

A randomized trial of aripiprazole vs blonanserin for the treatment of acute schizophrenia and related disorders

Taro Kishi¹
Yuki Matsuda¹
Shinji Matsunaga¹
Tomohiko Mukai^{1,2}
Masatsugu Moriwaki^{1,2}
Hideaki Tabuse³
Kiyoshi Fujita²
Nakao Iwata¹

¹Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, ²Department of Psychiatry, Okehazama Hospital, Toyoake, Aichi, ³Department of Psychiatry, Holy Cross Hospital, Toki, Gifu, Japan

Objective: There has been no direct comparison of aripiprazole and blonanserin for schizophrenia treatment. We conducted a 24-week, rater-masked, randomized trial of aripiprazole (6–30 mg/d) vs blonanserin (4–24 mg/d) in schizophrenia patients who were not taking any antipsychotic medication for more than 2 weeks before enrollment (UMIN000011194).

Methods: The primary outcome measure for efficacy was improvement of Positive and Negative Syndrome Scale (PANSS) total score at week 24. Secondary outcomes were PANSS subscale scores, 21-item Hamilton Rating Scale for Depression (HAMD-21) score, response rate, discontinuation rate, and individual adverse events.

Results: Forty-four patients were recruited. The discontinuation rate was 86.4% in the aripiprazole group and 68.2% in the blonanserin treatment group. There was no significant difference in mean time to discontinuation between the groups. Although both treatment groups showed significant reductions in the PANSS total score, PANSS subscale scores, and HAMD-21 scores at week 24, the magnitudes of the changes did not differ between the groups. There were no significant differences in the incidences of adverse events including somnolence, extrapyramidal symptoms, prolactin-related adverse events, and weight change between the groups.

Conclusion: Our results suggest similar efficacy and safety profiles of aripiprazole and blonanserin in the patients with schizophrenia. Double-blind controlled studies are needed to further explore the efficacy and safety of aripiprazole and blonanserin in schizophrenia.

Keywords: aripiprazole, blonanserin, schizophrenia, efficacy, safety, randomized trial

Introduction

Several schizophrenia treatment guidelines recommend that antipsychotics with lower risk of adverse events be selected for the treatment of schizophrenia.^{1–3} For example, weight gain is one of the metabolic adverse events in patients treated with antipsychotics. This has serious implications on patient's health and quality of life.⁴ Obesity causes diabetes and hyperlipidemia. Moreover, these chronic health conditions can lead to arteriosclerotic cardiovascular disease.⁴ Aripiprazole, lurasidone, and ziprasidone are known to be low-risk antipsychotics when metabolic adverse events are taken into consideration, whereas clozapine, olanzapine, and zotepine are considered high-risk.^{4–6} These antipsychotics are classified as a second-generation antipsychotic (SGA).

Our meta-analysis⁷ revealed that blonanserin (one of the SGAs) is superior to haloperidol in the improvement of the negative symptoms.⁸ In addition, blonanserin carries a lower risk of hyperprolactinemia and weight gain than risperidone.^{7,9} One recent randomized trial reported that there were no significant differences for change in

Correspondence: Taro Kishi
Department of Psychiatry, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan
Tel +81 562 93 9250
Fax +81 562 93 1831
Email tarok@fujita-hu.ac.jp

Positive and Negative Syndrome Scale (PANSS) total scores and PANSS 5-factor model (negative symptoms, excitation, cognitive disorders, positive symptoms, anxiety/depression) scores between the blonanserin and risperidone treatment groups.¹⁰ On the other hand, an 8-week, nonrandomized, open-label study reported that blonanserin was superior to risperidone for improvement of depressive symptoms and quality of daily living.¹¹ Moreover, blonanserin improved impairments in verbal fluency and executive function as well as work skills.¹¹ Another 1-year, open-label study reported that blonanserin improved psychotic symptoms as well as depressive symptoms, and the reduced depressive symptoms were associated with enhanced subjective well-being, subjective quality of life, and verbal memory.¹² Moreover, no significant changes were shown in any safety measures, such as extrapyramidal and cardiometabolic symptoms, during the study.¹² These results suggest that, like aripiprazole, blonanserin can be used as a first-line antipsychotic for the treatment of schizophrenia. Aripiprazole and blonanserin are similar in their receptor profiles, ie, these antipsychotics have high affinity to the serotonin 2A receptor, dopamine D₂ receptor, and dopamine D₃ receptor as well as weak affinity to the dopamine D₁ receptor, histamine H₁ receptor, muscarinic M₁ receptor, and adrenergic α_1 receptor.^{10,13} However, there has been no direct comparison between aripiprazole and blonanserin in patients with schizophrenia. Therefore, we conducted a 24-week, rater-masked, randomized trial of aripiprazole vs blonanserin in patients with acute schizophrenia and related disorders.

