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Blonanserin versus haloperidol in Japanese patients with schizophrenia: A phase 3, 8-week, double-blind, multicenter, randomized controlled study

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Abstract

Objective: This Japanese, multicenter, randomized, double-blind trial, evaluating the efficacy and safety of blonanserin compared with haloperidol in patients with schizophrenia, was previously published by Murasaki in the Japanese language. In this article, we present the results of the trial based on full analysis dataset instead of per protocol dataset formerly reported and discuss the findings in light of the latest knowledge of pharmacological treatment for schizophrenia.

Methods: A total of 265 patients were randomized to receive blonanserin (8 to 24 mg/d) or haloperidol (4 to 12 mg/d) twice daily for 8 weeks. Efficacy assessments included the Clinical Global Impressions—Improvement (CGI-I) and the Positive and Negative Syndrome Scale (PANSS).

Results: Blonanserin was not inferior to haloperidol with a margin of 10% with respect to the improvement rate on CGI-I at end of study (60.5% vs 50.0%, $P < 0.001$). The decrease in the PANSS total score did not differ between the drugs (−10.3 vs −7.1). For the PANSS negative symptom score, the decrease was significantly greater with blonanserin than with haloperidol ($P = 0.006$). Blonanserin was well tolerated. The incidence of adverse events was similar for the two drugs. Extrapyramidal adverse events, sedation, hypotension, and prolactin increase were rarer with blonanserin than with haloperidol. No clinically important weight gain was observed.

Conclusions: Blonanserin is as effective as haloperidol for the treatment of schizophrenia. Blonanserin is more effective for negative symptoms with a lower risk of extrapyramidal symptoms compared with haloperidol.

KEYWORDS

antipsychotic agents, blonanserin, haloperidol, randomized controlled trial, schizophrenia

Institutions at which the work was carried out: The study was conducted at 83 medical institutions in Japan.

1 | INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by various psychotic symptoms including positive symptoms (eg, hallucinations and delusions) and negative symptoms (eg, affective flattening, alogia, and avolition). In addition, cognitive impairment is commonly observed in patients with schizophrenia, with deficits in processing speed, sustained attention, verbal memory, and executive function.[1]

The most popular etiological theory of schizophrenia is a neurodegenerative hypothesis, which claims that the disorder is caused by the degeneration of the brain and follows a chronic downhill course.[2] Positive symptoms are usually episodic with rapid onset and manageable with dopamine D_2 receptor blockade by first- and second-generation antipsychotics (FGAs and SGAs) in most cases. In contrast, negative symptoms typically remain stable across the course of schizophrenia along with cognitive impairment,[3] although some studies have suggested that some newer-generation antipsychotic medications have higher efficacy than FGAs against negative symptoms.[4] Increased negative symptoms and cognitive impairment are longitudinal predictors of poor social functioning in schizophrenia.[6,7] In addition, suboptimal medication adherence often seen in the treatment of schizophrenia is considered to be a primary cause of relapse, necessitating the development of formulations expected to improve the adherence to provide stable blood drug concentrations. A recently recognized treatment goal of schizophrenia is not only clinical recovery such as the control of psychiatric symptoms and functional recovery but also personal recovery, as represented by subjective well-being, employment status, social relationships, and hope for the future.[8] To facilitate personal recovery, management of negative symptoms, and cognitive impairment that still remain after remission in chronic patients should be necessary, leading to various pharmacological, nonpharmacological, or combined clinical approaches to date, although sufficient evidence is still to be established.

Blonanserin is a relatively new antipsychotic agent that received the first regulatory approval in Japan in 2008, followed by Korea, and most recently in China in 2017, with an indication for schizophrenia. Blonanserin has high receptor selectivity not only with SGA characteristics of potent dopamine D_2 and serotonin 5-HT_{2A} receptor binding affinities, but also with potent affinity for the D_3 receptor, and low affinity for the dopamine D_1, serotonin 5-HT_{2C}, adrenaline α_1, histamine H_1, and muscarinic M_1 receptors.[9] The superiority of blonanserin over placebo with regard to the primary efficacy endpoint has been demonstrated in Japanese and non-Japanese randomized control studies using the transdermal patch formulation (being filed for approval in Japan) and the tablet formulation, respectively, in patients with schizophrenia.[10,11]

Murasaki reported the results of a phase 3, double-blind, multicenter, randomized controlled study comparing the efficacy and safety of blonanserin with those of haloperidol in Japanese patients with schizophrenia based on per protocol set (PPS).[9] In his report on PPS, noninferiority in efficacy of blonanserin against haloperidol was demonstrated along with its favorable safety profile. The efficacy finding was also supported by other intergroup comparisons. For evaluation of intergroup differences in a randomized controlled study, on the other hand, analysis based on full analysis set (FAS) is recommended to maintain random assignment. FAS analysis also allows clinicians to generalize the results to actual practice in a clinical setting. In this article, we report the results of the study based on FAS analysis, which is completely new in this version of the report. In addition, we discuss our findings in light of the latest knowledge of pharmacological treatment for schizophrenia especially focusing on the importance of management of negative symptoms and cognitive impairment to achieve recovery of social function and behavior. The trial was conducted based on the regulatory submission requirement and included as a pivotal study in the application package for approval of blonanserin in Japan.

