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Efficacy and safety of blonanserin transdermal patch in patients with schizophrenia: A 6-week randomized, double-blind, placebo-controlled, multicenter study

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ABSTRACT

Background: Blonanserin is a second-generation antipsychotic used for the treatment of schizophrenia. This study determined the efficacy, safety and pharmacokinetics of a blonanserin transdermal patch in patients with acutely exacerbated schizophrenia.

Methods: This double-blind, multicenter, phase 3 study consisted of a 1-week observation period during which patients were treated with two patches of placebo, followed by a 6-week double-blind period where patients were randomized (1:1:1) to receive once-daily blonanserin 40 mg, blonanserin 80 mg, or placebo patches. The primary endpoint was the change from baseline in the total Positive and Negative Symptom Scale (PANSS) score. Safety assessments included treatment-emergent adverse events (TEAEs).

Results: Between December 2014 and October 2018, patients were recruited and randomly assigned to blonanserin 40 mg ($n = 196$), blonanserin 80 mg ($n = 194$), or placebo ($n = 190$); of these, 77.2% completed the study. Compared with placebo, blonanserin significantly improved PANSS total scores at 6 weeks (least square mean [LSM] difference vs placebo: −5.6 with blonanserin 40 mg; 95% confidence interval [CI] −9.6, −1.6; adjusted $p = 0.007$, and − 10.4 with blonanserin 80 mg; 95% CI −14.4, −6.4; adjusted $p < 0.001$). Blonanserin was well tolerated; the most common TEAEs reported were application-site erythema and pruritus, akathisia, tremor, and insomnia.

Conclusions: Blonanserin transdermal patch improved the symptoms of acute schizophrenia with acceptable tolerability.

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1. Introduction

Despite the availability of various dopamine-derived drugs, a consistent issue in the management of schizophrenia is a poor adherence to antipsychotic medication (Alvarez-Jimenez et al., 2012; Weiden et al., 2004). Factors associated with poor adherence vary among studies, and include lower socio-economic and education status, lack of self-recognition of the mental disorder, substance abuse, debatable effectiveness, adverse events (AEs), stigma, and cognitive impairment (Kreyenbuhl et al., 2009; Velligan et al., 2017).

Antipsychotics are currently available only as oral and injectable formulations. Injectable preparations obviate the need for daily pill-taking but are used in only a minority of patients (Correll et al., 2018). These agents are often seen as a "treatment of last resort", and many patients find injectable therapy stigmatizing or too uncomfortable (Das et al., 2014; Patel et al., 2009). There is an unmet need for antipsychotic formulations that are acceptable to patients but can also enhance adherence and adherence monitoring. Transdermal formulations may be beneficial for the treatment of schizophrenia, as the patch can be hidden under clothing and may be a better option for patients who are embarrassed to be seen swallowing tablets or attending the clinic for injections. Additionally, a transdermal patch expands the range of treatment options for physicians and patients to consider when engaged in shared decision-making (SDM). Transdermal patches may also have an advantage of easy supervision by the medical staff or caregiver, and of providing observable proof of treatment adherence. With these advantages, a transdermal patch of blonanserin may improve treatment adherence in patients with schizophrenia, with reduced AEs (Sumitomo Dainippon Pharma Co., Ltd., 2018).

Blonanserin is a second-generation antipsychotic that improves the positive, negative, and cognitive symptoms of schizophrenia by blocking the D_2, D_3, and 5-HT_{2A} receptors (Hori et al., 2014; Kishi et al., 2019; Une and Kurumiya, 2007). Blonanserin has negligible affinities for 5-HT_{2C}, adrenergic α1, histamine H_1, and muscarinic M_1 receptors. Blonanserin is associated with a low risk of weight gain, abnormal lipid or glucose metabolism, and cardiovascular complications (Kishi et al., 2014; Kishi et al., 2019; Miura, 2008; Murasaki, 2007), as well as a low risk of excessive sedation due to low affinity to H_1 and histaminergic receptors. It is approved to treat schizophrenia in Japan, Korea, and China, and is currently available as tablet or powder formulations (Korea Food and Drug Administration; Osaka Dainippon Sumitomo Pharma Co. Ltd, 2009). The aim of this study was to determine the efficacy, safety, and pharmacokinetics of the blonanserin transdermal patch in patients with an acute exacerbation of schizophrenia.

2. Methods

2.1. Study design and participants

This was a randomized, double-blind, multicenter, placebo-controlled, phase 3 study (ClinicalTrials.gov identifier: NCT02287584). Patients aged ≥18 years with schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders, fifth edition diagnostic criteria, an exacerbation of psychiatric symptoms <2 months before screening, a Positive and Negative Symptom Scale (PANSS) score of ≥4 for ≥2 of the following items: delusions, conceptual disorganization, hallucinations, suspiciousness, and unusual thought content, a PANSS total score of ≥80, and who were hospitalized from the time of screening to the scheduled date of Week 2 were enrolled. Key exclusion criteria included: prior blonanserin treatment; receipt of a central nervous system depressant, adrenaline, azole antifungals (excluding external use), or human immunodeficiency virus protease inhibitors; history of neuroleptic malignant syndrome, tardive dyskinesia or water intoxication; suicidal tendency or previous suicide attempts; a hemoglobin A1c ≥8.4%; a history of drug or alcohol abuse/addiction <180 days before screening; receipt of a depot preparation (SR formulation) antipsychotic, clozapine, monoamine oxidase inhibitor, or fluoxetine or electroconvulsive therapy before screening; and patients considered resistant to treatment for psychiatric symptoms by the investigator. Patients with ≥20% reduction in the PANSS total score between screening and randomization were also excluded. Other major exclusion criteria were patients who received any depot preparation (SR formulation) of antipsychotics within <90 days of screening, clozapine within <120 days of screening, a MAO inhibitor or fluoxetine <30 days before screening and electroconvulsive therapy <180 days before screening. For a full list of exclusion criteria, see Supplementary Table S1.

The study protocol was reviewed and approved by the Institutional Review Board/Independent Ethics Committee at each study site, and the study was conducted according to the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients (or their caregivers) provided written informed consent.

2.2. Randomization and masking

The study included an observation period followed by a 6-week double-blind treatment period (Supplementary Fig. S1). During the observation period, patients applied two patches of placebo once daily for ≥3 days. All patients who completed the observation period were randomized using an interactive voice/web-response system (1:1:1) to receive once daily blonanserin 40 mg (1 blonanserin 40 mg patch +1 placebo patch), blonanserin 80 mg (2 blonanserin 40 mg patches), or placebo (2 placebo patches) applied to the back, chest, or abdomen. All patches and packaging were identical in appearance and investigators, patients and caregivers were blinded to the patient's treatment assignment.