Methods

Subjects

The present study was conducted from July 2012 to December 2015 at Fujita Health University Hospital, Holy Cross Hospital, and Okehazama Hospital. This trial was registered at the University hospital Medical Information Network Clinical Trials Registry (UMIN000011194). The patients were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria with consensus of at least two experienced psychiatrists on the basis of unstructured interviews and a review of all medical records. All subjects met the following inclusion criteria: 1) had acute schizophrenia but had not taken any antipsychotic medication for more than 2 weeks before enrollment, 2) were aged between 20–70 years, 3) had no neurologic or systemic diseases, including disturbance of hematopoiesis, 4) had no history of electroconvulsive therapy within 6 months prior to study enrollment, 5) were not

pregnant, and 6) had no dependence on any addictive substances other than nicotine in the past 5 years before enrollment. All subjects underwent laboratory blood testing and electrocardiography at the time of enrollment, and no patient was excluded from the study due to a medical condition.

The clinical trial was described in detail, and written informed consent was obtained from all participants and their guardians. This study was approved by the three Ethics Committees of Fujita Health University, Holy Cross Hospital, and Okehazama Hospital.

Procedures

All patients were randomly assigned to one of the two treatment groups by the central registration office. When the patients satisfied the inclusion and exclusion criteria for this multicenter trial, the randomization procedure (using a random number table) was carried out by the authors, in contact with a central registration office, by telephone. The doses of aripiprazole and blonanserin were slowly increased (initial dose, aripiprazole: 6 mg/d, blonanserin: 4 mg/d) as a rule unless severe side effects occurred (in such cases, it was slowly decreased). The maximum doses of aripiprazole and blonanserin were 30 mg/d and 24 mg/d, respectively. The subsequent antipsychotic dosage was increased or decreased according to the patient's tolerance and therapeutic response. Lorazepam as an anxiolytic, brotizolam and eszopiclone as hypnotics, and biperiden as an anticholinergic drug were allowed during our clinical trial (by prescription and for valid clinical reasons).

Evaluation of psychopathology, tolerability, and safety

The PANSS and 21-item Hamilton Rating Scale for Depression (HAM-D-21)¹⁴ were completed at baseline and at 4, 8 (PANSS only), 12, and 24 weeks after starting administration or at all of these times until discontinuation as well as at discontinuation. Treatment-emergent adverse events were recorded at each time point, including immediately before the study, upon spontaneous complaint, and through clinical observation using the Udvalg for Kliniske Undersogelser Side Effect Rating Scale.¹⁵ The Drug-induced Extrapyramidal Symptoms Scale (DIEPSS)^{16,17} was used for evaluation of extrapyramidal symptoms.

The raters who administered the psychometric tests were masked to treatment group allocation, but patients and physicians knew the type of treatment received. Raters were psychologists not involved in any treatment decisions or evaluation of side effects. Therefore, they did not need to

Table 1 Baseline characteristics of the patients

Variable	Aripiprazole	Blonanserin	Group difference (Student's <i>t</i> -test or χ^2 test and <i>P</i> -value)	
Male (%)	7 (31.8)	11 (50.0)	$\chi^2=1.51$	<i>P</i> =0.219
Age, years	42.4±12.6	36.5±9.72	<i>t</i> =-1.75	<i>P</i> =0.0871
First episode (%)	13 (59.1)	14 (63.6)	$\chi^2=0.096$	<i>P</i> =0.757
Educational history, years	12.4±2.70	13.8±2.02	<i>t</i> =1.96	<i>P</i> =0.0566
Hospitalization (%)	14 (63.6)	16 (72.7)	$\chi^2=0.420$	<i>P</i> =0.517
Study center (Okehazama Hospital, %)	14 (63.6)	14 (63.6)	$\chi^2=0.00$	<i>P</i> =1.00
Married (%)	10 (45.5)	9 (40.9)	$\chi^2=0.093$	<i>P</i> =0.761
Unemployed (%)	17 (77.3)	13 (59.1)	$\chi^2=1.69$	<i>P</i> =0.193
Current smoker (%)	4 (18.2)	7 (31.8)	$\chi^2=1.10$	<i>P</i> =0.294
PANSS total score	102.1±15.6	112.5±29.1	<i>t</i> =1.47	<i>P</i> =0.149
HAMD-21 total scores	22.7±8.96	26.3±5.62	<i>t</i> =1.53	<i>P</i> =0.133
Body weight (kg)	54.4±12.6	62.0±13.6	<i>t</i> =1.94	<i>P</i> =0.0587
DIEPSS total scores	0.409±0.210	0.182±0.210	<i>t</i> =-0.767	<i>P</i> =0.448