2 | METHODS

Most of the methods used in the study were previously described,[9] however, since the previous study was published in the Japanese language, the details of the methods for entire the study are shown below.

2.1 | Design

This multicenter, randomized, double-blind, active-controlled study were conducted at 83 medical institutions in Japan from March 1997 through September 2000. The study duration was extended during the study by 2 years to achieve the planned sample size. The study was conducted in accordance with the Good Clinical Practice and local regulatory requirements. The study protocol was approved by the institutional review board of each study site. Before the initiation of any study procedures, all patients (and/or their legal representatives if patients were unable to give consent or younger than 20 years old) provided written-informed consent.

2.2 | Patients

Patients were eligible if they were between 16 and 64 years of age and met the F20 schizophrenia criteria of the International Classification of Diseases (ICD) 10, Diagnostic Criteria for Research. Patients were excluded if they had a prominent state of excitement or stupor; had personality disintegration or treatment resistance; used any prior long-acting antipsychotic drug; had a history of neuroleptic malignant syndrome or water intoxication; or met the guidance of contraindication or careful administration of haloperidol.

2.3 | Study procedures

Eligible patients were randomized to blonanserin or haloperidol in a 1:1 ratio with the use of computer-generated block randomization (four patients per block) and received the study drugs orally

twice daily for 8 weeks. Blinding of the treatment assignment was ensured by the supply of the active drugs and matching placebos in identical, masked packaging (each tablet manufactured by Sumitomo Dainippon Pharma Co, Ltd). The initial dose was 8 mg/d for blonanserin and 4 mg/d for haloperidol. Dose adjustment was allowed within the range of 8 to 24 mg/d for blonanserin and 4 to 12 mg/d for haloperidol, in increments of 4 mg/d for blonanserin and 2 mg/d for haloperidol, according to the treatment response and tolerability. The dose was escalated when the Clinical Global Impressions—Improvement (CGI-I, see Section 3.2.2) at the study visit was minimally improved, no change, or worse from baseline and no major safety concern was found. If any safety concern was found, a dose reduction was allowed. Any prior antipsychotics were discontinued before the start of study treatment, and patients were then switched to the study drug. Concomitant use of antipsychotics, epinephrine, terfenadine, and astemizole was prohibited. Prophylactic antiparkinsonian medication was prohibited. Prior antiparkinsonian drugs were discontinued by 2 weeks after the initiation of study treatment, but its concomitant use was allowed if extrapyramidal symptoms worsened or emerged. Prior hypnotic drugs could be continued during the study, and the addition of the drugs was allowed if insomnia worsened or newly emerged. Concomitant use of other drugs (eg, antidepressant medications) was allowed without changing the drug or dosage.

2.4 | Endpoints

The primary efficacy endpoint was the CGI-I rating at the end of study. The CGI-I is a physician-rating scale to assess the general change from baseline in the patient's condition. The change is rated on a 7-rank scale of very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse compared with baseline, or otherwise reported as not assessable. For patients with prior antipsychotics, the rating on CGI-I was adjusted according to the guidelines presented in Table 1 to exclude the effect of the prior drugs on the efficacy evaluation for this study. The other efficacy variables were the Positive and Negative Syndrome Scale (PANSS)[12] Japanese edition and the Brief Psychiatric Rating Scale (BPRS)[13] Japanese edition. The PANSS was assessed at baseline and after 8 weeks of study treatment (ie, week 8) or at study discontinuation, and the CGI-I and BPRS were assessed at baseline (CGI-I was assessed for on-treatment patients only), weeks 1, 2, 3, 4, 6, and 8 or at study discontinuation.

TABLE 1 Adjustment guideline for postbaseline rating on CGI-I for patients with prior antipsychotics

Unadjusted postbaseline rating on CGI-I	Adjusted postbaseline rating on CGI-I
Similar to baseline rating	Same as unadjusted postbaseline rating
Higher rank than baseline rating	Higher rank than unadjusted postbaseline rating
Lower rank than baseline rating	Lower rank than unadjusted postbaseline rating

Note. Baseline CGI-I ratings reflected baseline improvement associated with prior antipsychotics. Adapted from Murasaki M. 2007, table 2.
Abbreviation: CGI-I, Clinical Global Impressions—Improvement.

Safety assessments included treatment-emergent adverse events, adverse drug reactions, the Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS) scores,[14] laboratory data (hematology, blood chemistry, and urinalysis), vital signs (blood pressure, pulse rate, and body temperature), weight, 12-lead electrocardiography at rest, and electroencephalography. Adverse events were coded and classified according to the Japanese Adverse Reaction Terminology 1996 and translated into English. A relationship with the study drug was classified as definitely related, probably related, probably not related, and not related. An adverse drug reaction was defined as an event considered definitely or probably related to the study drug or for which a relationship was unknown. The DIEPSS is a physician-rating scale to assess the severity of extrapyramidal symptoms induced by antipsychotics on a 5-rank scale of 0 (normal) to 4 (severe) for each of 8 symptom categories (gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia) and one global assessment (overall severity). Although the study protocol defined the primary safety endpoint as the incidence of extrapyramidal side effects, we have reported the incidence of extrapyramidal adverse events instead, to exclude potential subjectivity of causality assessment.