2.3. Procedures

PANSS and Clinical Global Impressions-Severity of Illness (CGI-S) were scored on Day 1 (baseline) and at 1, 2, 4, and 6 weeks. The use of antipsychotic, antimanic, anticonvulsant, monoamine oxidase inhibitor, antiparkinsonian (excluding upon onset or exacerbation of extrapyramidal symptoms), psychotropic (excluding upon onset of restlessness, excitement, agitation, etc. when lorazepam 3 mg/day could be used), or hypnotic (excluding upon onset/exacerbation of insomnia when patients could receive triazolam, brotizolam or lormetazepam; zopiclone or eszopiclone; zolpidem; or rilmafazone) drugs was prohibited during the study. When concomitant therapies were required during the study to control persistent or emergent aggravated symptoms, the name and class of the drug, route of administration, start and stop dates, and reason for use were recorded. For antipsychotics and antiparkinsonian drugs, data on their use and daily dose in the 7 days before screening were recorded, and all psychotropic drugs and hypnotic drugs were discontinued <12 h before the PANSS, CGI-S and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments.

2.4. Outcomes

The primary endpoint was the change from baseline in the PANSS total score after 6 weeks. Other endpoints included: change from baseline to Week 6 in the PANSS subscale scores, PANSS five-factor model (Lindenmayer et al., 1994), and CGI-S scores, and the percentage of patients with a ≥20% improvement in total PANSS score after 6 weeks.

All treatment-emergent AEs (TEAEs) reported during the double-blind treatment period were recorded and classified using MedDRA Version 19.1. The safety endpoints included: all TEAEs, extrapyramidal TEAEs, skin-related TEAEs at the application site, assessment of skin irritation reactions at the application site, change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada et al., 2003) total score from baseline to Week 6 (excluding overall severity), serum prolactin levels, electrocardiogram (ECG) parameters (QTc), concomitant use of

antiparkinsonian drugs, suicidal ideation and behavior (as assessed by the C-SSRS (Posner et al., 2011) scores), and laboratory test values, vital signs, and bodyweight.

DIEPSS (Inada et al., 2003), C-SSRS (Posner et al., 2011), skin irritation, bodyweight, and vital signs were evaluated on Day 1 and 1, 2, 4, and 6 weeks; laboratory tests were conducted on Day 1 and 2 and 6 weeks, and 12-lead ECG was performed on Day 1 and 1, 2 and 6 weeks. Skin irritation was assessed on a 6-grade score as negative; faint erythema; erythema; erythema + edema; erythema + edema + papules, serous papules, vesicles; and coalescing vesicles (Kawamura et al., 1970).

Blood samples of patients were collected under fasting conditions at Week 1, 2, and 6 during the double-blind treatment period and used for the determination of plasma concentrations of blonanserin.

2.5. Pharmacokinetics

Plasma blonanserin and the major metabolite (N-deethyl compound) concentrations were measured. Blood sampling was conducted at weeks 1, 2 and 6. The sampling timings in hours after administration were not defined. LC-MS/MS was used to measure the concentrations.

2.6. Statistical analysis

A sample size of 167 patients per group was estimated to demonstrate a significant difference in the primary endpoint. The sample size calculations are described in more detail in Supplementary Methods.

The efficacy analysis was conducted in the modified intention-to-treat population (mITT), including all patients who applied ≥1 transdermal patches during the study period and who had baseline and ≥ 1 post-baseline total PANSS scores available. Safety was analyzed in the safety analysis set, which included all patients who applied ≥1 patch during the study period. Pharmacokinetics were analyzed in all patients who received treatment with ≥1 blonanserin patch during the study period, and for whom valid data for plasma blonanserin levels were available.

The change from baseline to Week 6 in PANSS, CGI-S and DIEPSS scores were analyzed using the Mixed Model for Repeated Measures (covariates: treatment group, study visit, study site, relevant baseline scores, treatment-by-visit interaction). The analysis of the primary endpoint involved multiplicity adjustment using the Hochberg method tested with a two-sided 5% significance level ($p < 0.05$); multiplicity adjustment was not used for other analyses, but $p < 0.05$ was still considered significant in these analyses.

The number and the frequency of TEAEs and patients showing suicidal ideation or suicide attempt at least once in C-SSRS, as well as summary statistics of laboratory test parameters, vital signs, bodyweight, and 12-lead ECG were calculated for each treatment group. Plasma blonanserin levels were determined in each treatment group and the timing for each evaluation was noted.

3. Results

3.1. Patient disposition and baseline characteristics

The study was conducted between December 2014 and October 2018 at 108 medical facilities across Japan, China, Korea, Malaysia, Philippines, Russia, Taiwan, and Ukraine. Of the 675 patients who consented to participate in the study, 580 were randomized and 77.2% completed treatment (72.6%, 76.0%, and 83.0% in the placebo, blonanserin 40 mg, and blonanserin 80 mg groups, respectively; Fig. 1). The main reasons for patient withdrawal were: AEs, withdrawal of consent, and lack of efficacy.

There were no major differences in the demographic or clinical characteristics of patients in the three groups at baseline (Table 1).

The mean duration of patch application in the mITT population was 35.6 ± 12.05 days. During the treatment period, 73.8% of patients received concomitant medications, including antiparkinsonian drugs (3.2%, 6.6%, and 14.1% of patients in the placebo, blonanserin 40 mg, and blonanserin 80 mg groups, respectively), psychotropic agents (43.9%, 43.9%, and 43.8%), and hypnotic agents (38.6%, 35.7%, and 41.1%).

3.2. Efficacy

After 6 weeks of treatment, the difference in the least squares mean (LSM) change from baseline in PANSS total score compared with placebo was −5.6 with blonanserin 40 mg (95% confidence interval [CI] −9.6, −1.6; adjusted $p = 0.007$) and − 10.4 with blonanserin 80 mg (95%CI −14.4, −6.4; adjusted $p < 0.001$; Fig. 2A). The proportion of patients with ≥20% reduction from baseline in the PANSS total score at 6 weeks was 42.3% with placebo versus 50.5% with blonanserin 40 mg (odds ratio [OR] 1.49; 95%CI 0.97, 2.30; $p = 0.068$, number needed-to-treat [NNT] = 13) and 55.7% with blonanserin 80 mg (OR 1.92; 95%CI 1.24, 2.97; $p = 0.003$, NNT = 8).

