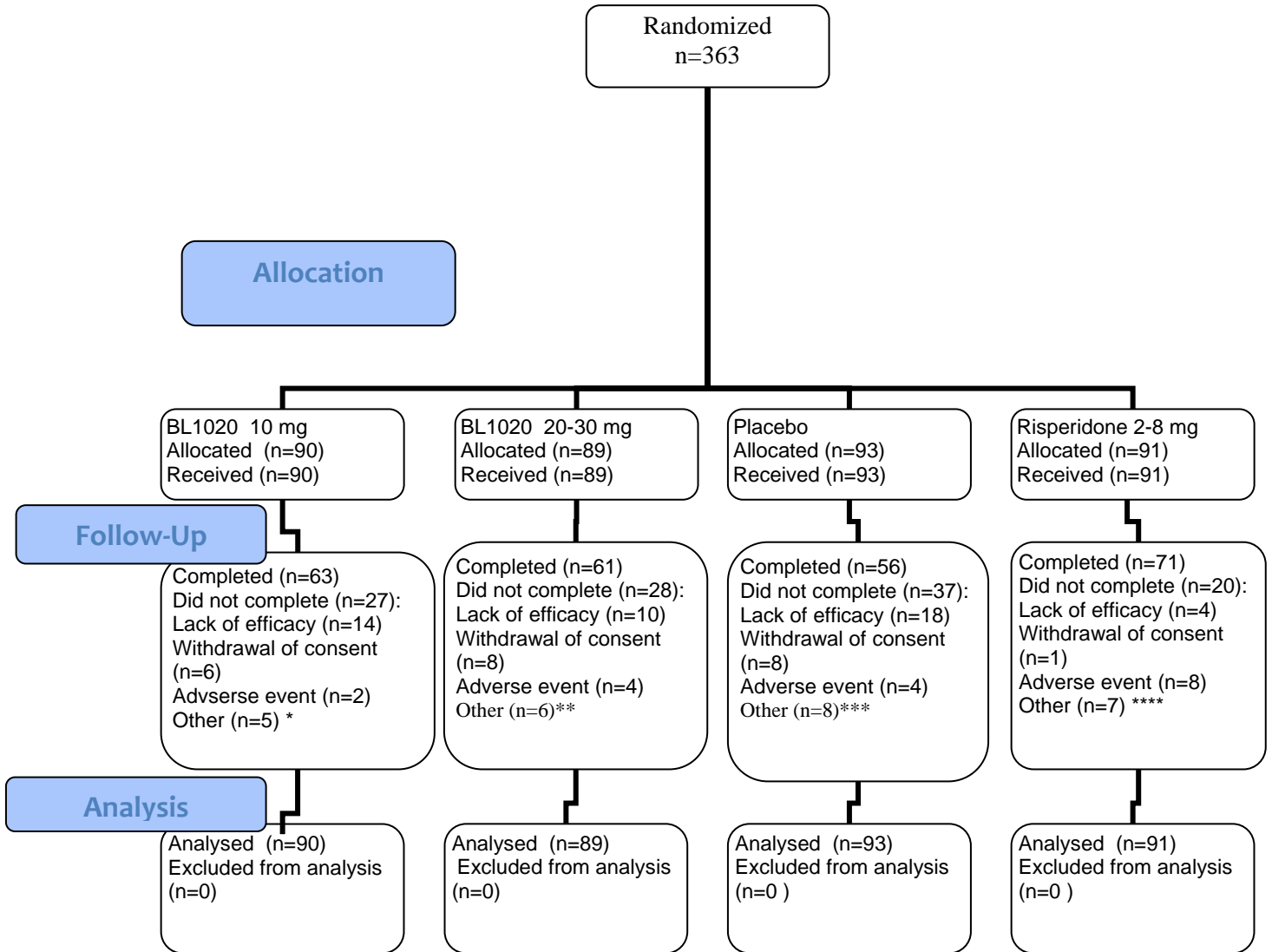
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eFigure 1. Summary of participant flow in the randomized clinical trial (Asterisk indicates consent withdrawal, protocol violation, noncompliance, and loss to follow-up)



*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)
<i>Age (yr) mean (sd) (a)</i>	33.1 (10.13)	33.6 (10.11)	34.2 (10.34)	35.2 (10.26)
<i>Male sex (%) (b)</i>	68.9% (n=62)	69.7% (n=62)	71.4% (n=65)	60.2% (n=56)
<i>Race or ethnic group (%) (c)</i>				
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)
<i>Education (%) (d)</i>				
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)
<i>Marital status (e)</i>				
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)
<i>Height (f)</i>	164.1 (9.34), n=90	163.9 (10.21), n=89	163.9 (9.20), n=91	161.9 (9.32), n=93
<i>Weight (g)</i>	62.07 (14.31), n=90	62.39 (16.28), n=89	60.94 (13.17), n=91	61.38 (15.94), n=93
<i>BMI (h)</i>	22.90 (4.20), n=90	23.00 (4.72), n=89	22.58 (4.02), n=91	23.37 (5.70), n=93
<i>Duration of illness (years) (i)</i>	8.83 (9.01)	7.93 (8.31)	8.26 (8.92)	9.34 (8.88)
<i>Current cigarette smokers (j)</i>	25.6% (n=23)	24.7% (n=22)	34.1% (n=31)	26.59% (n=25)
<i>Caffeine (k) Less than one cup per day</i>	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) $\chi^2=3.16$, $df=1$, $p=0.37$; (c) $\chi^2=0.12$, $df=9$, $p=0.99$; (d) $\chi^2=7.00$, $df=9$, $p=0.64$; (e) $\chi^2=11.00$, $df=9$, $p=0.27$; (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) $\chi^2=2.46$, $df=3$, $p=.48$; (k) $\chi^2=1.32$, $df=6$, $p=.97$

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)