Abbreviations: PANSS, Positive and Negative Syndrome Scale; HAMD-21, 21-item Hamilton Rating Scale for Depression; DIEPSS, Drug-induced Extrapyramidal Symptoms Scale.

know the pharmacologic treatment. The following measures were taken to maintain the masking of raters: 1) electronic data from the trial were password protected, 2) all case report forms were securely stored, and 3) discussions about patients across research teams were restricted. Moreover, participants were reminded to avoid open discussion of treatment assignment with the raters.

The primary outcome measure was the improvement of PANSS total scores at week 24. The secondary outcomes were the PANSS subscale and HAMD-21 scores, response rate (clinical response defined as $\geq 20\%$ reduction in the PANSS total score from baseline to end point), discontinuation rate, individual adverse events, and DIEPSS total score.

Statistical analysis

Modified intent-to-treat analysis was conducted using the last observation carried forward method. Baseline continuous and categorical variables were compared between the treatment groups using independent *t*-test and the χ^2 test, respectively. Paired student's *t*-tests were used to evaluate the changes in the psychopathology scores from baseline to end point. The primary comparison between the aripiprazole and blonanserin treatment groups was the change in PANSS score from baseline based on an analysis of covariance (ANCOVA) model, with the baseline PANSS score, educational history, and age as covariates (because we found marginal differences in age [*P*=0.0871] and educational history [*P*=0.0566] at baseline between aripiprazole and blonanserin treatment groups [Table 1]). We also used multiple logistic regression analyses to examine which antipsychotic was associated with

a higher response rate (dependent variable: response rate; independent variable: treatment group; covariates: baseline PANSS score, educational history, and age). To determine which antipsychotic was more effective for depressive symptoms, we used ANCOVA to analyze the relationship between the antipsychotic and the baseline to end point change in the HAMD-21 total score, with the baseline HAMD-21 score, educational history, and age as covariates. Kaplan–Meier analysis was used to estimate the time to discontinuation for the aripiprazole and blonanserin groups, and results were compared using the log-rank test. We also compared the change in body weight and DIEPSS total score from baseline to end point between aripiprazole and blonanserin treatment groups based on an ANCOVA model with each baseline value as a covariate. Incidences of individual adverse events during the study were compared between aripiprazole and blonanserin treatment groups using the χ^2 test.

Statistical analyses were performed using SPSS Statistics for Windows (IBM, Tokyo, Japan) and JMP (JMP 12.2. 1J; SAS Japan Inc., Tokyo, Japan). A *P*-value of <0.05 was considered statistically significant for all tests.

Results

The demographics and other characteristics of the patients are presented in Table 1. Forty-four patients were recruited, all of whom were diagnosed as schizophrenic at enrollment, and 61.4% were first-episode patients. There were no significant differences in most variables, such as sex ratio, study center distribution, and percentage of first-episode patients, between the treatment groups; however, there were marginal differences in age (*P*=0.0871), educational history (*P*=0.0566), and

Table 2 End point change in PANSS scores at 4, 8, 12, and 24 weeks from the baseline