After 6 weeks, the LSM changes from baseline in PANSS subscale scores were significantly better with blonanserin 80 mg compared with placebo for the positive subscale (−2.9; 95%CI −4.2, −1.6; $p < 0.001$; Fig. 2B), negative subscale (−2.7; 95%CI −3.7, −1.6; $p < 0.001$; Fig. 2C), and general psychopathology subscale (−4.6; 95%CI −6.6, −2.6; $p < 0.001$; Fig. 2D), and significantly better with blonanserin 40 mg compared with placebo for the negative subscale (−1.6; 95%CI −2.7, −0.5; $p = 0.004$; Fig. 2C) and general psychopathology subscale (−2.8; 95%CI −4.8, −0.8; $p = 0.005$; Fig. 2D).

The scores of each factor of the PANSS five factor model except anxiety/depression decreased significantly from baseline at Week 6 with blonanserin 80 mg versus placebo (treatment difference for negative symptoms: −2.2, 95%CI −3.2, −1.2, $p < 0.001$; excitement: −1.4, 95% CI −2.1, −0.7, $p < 0.001$; cognitive disorders: −1.9, 95%CI −2.6, −1.2, $p < 0.001$; positive symptoms: −1.5, 95%CI −2.3, −0.7, $p < 0.001$; anxiety/depression: −0.6, 95%CI, −1.3, 0.0, $p = 0.056$; Supplementary Fig. S2). Blonanserin 40 mg showed significant improvements compared with placebo for negative symptoms (treatment difference −1.5; 95%CI −2.5, −0.5; $p = 0.004$) and cognitive disorders (−1.1; 95%CI −1.8, −0.4; $p = 0.002$).

The CGI-S score decreased from baseline to Week 6 with blonanserin 40 mg and 80 mg; this improvement was significant versus placebo with blonanserin 80 mg (treatment difference − 0.40; 95%CI −0.62, −0.18; $p < 0.001$; Supplementary Fig. S3), but not with blonanserin 40 mg (−0.16; 95%CI −0.38, 0.06; $p = 0.149$).

3.3. Safety

TEAEs were reported in similar proportions of patients receiving placebo, blonanserin 40 mg, and 80 mg (Table 2). TEAEs rated as severe were akathisia (80 mg, 0.5%), schizophrenia (placebo, 2.6%; 40 mg, 2.0%; 80 mg, 1.5%), and psychotic disorder (placebo, 0.5%; 40 mg, 1.0%). The incidence of serious TEAEs reported during the study was similar among the three groups and TEAEs requiring treatment discontinuation were reported in 17 (8.9%), 16 (8.2%), and 11 (5.7%) patients receiving placebo, blonanserin 40 mg, and 80 mg, respectively. None of the TEAEs that caused treatment discontinuations were specifically related to the application site. One patient in the blonanserin 80 mg group died from an acute myocardial infarction, which was not considered treatment related.

Serious TEAEs in which a causal relationship to blonanserin could not be ruled out included: schizophrenia ($n = 2$), generalized tonic-clonic seizure ($n = 1$), psychiatric disorder ($n = 1$), and psychiatric symptom ($n = 1$) with blonanserin 40 mg; schizophrenia ($n = 2$) and suicide attempt ($n = 1$) with blonanserin 80 mg; and catatonia ($n = 1$) and loss of consciousness ($n = 1$) with placebo.

Extrapyramidal TEAEs were reported in 7.9%, 10.7%, and 20.6% of patients in the placebo, blonanserin 40 mg, and 80 mg groups, respectively

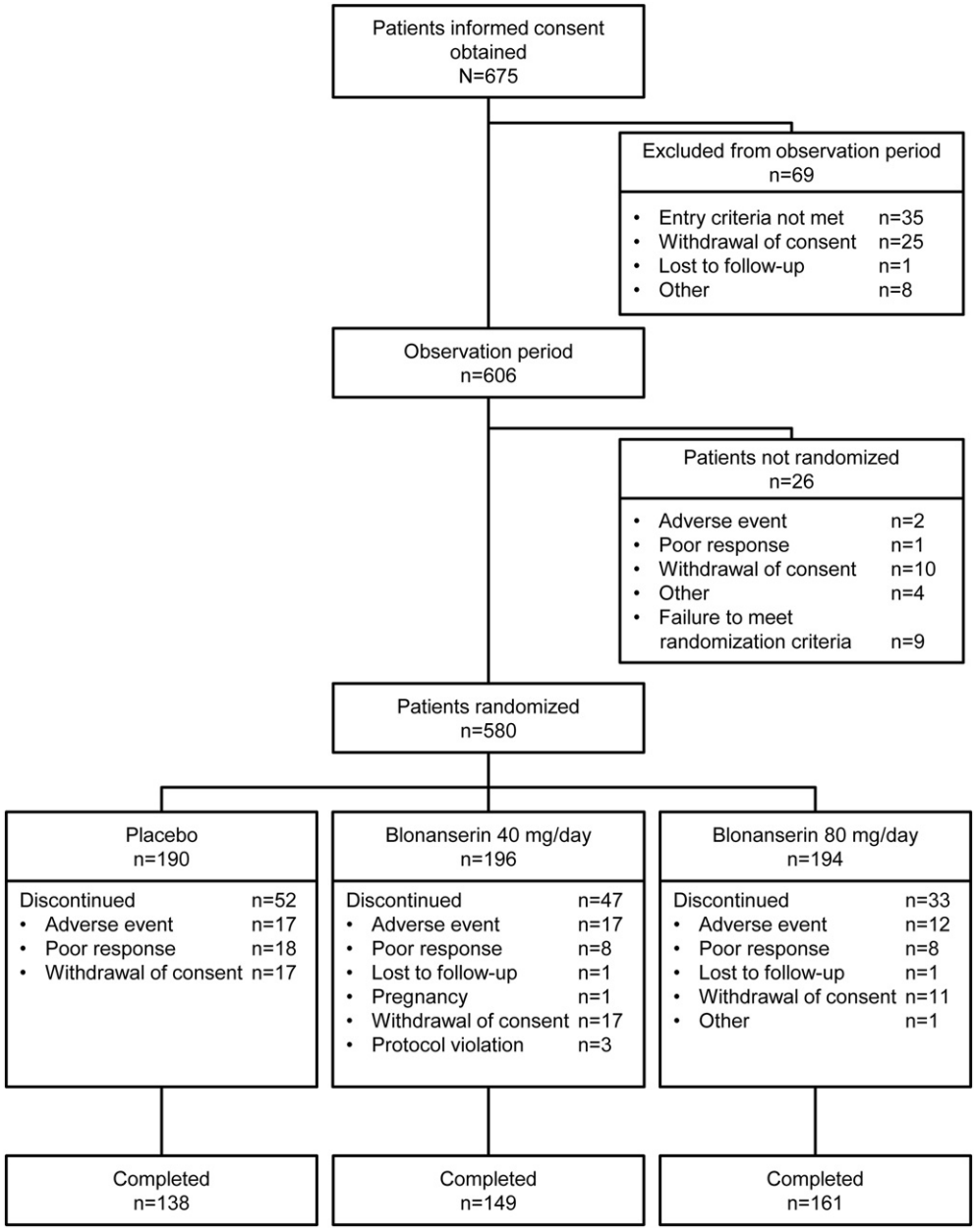

Fig. 1. Patient disposition.