2.5 | Statistical analysis

SAS version 6.12 (SAS Institute Japan Ltd.) was used for statistical analyses. In the previous report by Murasaki, results of statistical analyses based on PPS were presented. In this article, on the other hand, results based on FAS are described. The efficacy analysis population in the previous report included patients who were judged eligible for PPS by the controller committee prior to key code breaking. The safety analysis population in the previous report and the efficacy and safety analysis population in this article, that is, FAS, comprised all patients with schizophrenia who were randomized and treated with at least one dose of the study drug and had at least one postbaseline data point. Analyses of the change from baseline were based on those who had both baseline and postbaseline evaluable data. The Mantel-Haenszel method was used to test noninferiority of blonanserin to haloperidol for the improvement rate (the percentage of patients rated as very much or much improved) on the final CGI-I rating, with a margin of 10% at a one-sided significance level of 0.025. Intergroup comparisons of changes from baseline at end of study were performed with the Wilcoxon rank sum test at a significance level of 0.05 (two-sided). The tests were not adjusted for multiplicity. Missing data at week 8 were imputed with last observation carried forward. The incidence of adverse events and abnormal changes in laboratory data, vital signs, weight, and electrocardiography and electroencephalography parameters was calculated for each group. To provide a power of 80% to establish noninferiority with regard to the improvement rate with a margin of 10% at a one-sided

significance level of 0.05 (Note: The significance level was initially 0.05 and then revised for the noninferiority analysis to 0.025 before unblinding according to the ICH E9.) and to provide a power of 70% to detect treatment difference with regard to the incidence of drug-related extrapyramidal symptoms at a two-sided significance level of 0.05, a sample size of 220 patients (110 per group) were required.

3 | RESULTS

The results shown here are based on FAS which is newly presented in this article instead of PPS previously reported by Murasaki.[9]

3.1 | Patient characteristics

Patients were enrolled in the study at Japanese medical institutions, and 265 patients were randomized to receive blonanserin or haloperidol (Figure 1). Of these patients, 263 received at least one dose of the study drug. Seventy patients discontinued study treatment, and the withdrawal rate was similar in the two groups: 24.0% in the blonanserin group and 29.1% in the haloperidol group. Of the 263 treated patients, two had a GCP violation, and the remaining 261 (129 in the blonanserin group, 132 in the haloperidol group) were included in the efficacy and safety analyses.

Baseline characteristics were comparable across treatment groups (Table 2). The mean age was 41.9 years in the blonanserin group and 42.9 years in the haloperidol group. In each group, nearly 60% of patients were male. Duration of schizophrenia was 3 years or longer in more than 75% of the patients. The most prominent schizophrenia subtypes were hebephrenic, paranoid, and residual schizophrenia according to the ICD-10. The mean baseline PANSS total score was approximately 80, and the negative symptoms were prominent in almost 80% of patients. Most patients were treated with prior antipsychotics at baseline. More than 75% of the patients were receiving antiparkinsonian medication.

3.2 | Efficacy

Efficacy results based on FAS were quite similar to those on PPS.

3.2.1 | Final global improvement rating

The final improvement rate on CGI-I demonstrated the noninferiority of blonanserin to haloperidol with a margin of 10% ($P < 0.001$), although the rate was higher for blonanserin by about 10% (Table 3). During the study, the improvement rate gradually increased for both blonanserin and haloperidol, and the rate was higher for blonanserin than for haloperidol at each evaluation point (Table S1 and Figure 2).

3.2.2 | PANSS

The mean PANSS total score at end of study was lower than baseline in each group (Table 4 and Figure S1). No statistically significant difference was found in the decrease between blonanserin