	Baseline score	F_{df} P-value	Change score at 4 weeks	F_{df} P-value	Change score at 8 weeks	F_{df} P-value	Change score at 12 weeks	F_{df} P-value	Change score at 24 weeks	F_{df} P-value
PANSS total score										
Aripiprazole	102.1±15.6	$F_{1,42}=2.16$	-19.3±17.6	$F_{1,39}=0.001$	-22.2±17.6	$F_{1,39}=0.012$	-21.9±17.6	$F_{1,39}=0.032$	-23.4±18.2	$F_{1,39}=0.027$
Blonanserin	112.5±29.1	$P=0.149$	-24.4±26.4	$P=0.974$	-26.6±25.6	$P=0.912$	-29.2±26.3	$P=0.858$	-30.7±27.4	$P=0.869$
PANSS positive subscale score										
Aripiprazole	25.4±5.07	$F_{1,42}=0.774$	-6.21±5.87	$F_{1,39}=0.119$	-7.05±5.82	$F_{1,39}=0.147$	-7.00±5.65	$F_{1,39}=0.027$	-7.42±6.01	$F_{1,39}=0.019$
Blonanserin	27.1±7.69	$P=0.384$	-6.05±7.11	$P=0.732$	-6.91±7.22	$P=0.704$	-7.55±7.78	$P=0.871$	-8.00±7.83	$P=0.890$
PANSS negative subscale score										
Aripiprazole	24.4±6.99	$F_{1,42}=1.66$	-3.95±4.90	$F_{1,39}=0.020$	-4.32±4.94	$F_{1,39}=0.052$	-4.16±5.34	$F_{1,39}=0.417$	-4.63±5.07	$F_{1,39}=0.277$
Blonanserin	27.5±8.59	$P=0.204$	-6.14±7.22	$P=0.890$	-6.09±7.55	$P=0.821$	-7.32±7.07	$P=0.522$	-7.73±7.32	$P=0.602$
PANSS general subscale score										
Aripiprazole	52.3±8.65	$F_{1,42}=2.25$	-9.16±9.00	$F_{1,39}=0.042$	-10.8±9.22	$F_{1,39}=0.007$	-10.8±9.22	$F_{1,39}=0.011$	-11.4±9.54	$F_{1,39}=0.014$
Blonanserin	57.9±15.2	$P=0.141$	-12.2±14.3	$P=0.838$	-13.6±14.1	$P=0.934$	-14.3±14.4	$P=0.915$	-15.0±15.1	$P=0.905$

Note: Covariate: educational history, age, PANSS scores at baseline.

Abbreviations: PANSS, Positive and Negative Syndrome Scale; *df*, degrees of freedom.

body weight ($P=0.0587$) at baseline between the treatment groups (Table 1).

The discontinuation rate during the study was 86.4% in the aripiprazole group and 68.2% in the blonanserin treatment group (Table S1). The main reasons for discontinuation were lack of efficacy ($n=3$ for aripiprazole and $n=7$ for blonanserin), adverse events ($n=5$ for aripiprazole and $n=4$ for blonanserin), and other reasons such as moving and withdrawal of informed consent ($n=11$ for aripiprazole and $n=6$ for blonanserin) (Table S1). There was no significant difference in mean time to discontinuation between the aripiprazole and blonanserin treatment groups (9.21 ± 8.75 weeks vs 11.4 ± 9.56 weeks; $\chi^2(1)=0.763$, $P=0.382$; Figure S1). The modified intent-to-treat sample for psychopathology and response rate analyses consisted of 41 patients with baseline assessment and at least one follow-up assessment (aripiprazole =19 patients, blonanserin =22 patients), while all 44 patients were entered into the safety analyses. The mean aripiprazole and blonanserin doses at the end point were 11.5 ± 9.01 mg/d and 10.3 ± 6.51 mg/d, respectively.

Both aripiprazole and blonanserin treatments were associated with significant improvements in the PANSS total score and positive, negative, and general subscale scores at weeks 4, 8, 12, and 24 (Tables S2 and S3). However, there were no significant differences in the magnitudes of the PANSS total and subscale score decreases at any time between the aripiprazole and blonanserin treatment groups (Table 2). There were also no significant differences in response rate at any time point between the treatment groups (Table 3).

Both aripiprazole and blonanserin significantly improved the HAMD-21 scores at all of the time points (Table S4).

There were also marginal differences in the magnitude of the HAMD-21 score decrease at 24 weeks between the aripiprazole and blonanserin treatment groups ($F_{1,39}=3.94$, $P=0.055$; Table 4).

There were no significant differences in the incidence of individual adverse events between the groups (Table 5). There were no significant differences in body weight and DIEPSS total score at the end point between the treatment groups (Table 5). No patients had prolactin-related adverse events, corrected QT interval prolongation (on an electrocardiogram), or blood test abnormalities.