(Table 2), most of which were considered mild/moderate (one case of akathisia in the blonanserin groups and one case of psychomotor hyperactivity in the placebo group were considered as severe). Extrapyramidal TEAEs reported in ≥2% of patients included tremor (2.6%) and restlessness (2.1%) in the placebo group, akathisia (5.6%) and tremor (4.1%) in the blonanserin 40 mg group, and gait disturbance (2.1%), muscle rigidity (3.6%), akathisia (9.8%), tremor (8.8%), bradykinesia (3.1%), and dyskinesia (2.6%) in the blonanserin 80 mg group.

Skin-related TEAEs at the site of patch application were reported in 4.2%, 13.3%, and 18.6% of patients in the placebo, blonanserin 40 mg, and 80 mg groups, respectively, none of which were considered severe. Most skin-related TEAEs in the blonanserin treatment groups occurred within 2 weeks of starting treatment (Supplementary Table S2). Skin-related TEAEs reported in ≥2% of patients included application site erythema (5.6%), pruritus (5.1%), and dermatitis (2.0%) in the blonanserin 40 mg group, and application site erythema (9.3%) and pruritus (7.2%) in the blonanserin 80 mg group. Topical steroids and topical antihistamines were used by 2.9% and 0.3% of patients in the whole cohort. Among the patients who showed skin-related TEAEs ($n = 70$), approximately half ($n = 36$) received any treatment, including topical steroids ($n = 17$), topical antihistamines ($n = 2$) and others ($n = 17$, e.g., moisturizer). Most patients with skin-related TEAEs recovered from these by the end of the study. Twenty-four patients were not recovered by the end of the study and nine among them were still on treatment with topical steroids at the end of the study period. All of these nine patients had skin-related TEAEs considered as mild.

Overall, 5.9%, 7.7%, and 8.3% of patients in the placebo, blonanserin 40 mg, and 80 mg groups, respectively, gained ≥7% bodyweight from baseline, and 2.7%, 5.6%, and 4.1%, respectively lost ≥7% bodyweight from baseline. Mean change in the bodyweight from baseline at Week 6 was -0.30 ± 2.44 kg, 0.10 ± 2.76 kg, and 0.22 ± 2.47 kg with placebo, blonanserin 40 mg, and 80 mg, respectively. The incidence of metabolism-related TEAEs, abnormal laboratory findings (Supplementary Table S3) and abnormal ECG findings (Table 2) were also similar between the three groups at the end of the treatment period.

Table 1
Baseline characteristics in the safety population ($n = 580$).

	Placebo ($n = 190$)	Blonanserin 40 mg ($n = 196$)	Blonanserin 80 mg ($n = 194$)	Overall ($n = 580$)
Male	113 (59.5)	116 (59.2)	115 (59.3)	344 (59.3)
Mean ± SD age, years	41.5 ± 13.7	40.7 ± 13.3	40.6 ± 14.3	40.9 ± 13.8
Race				
Asian	162 (85.3)	167 (85.2)	167 (86.1)	496 (85.5)
Caucasian/White	28 (14.7)	29 (14.8)	27 (13.9)	84 (14.5)
Concomitant diseases	110 (57.9)	112 (57.1)	112 (57.7)	334 (57.6)
Hospitalization status at informed consent				
Inpatient	184 (96.8)	188 (95.9)	189 (97.4)	561 (96.7)
Outpatient	6 (3.2)	8 (4.1)	5 (2.6)	19 (3.3)
Mean ± SD no. of schizophrenia episodes	3.7 ± 1.4	3.7 ± 1.3	3.8 ± 1.4	3.7 ± 1.4
Mean ± SD age at the first onset of schizophrenia, years	27.6 ± 10.1	26.8 ± 9.5	26.5 ± 9.6	27.0 ± 9.7
Mean ± SD duration of illness[a], years	13.9 ± 11.9	13.8 ± 11.2	13.8 ± 12.2	13.8 ± 11.7
Mean ± SD duration of current episode[b], months	2.9 ± 22.0	3.7 ± 25.9	3.8 ± 32.1	3.5 ± 27.0
Mean ± SD PANSS total score	99.5 ± 13.8	101.6 ± 15.6	101.5 ± 14.7	100.9 ± 14.7
PANSS composite subscale at baseline				
Positive score > Negative score	96 (50.5)	104 (53.1)	85 (43.8)	285 (49.1)
Positive score = Negative score	11 (5.8)	11 (5.6)	11 (5.7)	33 (5.7)
Positive score < Negative score	83 (43.7)	81 (41.3)	98 (50.5)	262 (45.2)
Mean ± SD CGI-S score	4.8 ± 0.7	4.8 ± 0.8	4.9 ± 0.7	4.9 ± 0.7
Mean ± SD DIEPSS total score[c]	0.9 ± 2.2	0.8 ± 2.3	1.0 ± 2.4	0.9 ± 2.3
Medications at baseline				
Any medication	174 (91.6)	182 (92.9)	180 (92.8)	536 (92.4)
Antipsychotics	162 (85.3)	170 (86.7)	167 (86.1)	499 (86.0)
Anxiolytics/antidepressants	62 (32.6)	75 (38.3)	73 (37.6)	210 (36.2)
Hypnotic agents	60 (31.6)	68 (34.7)	64 (33.0)	192 (33.1)
Antiparkinsonian drugs	48 (25.3)	43 (21.9)	44 (22.7)	135 (23.3)

Values are presented as n (%) unless otherwise stated.
BMI, body mass index; CGI-S, clinical global impressions-severity of illness scale; DIEPSS, drug-induced extrapyramidal symptoms scale; No. number; PANSS, positive and negative syndrome scale; SD, standard deviation.
[a] Duration of illness indicates years from the initial episode of schizophrenia to the informed consent.
[b] Duration of current episode is months from the onset of current episode to the informed consent.
[c] Score excluding overall severity.