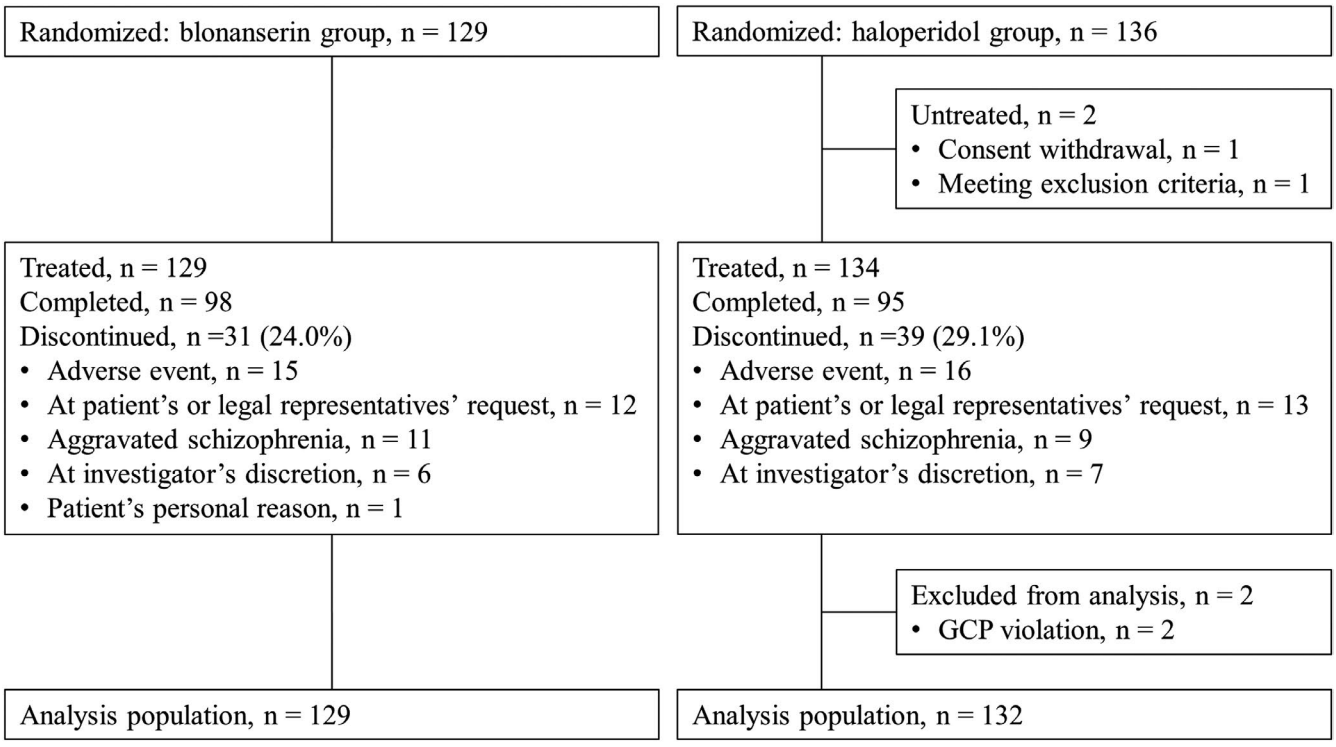

FIGURE 1 CONSORT diagram for study flow. Patients who discontinued the study for more than one reasons were counted for each category

TABLE 2 Baseline patient characteristics

Category	Blonanserin (N = 129)	Haloperidol (N = 132)
Sex, n (%)		
Male	75 (58.1)	78 (59.1)
Age (years), mean ± SD	41.9 ± 12.7	42.9 ± 13.2
Weight (kg), mean ± SD	61.5 ± 12.9	61.7 ± 14.2
Duration of disease (years), n (%)		
<1	7 (5.4)	11 (8.3)
≥1, <2	13 (10.1)	4 (3.0)
≥2, <3	8 (6.2)	4 (3.0)
≥3, <5	13 (10.1)	10 (7.6)
≥5, <10	20 (15.5)	21 (15.9)
≥10	65 (50.4)	81 (61.4)
Unknown	3 (2.3)	1 (0.8)
Disease type by ICD-10, n (%)		
Hebephrenic	36 (27.9)	48 (36.4)
Paranoid	36 (27.9)	45 (34.1)
Residual	32 (24.8)	25 (18.9)
Undifferentiated	17 (13.2)	8 (6.1)
Catatonic	6 (4.7)	4 (3.0)
Simplified	1 (0.8)	1 (0.8)
Unspecified	1 (0.8)	0
Postschizophrenic depression	0	1 (0.8)
Disease type by DSM-IV, n (%)		
Paranoid	36 (27.9)	45 (34.1)
Residual	35 (27.1)	25 (18.9)
Disorganized	33 (25.6)	44 (33.3)
Undifferentiated	19 (14.7)	13 (9.8)
Catatonic	6 (4.7)	4 (3.0)
Others	0 (0.0)	1 (0.8)
Use of prior antipsychotics, n (%)		
Yes	116 (89.9)	123 (93.2)
Use of antiparkinsonian drugs, n (%)		
Yes	98 (76.0)	108 (81.8)
PANSS total score, mean ± SD	81.5 ± 21.6	82.3 ± 21.7
Dominance in PANSS, n (%)[a]		
Negative symptoms	103 (79.8)	102 (77.3)
Positive symptoms	18 (14.0)	23 (17.4)
Comparable	8 (6.2)	7 (5.3)

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ICD-10, International Classification of Diseases 10; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.
[a]Positive symptoms are dominant when the total score on PANSS positive symptom scale is higher than the total score on PANSS negative symptom scale, and vice versa.

and haloperidol. Of the PANSS subscales, the negative subscale score decreased significantly more with blonanserin than with haloperidol (P = 0.006).