Discussion

The present study is the first randomized trial of aripiprazole vs blonanserin in Japanese patients with schizophrenia and related disorders. There were no significant differences in the efficacy and safety outcomes between the aripiprazole and blonanserin treatment groups. Previous meta-analyses have shown more beneficial effects of aripiprazole for the treatment of depressive symptoms in patients with schizophrenia than those of first-generation antipsychotics¹⁸ and olanzapine.¹⁹ Although one recent randomized trial reported

Table 3 Response rate

	Aripiprazole (n=19)	Blonanserin (n=22)	Group difference (χ^2 test and P-value)	
4 weeks	9 (47.4%)	10 (45.5%)	$\chi^2=0.192$	$P=0.661$
8 weeks	10 (52.6%)	12 (54.5%)	$\chi^2=0.262$	$P=0.609$
12 weeks	11 (57.9%)	14 (63.6%)	$\chi^2=0.0133$	$P=0.908$
24 weeks	11 (57.9%)	14 (63.6%)	$\chi^2=0.0133$	$P=0.908$

Note: Covariate: educational history, age, PANSS scores at baseline.

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

Table 4 End point change in HAMD-21 at 4, 12, and 24 weeks from the baseline

	Baseline score	F_{df} P-value	Change score at 4 weeks	F_{df} P-value	Change score at 12 weeks	F_{df} P-value	Change score at 24 weeks	F_{df} P-value
Aripiprazole	22.7±8.96	$F_{1,42}=2.36$	-6.89±8.23	$F_{1,39}=0.078$	-9.16±7.38	$F_{1,39}=1.21$	-9.53±7.54	$F_{1,39}=3.94$
Blonanserin	26.3±5.62	$P=0.133$	-9.14±6.06	$P=0.781$	-15.0±9.68	$P=0.279$	-16.5±8.25	$P=0.055$

Note: Covariate: educational history, age, HAMD-21 scores at baseline.

Abbreviations: HAMD-21, 21-item Hamilton Rating Scale for Depression; df , degrees of freedom.

that there were no significant differences for change in PANSS 5-factor “anxiety/depression” model scores between blonanserin and risperidone treatment groups,¹⁰ an 8-week cohort study reported that blonanserin was superior to risperidone for improvement of the PANSS depression subscale score in Japanese patients with schizophrenia.¹¹ Although the number of patients was small in this study, evidence suggests that blonanserin has both antipsychotic and antidepressive effects in patients with schizophrenia. Blonanserin has much greater affinity with serotonin 2A receptor than aripiprazole. Serotonin 2A receptor antagonism might account for reduced depressive symptoms. Depressive symptoms are associated with increased risk of suicide,^{20,21} cognitive impairment, poor subjective well-being, and reduced subjective quality of life,^{11,12} and so it is vital that medication regimens target depressive symptoms as well as positive and negative symptoms.

The discontinuation rates in this study were high. We considered the following possible reasons for high discontinuation rate in this study. First, both antipsychotics do not have a sedative effect, and sedation is often required for the agitated patients.²² Second, the discontinuation rate due to other reasons such as moving and withdrawal of informed consent were relatively high. Some patients were no longer willing to continue the study owing to improved conditions.

One of the main limitations of this study is the small sample size. Several guidelines¹⁻³ have shown that a subpopulation of first-episode patients exhibit a delayed response to antipsychotics relative to that in chronically ill patients. However, we did not perform separate subgroup analyses of PANSS and HAMD-21 scores in first-episode and multiple-episode patients because our sample size was small. We found that there were marginal differences in the

Table 5 Adverse events observed in the study (incidence ≥5%)