The LSM difference in change in DIEPSS total score from baseline to Week 6 compared with placebo was 0.2 (95%CI −0.1, 0.5; $p = 0.259$) with blonanserin 40 mg and 0.3 (95%CI 0.0, 0.6; $p = 0.032$) with blonanserin 80 mg. The C-SSRS evaluation showed suicidal ideation after baseline in 2.6%, 5.6%, and 3.1% of patients in the placebo, blonanserin 40 mg, and blonanserin 80 mg groups; the maximum score of suicidal ideation worsened from baseline in 1.1% of patients in the placebo group versus 3.1% and 1.6% in the blonanserin 40 mg and 80 mg groups.

In skin irritation assessment, a negative score was most frequent in the three groups (82.5% vs 77.6% and 70.5% with placebo, blonanserin 40 mg and 80 mg), followed by faint erythema (12.2% vs 11.7% and 13.0%), and erythema (4.2% vs 8.7% and 14.5%). No patient developed coalescing vesicles during the double-blind treatment period.

3.4. Pharmacokinetics

Mean plasma blonanserin concentrations increased with treatment during the double-blind treatment period (Table 3). The mean plasma blonanserin concentration with blonanserin 80 mg was approximately twice that of blonanserin 40 mg at each evaluation time point.

4. Discussion

This randomized, double-blind, placebo-controlled, phase 3 trial was the first study to investigate the efficacy and safety of the blonanserin transdermal patch in patients with acute schizophrenia. After 6 weeks of treatment the blonanserin transdermal patch improved the symptoms of schizophrenia, as reflected by reduced PANSS total and subscale scores and CGI-S scores. Treatment with transdermal blonanserin patch was well tolerated, with manageable TEAEs.

The change from baseline in PANSS total score with the 80 mg blonanserin patch at 6 weeks in this study was higher in magnitude than that at Week 8 of treatment with blonanserin tablets in the phase 3 studies conducted in Japanese patients (mean decrease of 10 to 11 points) (Kishi et al., 2019; Korea Food and Drug Administration, 2016). In contrast, the placebo-corrected change in PANSS total score with the 80 mg blonanserin patch at 6 weeks in this study was somewhat lower than that seen with blonanserin tablets in a randomized, placebo-controlled study in non-Japanese patients (Sumitomo Dainippon Pharma Co., Ltd., 2018). However, the effect size with the blonanserin 80 mg patch (0.555) is considered a “medium” effect size (Leppink et al., 2016), which suggests that blonanserin may not be inferior to other drugs available for the treatment of schizophrenia. It should be noted, however, that in this fixed dose study, neither responder rate nor CGI-S showed a significant difference with blonanserin 40 mg vs placebo. It is suggested to observe effectiveness carefully and to consider a clinically appropriate dose increase when insufficient effectiveness is observed on the blonanserin 40 mg patch.

The blonanserin 80 mg group also showed significantly greater reductions in the positive, negative, and general psychopathology PANSS subscale scores at 6 weeks compared with placebo, and improvements in all factors except anxiety/depression of the PANSS five-factor model. Antipsychotics have been shown to be less effective in treating the negative than the positive symptoms of schizophrenia (Krause et al., 2018; Leucht et al., 2017). Some negative symptoms, such as anhedonia and avolition, appear to be mediated by dopamine D_3 receptors (Duric et al., 2017; Simpson et al., 2014). Conversely, a PET study in patients with schizophrenia was unable to demonstrate a relationship between the extent of dopaminergic $D_{2/3}$ occupancy by antipsychotics and the magnitude of effect on negative symptoms (Fervaha et al., 2016). A clinical dose of blonanserin occupied D_3 receptors as much as D_2 receptors, which was demonstrated by a PET study in human (Tateno et al., 2018). Therefore, the effect on negative symptoms with blonanserin may reflect potent inhibition for the D_3 receptor in vivo. Further research using a longer duration of treatment in patients with