<i>PANSS Positive</i>	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)
<i>Calgary depression scale (b)</i>	1.1 (1.57) (n=90)	1.1 (1.73) (n=89)	1.6 (2.30) (n=91)	1.5 (2.45) (n=93)
<i>CGI-S (c)</i>	4.9 (0.44) (n=90)	5.0 (0.51) (n=89)	5.0 (0.57) (n=91)	5.0 (0.56) (n=93)
<i>Strauss Carpenter Level of Functioning Scale(d)</i>	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 <i>total (e)</i>	16.70 (15.5) (n=83)	15.30 (15.5) (n=72)	13.50 (12.3) (n=84)	16.50 (15.4) (n=80)
<i>Verbal memory</i>	29.00 (10.83) (n=85)	28.27 (12.67) (n=82)	28.16 (9.11) (n=87)	29.38 (11.44) (n=85)
<i>Digit Sequencing</i>	25.29 (14.03) (n=84)	23.11 (15.88) (n=78)	22.30 (11.12) (n=86)	24.75 (13.62) (n=85)
<i>Token Motor Task</i>	36.06 (12.16) (n=86)	33.22 (13.08) (n=80)	32.86 (10.50) (n=86)	33.56 (13.75) (n=85)
<i>Fluency</i>	24.24 (8.92) (n=86)	23.49 (8.25) (n=81)	23.75 (7.82) (n=87)	24.66 (9.25) (n=85)
<i>Symbol Coding</i>	24.12 (11.90) (n=84)	21.85 (9.72) (n=74)	21.90 (9.70) (n=84)	24.28 (9.81) (n=82)
<i>Tower of London</i>	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 <i>Total (f)</i>	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
Dyskinesia	.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	
	N	%	n	%	n	%	n	%	n	%
Completed the 6-week study¹										
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 ($\geq 5\%$ 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 n=90	30 mg/day n=89	8 mg/day n=91	n=93
<i>Subjects with at least one concomitant medication [n (%)]</i>	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- Lactulose	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%)