TABLE 3 Comparisons of CGI-I rating at end of study

Category	Blonanserin (N = 129), n (%)	Haloperidol (N = 132), n (%)
Very much improved	17 (13.2)	15 (11.4)
Much improved	61 (47.3)	51 (38.6)
Minimally improved	26 (20.2)	33 (25.0)
No change	8 (6.2)	14 (10.6)
Minimally worse	8 (6.2)	5 (3.8)
Much worse	9 (7.0)	8 (6.1)
Very much worse	0	6 (4.5)
Improvement rate[a]	60.5%	50.0%
95% CI of intergroup difference (%)	−1.5, 22.5	
P value[b]	<0.001	

Abbreviations: CGI-I, Clinical Global Impressions—Improvement; CI, confidence interval.
[a]The improvement rate was defined as the percentage of patients rated as very much or much improved on the CGI-I.
[b]The Mantel-Haenszel method was used to test noninferiority of blonanserin to haloperidol with a margin of 10% at a one-sided significance level of 0.025.

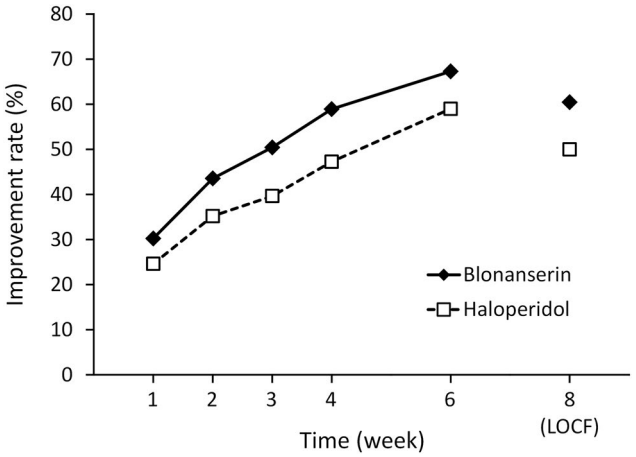

FIGURE 2 Abbreviations: LOCF, last observation carried forward. Time course of change in improvement rate, that is, the percentage of patients rated as very much or much improved from baseline on the Clinical Global Impressions—Improvement rating, during the study for blonanserin (n = 129, 124, 115, 112, 104, and 129 at week 1, 2, 3, 4, 6, and 8 [LOCF], respectively) and haloperidol (n = 130, 125, 116, 110, 100, and 132 at week 1, 2, 3, 4, 6, and 8 [LOCF], respectively). Noninferiority of blonanserin to haloperidol was demonstrated with a margin of 10% at end of study (P < 0.001)

3.2.3 | BPRS

Similar results were obtained for the BPRS. The mean BPRS total score at end of study was lower than baseline in each group (Table S2). No significant difference was found in the decrease at end of study between the groups. Of the BPRS clusters, the cluster scores of anergia and anxiety/depression decreased more largely with blonanserin than

TABLE 4 Comparisons of change from baseline in PANSS scores at end of study

Category	Group	N	Baseline, mean ± SD	Change from baseline, mean ± SD	*P* value[a]
Total	Blonanserin	127	82.5 ± 21.9	−10.3 ± 18.7	0.096
	Haloperidol	128	82.2 ± 22.3	−7.1 ± 18.3	
Positive	Blonanserin	127	16.6 ± 6.0	−2.0 ± 6.1	0.762
	Haloperidol	128	17.2 ± 6.3	−1.6 ± 5.7	
Negative	Blonanserin	127	24.2 ± 7.7	−3.5 ± 4.8	0.006
	Haloperidol	128	23.7 ± 7.5	−2.2 ± 5.1	
General psychopathology	Blonanserin	127	41.8 ± 11.6	−4.8 ± 9.8	0.149
	Haloperidol	128	41.3 ± 12.5	−3.4 ± 9.5	

Abbreviations: PANSS, Positive and Negative Syndrome Scale; SD, standard deviation.
[a]The Wilcoxon rank sum test was used for a comparison of the change from baseline at a significance level of 0.05. Missing data were imputed with last observation carried forward.

with haloperidol (anxiety/depression showed no statistical significance in the previous report based on PPS). During the study, the decrease in BPRS total score from baseline was greater for blonanserin at each evaluation point (Table S3 and Figure S2).

3.3 | Safety

Safety results based on FAS were exactly the same as those reported by Murasaki[9] for safety analysis population in his report corresponded to FAS.

The mean daily dose at end of study was 15.7 mg/d (standard deviation [SD], 6.0) for blonanserin and 7.9 mg/d (SD, 3.0) for haloperidol (Table S4).

3.3.1 | Adverse events

No obvious difference was found in the incidence of adverse events between blonanserin and haloperidol (93.0% vs 95.5%, Table 5). One death was reported in the study; a patient in the haloperidol group died 14 days after the completion of study treatment (completed suicide). Other serious adverse events occurred in three patients receiving blonanserin (blood sodium decreased, blood urea increased, insomnia, irritability/anxiety, and excitability in one patient each) and four patients receiving haloperidol (suicide attempt in two patients, neuroleptic malignant syndrome, hypokinesia, gait abnormal, musculoskeletal stiffness, bradykinesia, and dystonia in one patient each). The neuroleptic malignant syndrome, hypokinesia, gait abnormal, musculoskeletal stiffness, bradykinesia, and dystonia were considered related to haloperidol, and none of the serious adverse events were considered related to blonanserin. While adverse drug reactions were commonly reported in both groups with similar frequency, the incidence of those leading to medical intervention, dose reduction, and study discontinuation in the blonanserin group was generally lower than those in the haloperidol group. Of the adverse events commonly reported in the study, tremor, akathisia, bradykinesia, and somnolence occurred less frequently (ie, treatment difference in incidence >10%) with blonanserin than with haloperidol (Table 6). The other adverse events were reported in a similar incidence across groups. Most adverse events were mild or moderate in severity.