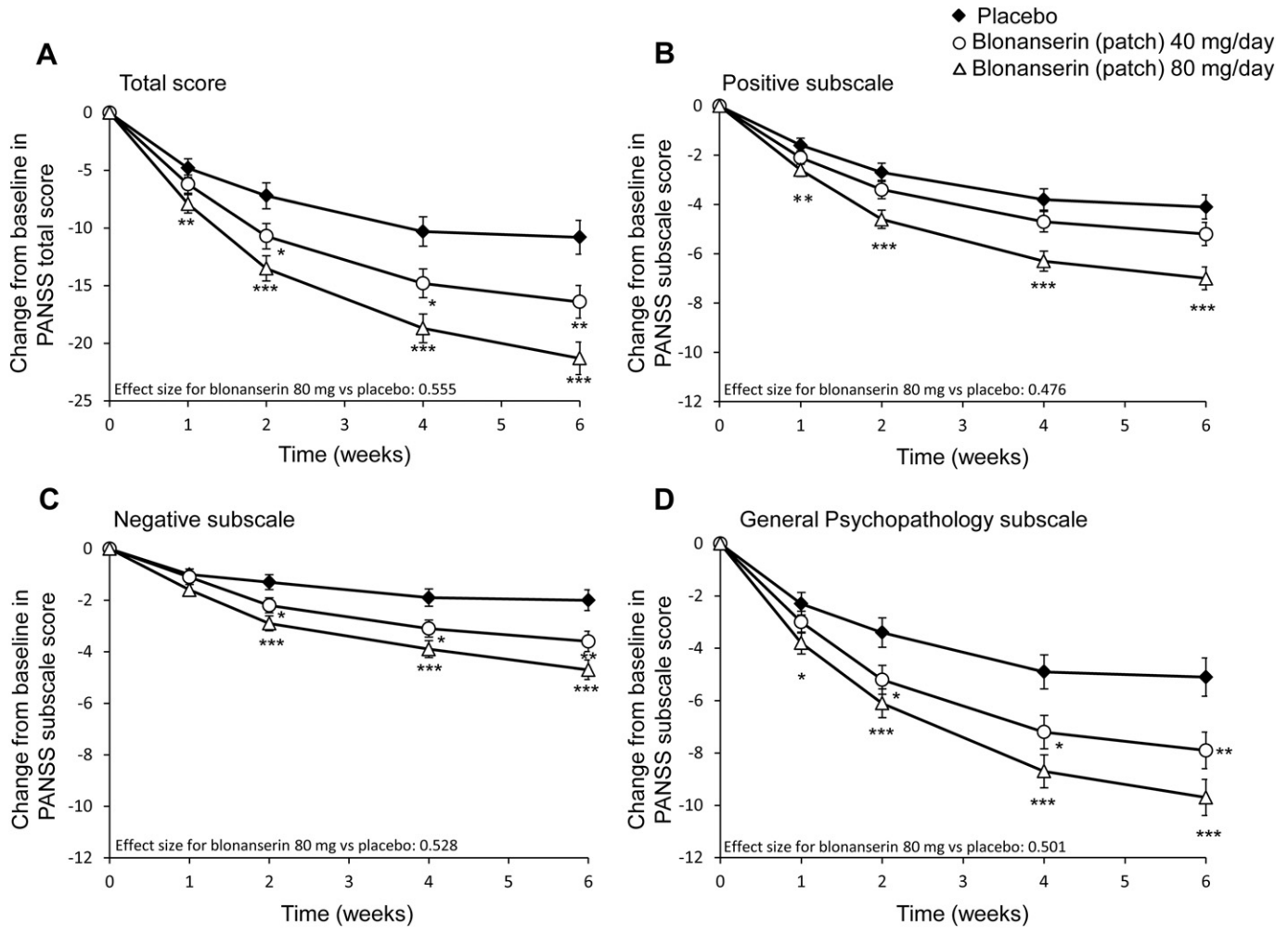

Fig. 2. Change from baseline in (A) PANSS total score, (B) PANSS positive symptoms subscale score, (C) PANSS negative symptoms subscale score, and (D) PANSS general psychopathology subscale scores in the mITT population ($n = 577$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs placebo. Data represent least squares mean estimate ± standard errors.

predominantly negative symptomatology is required to clarify the effects of blonanserin on negative symptoms.

Of the TEAEs reported by ≥5% of patients during this study, the incidence of schizophrenia was mainly higher in the placebo group, while application site erythema and pruritus, akathisia, and tremor were more common in the blonanserin treatment groups. In common with other dopamine receptor drugs antagonists/partial agonists (Divac et al., 2014) and with blonanserin tablets (Kishi et al., 2019), akathisia and tremor were the most frequently observed extrapyramidal TEAEs in the two treatment groups; however, none of these events were considered serious. In addition, the incidence of akathisia with blonanserin 80 mg was lower than that reported in previous clinical studies of blonanserin tablets (15.6–35.5%) (Garcia et al., 2009; Li et al., 2015; Murasaki, 2007). The overall incidence of extrapyramidal TEAEs reported with blonanserin 80 mg in the present study was also lower than that reported in previous clinical studies of blonanserin tablets (26.6–66.7%) (Garcia et al., 2009; Li et al., 2015; Murasaki, 2007). In addition, in contrast to the incidence of overall AEs with blonanserin tablets reported in other studies, which were comparable to the respective control groups (93% vs 96% [haloperidol] and 98% vs 99% [risperidone]), AEs with blonanserin patch in our study occurred in only 63% (40 mg) and 67% (80 mg) (Harvey et al., 2019; Miura, 2008). Although it may not be appropriate to make a direct comparison of these values due to the differences in study designs and baseline characteristics of enrolled patients, this lower incidence of overall AEs or extrapyramidal TEAEs could possibly be due to more stable plasma blonanserin levels observed with the transdermal patch compared with its oral formulations. A dose-dependent increase in the plasma concentrations of blonanserin during the double-blind treatment period was seen in this study. In terms of efficacy, PANSS total score, as well as subscale scores showed positive dose associations. In terms of safety, most events increased with blonanserin 80 mg vs 40 mg treatment, with some exceptions such as insomnia, sedation and psychiatric disorders. Plasma level stability with the patch formulation may be related to the direct absorption of blonanserin from the skin, which bypasses the gastrointestinal tract and therefore the typical effect of food on the bioavailability of oral blonanserin is not seen (Saruwatari et al., 2010). Furthermore, the blonanserin patch provides continuous release of blonanserin, which may also contribute to this stability (Sumitomo Dainippon Pharma Co., Ltd., 2018).

The incidence of skin-related TEAEs (application site erythema, pruritus, and dermatitis) increased dose-dependently with blonanserin during the study; however, none of these were considered serious and were managed with topical steroids or antihistamines. Moreover, no premature treatment discontinuation was reported due to these TEAEs.

Blonanserin may be associated with a low risk of weight gain and hyperprolactinemia (Kishi et al., 2014). The proportion of patients with a ≥ 7% weight gain in the current study was low in all three treatment groups. These safety findings also need to be confirmed in another long-term study of the blonanserin patch.

The treatment completion rate in the present study was 76% with the blonanserin 40 mg patch and 83% with blonanserin 80 mg, which

Table 2
Summary of treatment-emergent adverse events (TEAEs) reported during the study ($n = 580$).

System organ class/preferred term	Placebo ($n = 190$)	Blonanserin 40 mg ($n = 196$)	Blonanserin 80 mg ($n = 194$)
TEAEs	114 (60.0)	123 (62.8)	130 (67.0)
Serious TEAEs	9 (4.7)	8 (4.1)	10 (5.2)
Extrapyramidal symptoms[a]	15 (7.9)	21 (10.7)	40 (20.6)
Moderate + severe	4 (2.1)	3 (1.5)	11 (5.7)
Skin-related symptoms[b]	8 (4.2)	26 (13.3)	36 (18.6)
Moderate + severe	0	2 (1.0)	1 (0.5)
Psychiatric disorders	44 (23.2)	46 (23.5)	28 (14.4)
Sedation-related	5 (2.6)	3 (1.5)	3 (1.5)
QTc-prolonged/proarrhythmia-related	1 (0.5)	1 (0.5)	0
TEAEs reported in ≥2% of patients			
Gastrointestinal disorders			
Constipation	5 (2.6)	8 (4.1)	8 (4.1)
Toothache	4 (2.1)	5 (2.6)	3 (1.5)
Diarrhea	2 (1.1)	1 (0.5)	5 (2.6)
Salivary hypersecretion	1 (0.5)	0	4 (2.1)
General disorders and administration site conditions			
Application site erythema	3 (1.6)	11 (5.6)	18 (9.3)
Application site pruritus	1 (0.5)	10 (5.1)	14 (7.2)
Application site dermatitis	1 (0.5)	4 (2.0)	2 (1.0)
Gait disturbance	1 (0.5)	1 (0.5)	4 (2.1)
Infections and infestations			
Nasopharyngitis	8 (4.2)	5 (2.6)	9 (4.6)
Upper respiratory tract infection	1 (0.5)	4 (2.0)	3 (1.5)
Musculoskeletal and connective tissue disorders			
Muscle rigidity	0	3 (1.5)	7 (3.6)
Nervous system disorders			
Akathisia	2 (1.1)	11 (5.6)	19 (9.8)
Tremor	5 (2.6)	8 (4.1)	17 (8.8)
Headache	5 (2.6)	9 (4.6)	7 (3.6)
Bradykinesia	0	1 (0.5)	6 (3.1)
Dyskinesia	3 (1.6)	1 (0.5)	5 (2.6)
Psychiatric disorders			
Insomnia	9 (4.7)	10 (5.1)	10 (5.2)
Schizophrenia	14 (7.4)	10 (5.1)	3 (1.5)
Agitation	7 (3.7)	7 (3.6)	5 (2.6)
Psychotic disorder	6 (3.2)	8 (4.1)	4 (2.1)
Anxiety	2 (1.1)	2 (1.0)	5 (2.6)
Respiratory, thoracic and mediastinal disorders			
Cough	2 (1.1)	0	4 (2.1)
Skin and subcutaneous tissue disorders			
Pruritus	2 (1.1)	3 (1.5)	4 (2.1)

If a patient experienced ≥1 episodes of TEAEs within the category, it was counted only once.
TEAEs, treatment-emergent adverse events.
Values are presented as n (%).
[a] Extrapyramidal TEAE were determined by preferred term prior to data summary.
[b] Defined as a TEAE with the location of event of the application site.