Adverse event	Aripiprazole (n=22)	Blonanserin (n=22)	Group difference (χ^2 test and P-value)	
At least one adverse event	14 (63.6%)	16 (72.7%)	$\chi^2=0.42$	$P=0.517$
Somnolence	1 (4.55%)	2 (9.09%)	$\chi^2=0.364$	$P=0.546$
Anxiety	6 (27.3%)	9 (40.9%)	$\chi^2=0.915$	$P=0.339$
Insomnia	3 (13.6%)	7 (31.8%)	$\chi^2=2.12$	$P=0.146$
Dystonia	0 (0.00%)	2 (9.09%)	$\chi^2=2.87$	$P=0.0904$
Rigidity	0 (0.00%)	2 (9.09%)	$\chi^2=2.87$	$P=0.0904$
Akinesia	1 (4.55%)	3 (13.6%)	$\chi^2=1.15$	$P=0.284$
Tremor	2 (9.09%)	6 (27.3%)	$\chi^2=2.54$	$P=0.111$
Akathisia	7 (31.8%)	5 (22.7%)	$\chi^2=0.460$	$P=0.498$
Increased salivation	0 (0.00%)	2 (9.09%)	$\chi^2=2.87$	$P=0.0904$
Nausea/vomiting	2 (9.09%)	1 (4.55%)	$\chi^2=0.364$	$P=0.546$
Constipation	2 (9.09%)	3 (13.6%)	$\chi^2=0.227$	$P=0.634$
Dizziness	1 (4.55%)	2 (9.09%)	$\chi^2=0.364$	$P=0.546$
Use of biperiden	1 (4.55%)	2 (9.09%)	$\chi^2=0.364$	$P=0.546$
Use of lorazepam	6 (27.3%)	11 (50.0%)	$\chi^2=2.42z$	$P=0.120$
Use of hypnotic	5 (22.7%)	3 (13.6%)	$\chi^2=0.617$	$P=0.432$
≥7% body weight	2 (9.09%)	4 (18.2%)	$\chi^2=0.785$	$P=0.376$
	Aripiprazole (n=22)	Blonanserin (n=22)	Group difference (F_{df} and P-value)	
Mean weight change (kg) ^a	1.47±3.23	1.18±3.34	$F_{1,42}=-0.653$	$P=0.424$
DIEPSS total scores	1.14±2.12	1.59±2.44	$F_{1,42}=0.434$	$P=0.514$

Note: ^aCovariate: body weight at baseline.

Abbreviations: DIEPSS, Drug-induced Extrapyramidal Symptoms Scale; df , degrees of freedom.

magnitude of the HAMD-21 score decrease at 24 weeks between the aripiprazole and blonanserin treatment groups ($F_{1,39}=3.94$, $P=0.055$). However, it was possible that this result was a type I error due to small sample size. A second limitation is that we did not address for multiple comparisons because application of a more strict alpha level for the outcomes would have been excessively conservative in this small sample. The third limitation is that this study was not double blinded. Although raters were masked to the nature of the antipsychotic treatment and not involved in any side effect ratings or management decisions, it is possible that they were inadvertently informed of group allocation by patients. Finally, the intent-to-treat analysis using the last observation carried forward method may influence the results.²³ However, if we had selected a complete analysis, our sample size would have been too small (Table S1).

Conclusion

In conclusion, our findings suggest that aripiprazole and blonanserin are both effective and well tolerated in patients with schizophrenia not receiving antipsychotics for more than 2 weeks before the treatment. Additionally, adequately well-designed double-blind randomized controlled studies are needed to further characterize the efficacy and safety comparisons between aripiprazole and blonanserin.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

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Supplementary materials

Table S1 Discontinuation rate

Number of patients	Aripiprazole	Blonanserin
Randomized	22	22
Completed the trial (%)	3 (13.6)	7 (31.8)
Discontinued the trial (%)	19 (86.4)	15 (68.2)
The reasons of discontinuation		
Inefficacy (%)	3 (13.6)	7 (31.8)
Adverse events (%)	5 (22.7)	4 (18.2)
Other reasons (%)	11 (50.0)	4 (18.2)

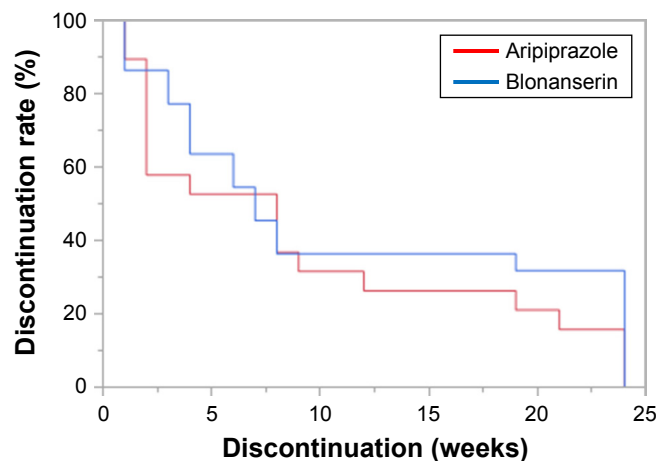


Figure S1 Discontinuation rate: Kaplan–Meier analysis.