TABLE 5 Summary of adverse events

	Blonanserin (N = 129), n (%)	Haloperidol (N = 132), n (%)
Adverse events	120 (93.0)	126 (95.5)
Death	0	1 (0.8)
Serious adverse events	3 (2.3)	4 (3.0)
Adverse drug reactions	106 (82.2)	110 (83.3)
Adverse drug reactions leading to medical intervention[a]	45 (34.9)	59 (45.0)
Adverse drug reactions leading to dose reduction[a]	18 (14.0)	22 (16.8)
Adverse drug reactions leading to discontinuation[a]	13 (10.1)	22 (16.8)
Patients with extrapyramidal adverse events	73 (56.6)	102 (77.3)

[a]One patient in the haloperidol group who discontinued the study but did not undergo the discontinuation visit was excluded from the analysis. This patient did not experience adverse drug reactions during the study. Adapted from and added to Murasaki M. 2007, table 10.

3.3.2 | Extrapyramidal symptoms

The incidence of extrapyramidal adverse events was lower in the blonanserin group than in the haloperidol group (56.6% vs 77.3%, Table 5). The mean (SD) DIEPSS total score was comparable in the two groups at baseline: 2.1 (2.9) in the blonanserin group and 2.3 (2.9) in the haloperidol group. During the study, the DIEPSS total score remained unchanged in the blonanserin group and increased in

TABLE 6 Incidence of adverse events (≥5% in either group)

System organ class Preferred term	Blonanserin (N = 129), n (%)	Haloperidol (N = 132), n (%)
Extrapyramidal system		
Tremor	39 (30.2)	59 (44.7)
Akathisia	35 (27.1)	55 (41.7)
Bradykinesia	29 (22.5)	49 (37.1)
Gait abnormal	26 (20.2)	36 (27.3)
Musculoskeletal stiffness	26 (20.2)	35 (26.5)
Salivary hypersecretion	25 (19.4)	35 (26.5)
Dyslalia	20 (15.5)	20 (15.2)
Hypokinesia	19 (14.7)	27 (20.5)
Dyskinesia	12 (9.3)	10 (7.6)
Dystonia	11 (8.5)	16 (12.1)
Psychophysiologic system		
Insomnia	53 (41.1)	62 (47.0)
Irritability/anxiety	38 (29.5)	38 (28.8)
Excitability	26 (20.2)	26 (19.7)
Somnolence	20 (15.5)	34 (25.8)
Depression	16 (12.4)	12 (9.1)
Headache/head discomfort	15 (11.6)	22 (16.7)
Sedation	7 (5.4)	14 (10.6)
General symptom		
Malaise	23 (17.8)	35 (26.5)
Dizziness/dizziness postural	10 (7.8)	20 (15.2)
Asthenia	10 (7.8)	16 (12.1)
Feeling hot	8 (6.2)	8 (6.1)
Circulatory system		
Tachycardia	7 (5.4)	6 (4.5)
Blood pressure decreased	4 (3.1)	9 (6.8)
Digestive system		
Anorexia	29 (22.5)	22 (16.7)
Constipation	20 (15.5)	31 (23.5)
Thirst	20 (15.5)	20 (15.2)
Nausea/vomiting	17 (13.2)	14 (10.6)
Diarrhea	5 (3.9)	17 (12.9)
Endocrine system		
Menstrual disorder[a]	6 (11.1)	2 (3.7)
Vital signs		
Weight decreased	11 (8.5)	10 (7.6)
Body temperature increased	9 (7.0)	10 (7.6)
Hematology test		
White blood cell count increased	3 (2.3)	7 (5.3)
Prolactin		
Blood prolactin increased	11 (8.5)	20 (15.2)
Biochemical examination of blood		
Blood creatine phosphokinase increased	10 (7.8)	17 (12.9)
ALT (GPT) increased	9 (7.0)	7 (5.3)
Blood triglycerides increased	8 (6.2)	6 (4.5)
AST (GOT) increased	8 (6.2)	4 (3.0)
Gamma-glutamyltransferase increased	3 (2.3)	7 (5.3)
Others		
Nasopharyngitis	10 (7.8)	10 (7.6)
Visual acuity reduced	8 (6.2)	9 (6.8)
Dysuria	3 (2.3)	12 (9.1)

[a]Menstruation abnormal was aggregated for female patients (54 patients each in the blonanserin and haloperidol groups). Adapted from Murasaki M. 2007, table 11.

the haloperidol group; the intergroup difference in the change from baseline was significant (P = 0.024, Table 7).