Table 3
Plasma concentrations of blonanserin during the treatment period ($n = 387$).

	Blonanserin 40 mg ($n = 194$)	Blonanserin 80 mg ($n = 193$)
Week 1		
n	187	192
Concentration, ng/mL	0.66665 ± 0.375905	1.32481 ± 0.760173
CV %	56.4	57.4
Week 2		
n	175	184
Concentration, ng/mL	0.88470 ± 0.515422	1.83108 ± 0.978002
CV %	58.3	53.4
Week 6		
n	162	169
Concentration, ng/mL	1.16236 ± 0.813989	2.22628 ± 1.306073
CV %	70.0	58.7

Values are presented as mean ± standard deviation unless otherwise stated.
CV, coefficient variation; SD, standard deviation.

compares favorably with the 73.3% treatment completion rate seen with blonanserin tablets in a randomized, multicenter trial of blonanserin versus risperidone in the management of Chinese patients with schizophrenia (Li et al., 2015). Our finding suggests that the blonanserin patch may improve treatment persistence in patients with schizophrenia, although this possibility needs to be confirmed in additional studies of longer duration and with a direct pill comparator.

Patients with schizophrenia require long-term treatment (Correll et al., 2018), but adherence to treatment is often poor, which increases the risk of re-hospitalization (Weiden et al., 2004). We hypothesized that using the transdermal route for drug administration would not only enhance adherence (relative to oral antipsychotics) but would allow treatment adherence to be easily monitored by the treating physicians and caregivers. Importantly, transdermal patches also offer an alternative to both oral and intramuscular antipsychotic agents, thereby expanding the options for consideration during treatment decisions. Having a range of treatment options is especially important in SDM models of psychiatric care, which are being increasingly adopted into mental health policy around the world. The transdermal option may be particularly useful for patients with a long duration of schizophrenia who may have developed preferences for and against particular antipsychotic agents during the course of their treatment.

The main limitation of the present study was that multiplicity adjustment was not used in the statistical analysis, except for analysis of the primary endpoint. Another limitation of the study is the relatively short study duration of 6 weeks, although results from the ongoing open-label extension of this study are expected to provide data on the long-term safety and efficacy (up to 52 weeks) of blonanserin transdermal patch in the treatment of schizophrenia. Also, the study only enrolled patients aged over 18 years and the results may not be fully generalizable to younger patient populations. Finally, the comparator was placebo and future studies should include a tablet version of blonanserin or another antipsychotic.

In conclusion, transdermal blonanserin patch showed efficacy in the treatment of acute stage schizophrenia, as indicated by effective management of the positive and negative symptoms of schizophrenia during the study period. Blonanserin was also well tolerated and showed a dose-dependent improvement in both psychopathology and treatment completion rates over placebo. These findings suggest that the once-daily transdermal patch formulation of blonanserin provides an effective and well-tolerated treatment option for patients with acute schizophrenia, and expands the options for patients to consider during schizophrenia management. We also found from this study that the incidence of some skin-related AEs increased in a dose-dependent manner. This phenomenon needs to be assessed further in future studies. The outcomes of this study are being further tested in a long-term follow-up in Japan, although another study with a comparator arm is needed to confirm its long-term efficacy on the negative and positive symptoms of schizophrenia.

Contributors

All authors meet all ICMJE contribution criteria. NI, JI, YI and TH contributed substantially to the conception and design of the study. WHK, BHY, SKL, AHS, RC, LW, YS and AA contributed to data acquisition. KW, TM, TS and YI contributed to the conception and design of the study and analysis and interpretation of data. CC and JK contributed substantially to interpretation of data and critical revision of the draft.

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Declaration of Competing Interest

NI reports personal fees from Otsuka, Sumitomo Dainippon, Janssen, Eli Lilly, and Pfizer, grants from Otsuka, Daiichi-Sankyo, outside the submitted work. JI reports grants from Sumitomo Dainippon during the conduct of the study, personal fees from Meiji Seika

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.055.

References

Alvarez-Jimenez, M., Priede, A., Hetrick, S., Bendall, S., Killackey, E., Parker, A., McGorry, P., Gleeson, J., 2012. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr. Res. 139 (1–3), 116–128.

Correll, C.U., Rubio, J.M., Kane, J.M., 2018. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? World Psychiatry 17 (2), 149–160.

Das, A.K., Malik, A., Haddad, P.M., 2014. A qualitative study of the attitudes of patients in an early intervention service towards antipsychotic long-acting injections. Ther Adv Psychopharmacol 4 (5), 179–185.

Divac, N., Prostran, M., Jakovcevski, I., Cerovac, N., 2014. Second-generation antipsychotics and extrapyramidal adverse effects. Biomed. Res. Int. 2014, 656370.

Duric, V., Banasr, M., Franklin, T., Lepack, A., Adham, N., Kiss, B., Gyertyan, I., Duman, R.S., 2017. Cariprazine exhibits anxiolytic and dopamine D_3 receptor-dependent antidepressant effects in the chronic stress model. Int. J. Neuropsychopharmacol. 20 (10), 788–796.

Fervaha, G., Caravaggio, F., Mamo, D.C., Mulsant, B.H., Pollock, B.G., Nakajima, S., Gerretsen, P., Rajji, T.K., Mar, W., Iwata, Y., Plitman, E., Chung, J.K., Remington, G., Graff-Guerrero, A., 2016. Lack of association between dopaminergic antagonism and negative symptoms in schizophrenia: a positron emission tomography dopamine D2/3 receptor occupancy study. Psychopharmacology 233 (21−22), 3803–3813.