Table S2 End point change in PANSS scores at 4, 8, 12, and 24 weeks from the baseline (aripiprazole group)

Mean score at baseline	Mean score at 4 weeks	t_{df} P-value	Mean score at 8 weeks	t_{df} P-value	Mean score at 12 weeks	t_{df} P-value	Mean score at 24 weeks	t_{df} P-value
PANSS total score								
102.1±15.6	84.1±18.3	$t_{18}=-4.80$ P=0.0001	81.3±20.1	$t_{18}=-5.47$ P<0.0001	81.5±19.6	$t_{18}=-5.44$ P<0.0001	80.0±21.6	$t_{18}=-5.61$ P<0.0001
PANSS positive subscale score								
25.4±5.07	19.2±5.71	$t_{18}=-4.61$ P=0.0002	18.4±6.08	$t_{18}=-5.29$ P<0.0001	18.4±6.09	$t_{18}=-5.40$ P<0.0001	18.0±6.60	$t_{18}=-5.38$ P<0.0001
PANSS negative subscale score								
24.4±6.99	20.6±5.31	$t_{18}=-3.51$ P=0.0025	20.3±5.30	$t_{18}=-3.80$ P=0.0013	20.4±5.19	$t_{18}=-3.40$ P=0.0032	19.9±5.49	$t_{18}=-3.98$ P=0.0009
PANSS general subscale score								
52.3±8.65	44.3±10.2	$t_{18}=-4.43$ P=0.0003	42.6±11.4	$t_{18}=-5.11$ P<0.0001	42.6±11.2	$t_{18}=-5.10$ P<0.0001	42.1±12.0	$t_{18}=-5.19$ P<0.0001

Abbreviations: PANSS, Positive and Negative Syndrome Scale; *df*, degrees of freedom.

Table S3 End point change in PANSS scores at 4, 8, 12, and 24 weeks from the baseline (blonanserin group)

Mean score at baseline	Mean score at 4 weeks	t_{df} P-value	Mean score at 8 weeks	t_{df} P-value	Mean score at 12 weeks	t_{df} P-value	Mean score at 24 weeks	t_{df} P-value
PANSS total score								
112.5±29.1	88.0±23.5	$t_{21}=-4.33$ $P=0.0003$	85.9±23.4	$t_{21}=-4.86$ $P<0.0001$	83.3±23.7	$t_{21}=-5.21$ $P<0.0001$	81.7±25.0	$t_{21}=-5.25$ $P<0.0001$
PANSS positive subscale score								
27.1±7.69	21.1±6.93	$t_{21}=-3.99$ $P=0.0007$	20.2±6.84	$t_{21}=-4.49$ $P=0.0001$	19.6±7.30	$t_{21}=-4.55$ $P=0.0002$	19.1±7.68	$t_{21}=-4.80$ $P<0.0001$
PANSS negative subscale score								
27.5±8.59	21.3±6.93	$t_{21}=-3.99$ $P=0.0007$	21.4±6.85	$t_{21}=-3.78$ $P=0.0011$	20.1±6.23	$t_{21}=-4.86$ $P<0.0001$	19.7±6.30	$t_{21}=-4.95$ $P<0.0001$
PANSS general subscale score								
57.9±15.2	45.6±11.5	$t_{21}=-4.00$ $P=0.0006$	44.3±11.8	$t_{21}=-4.53$ $P=0.0002$	43.5±11.7	$t_{21}=-4.67$ $P=0.0001$	42.9±12.5	$t_{21}=-4.66$ $P=0.0001$

Abbreviations: PANSS, Positive and Negative Syndrome Scale; *df*, degrees of freedom.

Table S4 End point change in HAMD-21 at 4, 12, and 24 weeks from the baseline

Treatment group	Mean score at baseline	Mean score at 4 weeks	t_{df} P-value	Mean score at 12 weeks	t_{df} P-value	Mean score at 24 weeks	t_{df} P-value
Aripiprazole	22.7±8.96	15.8±6.15	$t_{18}=-3.66$ $P=0.0018$	13.6±5.86	$t_{18}=-5.41$ $P<0.0001$	13.2±5.45	$t_{18}=-8.99$ $P<0.0001$
Blonanserin	26.3±5.62	17.1±6.24	$t_{21}=-7.07$ $P<0.0001$	11.3±6.01	$t_{21}=-7.27$ $P<0.0001$	9.82±4.37	$t_{21}=-14.9$ $P<0.0001$

Abbreviations: HAMD-21, 21-item Hamilton Rating Scale for Depression; *df*, degrees of freedom.

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