3.3.3 | Laboratory data

Of the laboratory parameters tested, those with the incidence of abnormal changes higher than 5% in either group were prolactin (11.0% for blonanserin and 19.4% for haloperidol), CPK (7.8% vs 13.4%), triglyceride (6.9% vs 3.3%), ALT (6.8% vs 5.7%), AST (5.9% vs 3.3%), and WBC (3.4% vs 6.6%). The incidence of abnormal change in prolactin was slightly higher in the haloperidol group. Mean (SD) prolactin levels decreased during the study in each group: 25.2 (25.1) ng/mL at baseline and 17.1 (19.4) ng/mL at end of study in the blonanserin group and 29.5 (30.7) ng/mL at baseline and 22.7 (21.5) ng/mL at end of study in the haloperidol group.

3.3.4 | Others

Weight did not change notably during the study in either group; mean (SD) weight was 61.8 (13.0) kg at baseline and 61.1 (12.6) kg at end of study in the blonanserin group and 61.4 (13.5) kg at baseline and 60.7 (13.5) kg at end of study in the haloperidol group. Weight gain was reported as an adverse event in as low as 2.3% of patients receiving blonanserin and none receiving haloperidol. Drug-related electrocardiographic abnormalities were reported in two patients receiving blonanserin, and two patients receiving haloperidol: ventricular extrasystoles/ventricular tachycardia (moderate) in one patient receiving blonanserin and mild sinus bradycardia in the remaining three patients. Drug-related electroencephalographic abnormalities were not reported in the blonanserin group and reported in two patients of the haloperidol group. No obvious change from baseline was found in mean vital signs in either group.

TABLE 7 Comparisons of change from baseline in DIEPSS total score

Group	N	Baseline, mean ± SD	Change from baseline, mean ± SD	*P* value[a]
Blonanserin	129	2.1 ± 2.9	0.3 ± 2.9	0.024
Haloperidol	131	2.3 ± 2.9	1.3 ± 3.7	

Abbreviations: DIEPSS, Drug-Induced Extra-Pyramidal Symptoms Scale; SD, standard deviation.
[a]The Wilcoxon rank sum test was used for a comparison of the change from baseline at a significance level of 0.05. Missing data were imputed with last observation carried forward. Adapted from Murasaki M. 2007, table 13.

4 | DISCUSSION

The study by Murasaki[9] was the first randomized controlled trial to investigate the safety and efficacy of blonanserin comparing with haloperidol. The daily dose administered to FAS population was 8-24 mg (mean, 15.7 mg at end of study) for blonanserin, which is the same as those instructed in the current local package insert; and 4-12 mg (mean, 7.9 mg at end of study) for haloperidol, being in agreement with its recommended optimal dose.[15,16] Very few of the enrolled patients were treatment-naïve or in the acute phase of the disease; the majority of patients had treatment experience with antipsychotics, indicating the chronic course of disease.

Murasaki previously reported the results of the trial based on PPS, showing favorable efficacy and safety of blonanserin in patients with schizophrenia.[9] PPS analysis well represents the efficacy and safety of a study drug in patients without major protocol deviations. From a modern statistical point of view, on the other hand, FAS analysis is recommended to evaluate intergroup difference for a randomized controlled study because it can maintain prognostic balance of the random allocation. In addition, in examination of non-inferiority as well, analyses based on FAS along with PPS are considered relevant for robust interpretation of the data. We discuss the findings of the study on the basis of both the analyses and in the context of the most recent knowledge of pharmacological treatment in schizophrenia.

In the present FAS analysis, consistent results were obtained which confirm the previous findings based on PPS,[9] demonstrating that blonanserin was not inferior to haloperidol with respect to the improvement rate on CGI-I after 8 weeks of treatment. The result was, in both PPS and FAS, supported by the other efficacy endpoint data; decrease in the PANSS total score from baseline did not differ between the drugs. When analyzed according to symptom type, improvement was significantly greater with blonanserin than with haloperidol in PANSS negative symptom scores in both PPS and FAS. With regard to efficacy of blonanserin, previous findings by Murasaki[9] were wholly sustained by the present FAS analysis. Those findings are consistent with the results obtained in another study that also compared blonanserin with haloperidol, where 5-10 mg/d of blonanserin was as effective as 10 mg/d of haloperidol with respect to reduction in PANSS total score, and showed greater efficacy than haloperidol against negative symptoms in non-Japanese patients with schizophrenia.[10]

As described by Murasaki,[9] blonanserin was well tolerated. The incidence of treatment-emergent adverse events was similar for blonanserin and haloperidol. None of the serious adverse events were related to blonanserin. Incidence of adverse drug reactions leading to study discontinuation was lower for blonanserin than for haloperidol. Extrapyramidal symptoms, sedation, and hypotension, which are clinically significant side effects of FGAs, were fewer with blonanserin. Prolactin increase, which often occurs in FGAs and some SGAs, was generally fewer with blonanserin. Weight gain is also one of the significant side effects of SGAs, but was observed in a small percentage of blonanserin-treated patients during the study. These safety findings are in agreement with the above-mentioned haloperidol-controlled study that demonstrated the tolerability of blonanserin with lower incidences of extrapyramidal symptoms and prolactin increase than haloperidol and a low frequency of weight gain.[10]