Garcia, E., Robert, M., Peris, F., Nakamura, H., Sato, N., Terazawa, Y., 2009. The efficacy and safety of blonanserin compared with haloperidol in acute-phase schizophrenia: a randomized, double-blind, placebo-controlled, multicentre study. CNS Drugs 23 (7), 615–625.

Harvey, P.D., Nakamura, H., Murasaki, M., 2019. Blonanserin versus haloperidol in Japanese patients with schizophrenia: a phase 3, 8-week, double-blind, multicenter, randomized controlled study. Neuropsychopharmacology reports.

Hori, H., Yamada, K., Kamada, D., Shibata, Y., Katsuki, A., Yoshimura, R., Nakamura, J., 2014. Effect of blonanserin on cognitive and social function in acute phase Japanese schizophrenia compared with risperidone. Neuropsychiatr. Dis. Treat. 10, 527–533.

Inada, T., Beasley Jr., C.M., Tanaka, Y., Walker, D.J., 2003. Extrapyramidal symptom profiles assessed with the Drug-Induced Extrapyramidal Symptom Scale: comparison with Western scales in the clinical double-blind studies of schizophrenic patients treated with either olanzapine or haloperidol. Int. Clin. Psychopharmacol. 18 (1), 39–48.

Kawamura, T., Sasagawa, S., Masuda, T., Honda, S., KInoshita, M., Harada, S., Ishizaki, T., Nagai, R., Hirokawa, K., Anzai, T., Anekoji, K., Hidano, A., Kawano, T., Ikegami, I., Sato, S., Aoyama, T., 1970. Basic studies on the standerdization of patch test. Nippon Hifu Gakkai Zasshi 80 (5), 301–314.

Kishi, T., Matsuda, Y., Iwata, N., 2014. Cardiometabolic risks of blonanserin and perospirone in the management of schizophrenia: a systematic review and meta-analysis of randomized controlled trials. PLoS One 9 (2), e88049.

Kishi, T., Matsui, Y., Matsuda, Y., Katsuki, A., Hori, H., Yanagimoto, H., Sanada, K., Morita, K., Yoshimura, R., Shoji, Y., Hagi, K., Iwata, N., 2019. Efficacy, tolerability, and safety of blonanserin in schizophrenia: an updated and extended systematic review and meta-analysis of randomized controlled trials. Pharmacopsychiatry 52 (2), 52–62.

Korea Food and Drug Administration, 2016. Ronasenjeong. Available from. http://ezdrug.mfds.go.kr/, Accessed date: 24 January 2019.

Krause, M., Zhu, Y., Huhn, M., Schneider-Thoma, J., Bighelli, I., Nikolakopoulou, A., Leucht, S., 2018. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur. Arch. Psychiatry Clin. Neurosci. 268 (7), 625–639.

Kreyenbuhl, J., Nossel, I.R., Dixon, L.B., 2009. Disengagement from mental health treatment among individuals with schizophrenia and strategies for facilitating connections to care: a review of the literature. Schizophr. Bull. 35 (4), 696–703.

Leppink, J., O'Sullivan, P., Winston, K., 2016. Effect size - large, medium, and small. Perspect Med Educ 5 (6), 347–349.

Leucht, S., Leucht, C., Huhn, M., Chaimani, A., Mavridis, D., Helfer, B., Samara, M., Rabaioli, M., Bächer, S., Cipriani, A., 2017. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am. J. Psychiatry 174 (10), 927–942.

Li, H., Yao, C., Shi, J., Yang, F., Qi, S., Wang, L., Zhang, H., Li, J., Wang, C., Wang, C., Liu, C., Li, L., Wang, Q., Li, K., Luo, X., Gu, N., 2015. Comparative study of the efficacy and safety between blonanserin and risperidone for the treatment of schizophrenia in Chinese patients: a double-blind, parallel-group multicenter randomized trial. J. Psychiatr. Res. 69, 102–109.

Lindenmayer, J.P., Bernstein-Hyman, R., Grochowski, S., 1994. A new five factor model of schizophrenia. Psychiatr Q 65 (4), 299–322.

Miura, S., 2008. Clinical evaluation of blonanserin for schizophrenia: a randomized controlled study comparing blonanserin with risperidone. Jpn J Clin Psychopharmacol 11 (2), 297–314.

Murasaki, M., 2007. Clinical evaluation of blonanserin for schizophrenia: a randomized controlled study comparing blonanserin with haloperidol. Jpn J Clin Psychopharmacol 10 (11), 2059–2079.

Osaka Dainippon Sumitomo Pharma Co., Ltd., 2009. Lonansen (Blonanserin): Prescribing Information. Available from. http://ds-pharma.jp/product/lonasen/kaitei.html, Accessed date: 24 January 2019.

Patel, M.X., De Zoysa, N., Bernadt, M., David, A., 2009. Depot and oral antipsychotics: patient preferences and attitudes are not the same thing. J. Psychopharmacol. 23 (7), 789–796.

Posner, K., Brown, G.K., Stanley, B., Brent, D.A., Yershova, K.V., Oquendo, M.A., Currier, G.W., Melvin, G.A., Greenhill, L., Shen, S., Mann, J.J., 2011. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168 (12), 1266–1277.

Saruwatari, J., Yasui-Furukori, N., Inoue, Y., Kaneko, S., 2010. Effect of dose timing in relation to food intake on systemic exposure to blonanserin. Eur. J. Clin. Pharmacol. 66 (9), 899–902.

Simpson, E.H., Winiger, V., Biezonski, D.K., Haq, I., Kandel, E.R., Kellendonk, C., 2014. Selective overexpression of dopamine D3 receptors in the striatum disrupts motivation but not cognition. Biol. Psychiatry 76 (10), 823–831.

Sumitomo Dainippon Pharma Co., Ltd., 2018. New Drug Application in Japan for Transdermal Patch Formulation of Atypical Antipsychotic LONASEN®.

Tateno, A., Sakayori, T., Kim, W.C., Honjo, K., Nakayama, H., Arakawa, R., Okubo, Y., 2018. Comparison of dopamine D_3 and D_2 receptor occupancies by a single dose of blonanserin in healthy subjects: a positron emission tomography study with [^{11}C]-(+)-PHNO. Int. J. Neuropsychopharmacol. 21 (6), 522–527.

Une, T., Kurumiya, S., 2007. Pharmacological profile of blonanserin. Jpn J Clin Psychopharmacol 10 (7), 1263–1272.

Velligan, D.I., Sajatovic, M., Hatch, A., Kramata, P., Docherty, J.P., 2017. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence 11, 449–468.

Weiden, P.J., Kozma, C., Grogg, A., Locklear, J., 2004. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. Psychiatr. Serv. 55 (8), 886–891.