The efficacy of blonanserin for schizophrenia is comparable with that of other SGAs, as shown in a meta-analysis of randomized controlled trials comparing blonanserin with other antipsychotics.[17] Of the SGAs other than blonanserin, however, only aripiprazole and olanzapine have data showing a significantly higher efficacy than haloperidol against negative symptoms in Japanese patients.[18,19]

The blonanserin-induced significant improvement of negative symptoms compared with haloperidol in the present study might be attributed to the selective dopamine D_3 antagonism of blonanserin as well as serotonin 5-HT_{2A} antagonism. Unlike other SGAs, blonanserin acts as a full antagonist of D_3 receptor, showing the binding affinity for human D_3 receptors higher than risperidone, olanzapine, and aripiprazole, and comparable to cariprazine (dopamine D_2/D_3 receptor partial agonist) in vitro, and high D_3 receptor occupancy in vivo in rats.[20,21] In healthy subjects, a clinical dose of blonanserin occupied D_3 receptor as much as D_2 receptor.[22] The dopamine D_3 receptor predominantly localizes in the ventral striatum, a region relevant to emotion, reward, and motivation, and the other limbic area in human brain, and modulates dopamine release.[23] Animal studies suggest that D_3 receptor antagonism might have beneficial effects on functions of the frontal cortex, such as the negative symptoms and cognitive deficits associated with schizophrenia, and might act on the reward system to enhance motivation.[23,24] Improvement of negative symptoms relates to improvement of social function, which is associated with intrinsic motivation enhancement or activation of the reward system. Therefore, the selective D_3 receptor antagonism of blonanserin might improve social function by enhancing

motivation and by reducing negative symptoms, and consequently contribute to the personal recovery.

Efficacy of psychosocial intervention against negative symptoms is currently limited, while moderate improvements in cognitive performance have been shown in cognitive remediation therapy in schizophrenia.[25] An important approach to enhance the effect of cognitive rehabilitation is to improve motivation; therefore, the combination of a drug that could enhance motivation with psychosocial therapy is considered promising.[26] Since D_3 receptor antagonists may improve motivation through the dopamine-mediated reward system, those compounds may synergistically improve the procognitive effects when combined with cognitive remediation therapy. Since the present study showed that blonanserin is effective for negative symptoms and recent studies suggested potential procognitive effects of blonanserin in animal models[27,28] and in patients with schizophrenia,[29,30] blonanserin is considered an appropriate antipsychotic drug to combine with cognitive remediation therapy.

There are several methodological limitations to this study. First, prior antipsychotics were not tapered off with the use of placebo and were switched to a low dose of the study drug alone in all patients regardless of the dose of the prior drug. Patients receiving a high dose of prior antipsychotics at baseline might have experienced aggravation of symptoms after initiation of study treatment. Placebo run-in was not included in the study because placebo use in psychiatry was commonly considered unethical at the time of the study in Japan. Second, the CGI-I, which measured the primary efficacy endpoint of this study, is not fully standardized since it does not define an anchor point to assess treatment effects. However, CGI-I was commonly used, at the time of the study, in Japanese clinical studies of psychiatry, and using CGI-I as a primary efficacy endpoint for the present study was the requirement from the local regulatory authority. This was also the case for previously approved antipsychotics, which obtained regulatory approval in Japan for the indication of schizophrenia based on studies that used CGI-I as a primary endpoint.

The remaining unmet medical need in schizophrenia, suboptimal medication adherence, could be expectedly dealt with a transdermal patch formulation of blonanserin now being filed for approval in Japan. The current tablet and upcoming patch formulations of blonanserin have shown efficacy for the positive and negative symptoms of schizophrenia and are expected to synergistically provide beneficial effects when combined with psychosocial therapy.

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CONFLICT OF INTEREST

Philip D. Harvey has received lecture honoraria from Sumitomo Dainippon Pharma Co, Ltd within the last 3 years. Hiroshi Nakamura is the employee of Sumitomo Dainippon Pharma Co., Ltd. Additional details are to be described, once all COI disclosure forms are collected.

DATA REPOSITORY

There are no data listings publicly available for this study, because information about public data sharing was not included in the informed consent form of this study.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The study protocol was approved by the institutional review board of each study site.

INFORMED CONSENT

All subjects (and/or their legal representatives if patients were unable to give consent or younger than 20 years old) provided written-informed consent.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The study has not been registered in any publicly accessible database since the study was started before November 1st, 2013, when the study registration became mandatory.

AUTHOR CONTRIBUTIONS

MM took responsibility for the design, data collection, case handling, and interpretation of data as a chief investigator for the study. HN wrote the first draft of the manuscript including literature searches. PH finalized the manuscript. All authors had full access to all study data, had final responsibility for the decision to submit for publication, took part in either drafting or revising the manuscript, and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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