ORIGINAL RESEARCH ARTICLE

Long-Term Safety and Efficacy of Blonanserin Transdermal Patches in Japanese Patients with Schizophrenia: A 52-Week Open-Label, Multicenter Study

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Abstract

Background Blonanserin transdermal patch therapy is now available in Japan for the treatment of schizophrenia and may provide several advantages over the tablet formulation.

Objective The aim was to evaluate the long-term safety and efficacy of blonanserin transdermal patches in Japanese patients with schizophrenia.

Methods An open-label study was conducted in adults with schizophrenia at 37 sites in Japan. Patients were enrolled in either cohort 1 or 2. Patients in cohort 1 received 8–16 mg/day blonanserin tablets for 6 weeks and then 40–80 mg/day blonanserin patches for 52 weeks. The dose of blonanserin patches was determined according to the dose of the tablets. In cohort 2, every patient started from 40 mg/day and then 40–80 mg/day blonanserin transdermal patches for 52 weeks. Both cohorts had 1–2 weeks of follow-up. Safety endpoints included the incidence of adverse events (AEs), treatment-related AEs, extrapyramidal AEs [also assessed using the change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) score], the use of any concomitant antiparkinsonian drugs, and skin-related AEs, including skin irritation. Patients also underwent assessment of laboratory values including for serum prolactin concentration, vital signs, body weight, electrocardiographic (ECG) changes, and the corrected QT (QTc) interval. Suicidal ideation was assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS) score. Efficacy was assessed via duration of blonanserin transdermal patch treatment, Positive and Negative Syndrome Scale (PANSS) total and subscale scores, and Clinical Global Impression-Severity (CGI-S) scores. Other endpoints included total Drug Attitude Inventory 10 (DAI-10) scores, EuroQol-5 Dimension (EQ-5D) effect values, and a patient questionnaire about the dosage form.

Results A total of 223 patients with consents, 117 in cohort 1 and 106 in cohort 2 were included in the study. Of the 117 patients in cohort 1, 108 were treated with blonanserin tablets, and 97 received blonanserin patches and were included in the safety analysis set. In cohort 2, 103 of the 106 patients were treated with blonanserin transdermal patches and were included in the safety analysis set. In total, 91 patients were male (45.5%). The mean age was 43.8 years. Discontinuation occurred in 40 patients (41.2%) in cohort 1 and 44 patients (42.7%) in cohort 2. Discontinuation resulted from AEs in 18.6% (cohort 1) and 11.7% (cohort 2) and from withdrawal of consent in 13.4% (cohort 1) and 20.4% (cohort 2), and seven patients overall discontinued due to skin reactions. AEs were reported in 174 patients (87.0%), and 13 serious AEs occurred in 12 patients (6.0%), of which six patients were in cohort 1 and six patients were in cohort 2. Serious AEs were six schizophrenia ($n=6$) and seven other AEs ($n=6$), which included impulse-control disorder, fracture, epistaxis, asthma, pneumonia aspiration, pneumonia hemophilus, and pneumonia. The most common AEs were nasopharyngitis ($n=62$, 31.0%), application site erythema ($n=45$, 22.5%), application site pruritus ($n=23$, 11.5%), and akathisia ($n=20$, 10.0%). AE incidence was similar in cohort 1 (84.5%) and cohort 2 (89.3%). Extrapyramidal and skin-related AEs were reported in 51 patients (25.5%) and 83 patients (41.5%), respectively. None of these AEs were serious. The mean change from baseline in total DIEPSS score

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at Week 52 {last observation carried forward [LOCF] (standard deviation [SD])} was −0.1 (1.55), indicating no marked effect. In terms of concomitant medications used in cohort 1 and cohort 2, 33.0% (32/97) and 22.3% (23/103) used antiparkinsonian drugs, respectively. The majority of skin-related AEs occurred early in treatment and were appropriately managed with topical therapies. Of the patients who answered "No" to all C-SSRS categories at baseline ($n = 129$), 13 patients (10.1%) were evaluated as having emergence of suicidal ideation. Among patients who answered "No" to all C-SSRS suicidal behavior categories at baseline ($n = 172$), one (0.6%) was evaluated as having suicidal behavior during blonanserin transdermal patch treatment. There were no clinically significant changes in laboratory tests or examinations, including prolactin level, vital signs, body weight, ECG, metabolism-related parameters, and QTc interval. The mean (SD) change in body weight was −0.04 (4.561) kg and −0.67 (6.841) kg in cohort 1 and cohort 2, respectively. The mean changes from baseline in PANSS total score at Week 52 (LOCF [SD]) were −0.1 [11.6] and −3.4 [15.3] in cohort 1 and 2, respectively. PANSS scores did not change after switching from tablet to patch formulation in cohort 1 and decreased over the 52 weeks of treatment with the blonanserin patches. The mean change from baseline in CGI-S score at Week 52 (LOCF [SD]) was −0.2 [1.03] in both cohorts combined. After 52 weeks of blonanserin patch treatment, the total DAI-10 score increased or remained unchanged compared with baseline in 82 of the 129 patients (63.6%) for whom these data were available. In the intention-to-treat population of the combined cohorts ($n = 200$), the mean (SD) change from baseline in EQ-5D score at the last assessment was −0.0365 (0.17603). Patients' attitudes to the blonanserin transdermal patches were generally positive.

Conclusions Blonanserin transdermal patches are safe and effective in the long-term treatment of schizophrenia.

ClinicalTrials.gov registration NCT02335658.

Key Points

Blonanserin transdermal patches were well tolerated over 52 weeks and showed maintained efficacy in patients with schizophrenia.

Blonanserin patches had a long-term safety profile similar to, or better than, that of blonanserin tablets; skin-related adverse events were all mild or moderate and mostly occurred early in treatment.

Long-term blonanserin transdermal patch therapy was associated with stabilization of both the positive and negative symptoms of schizophrenia, and patients' attitudes towards blonanserin transdermal patches were generally positive.

1 Introduction

Blonanserin is a second-generation antipsychotic (SGA) that is approved for the treatment of schizophrenia in Japan, South Korea, and China [1, 2]. It has strong affinity for D_2 and D_3 dopamine and 5-HT_{2A} serotonin receptors, where it exerts antagonist activity [1]. Blonanserin has low or very low affinity for other neurotransmitter receptor subtypes (dopamine D_1, D_4, and D_5, adrenoceptors α_1, α_2, and β, serotonin 5-HT_{1A}, 5-HT_{2B}, and 5-HT_{2C}, histamine H_1, and muscarinic M_1 and M_3) [1, 3]. In short- and long-term studies, blonanserin was effective and well tolerated in patients with schizophrenia [2, 4–9]. In a meta-analysis of randomized controlled clinical trials, blonanserin was more effective than aripiprazole in improving total Positive and Negative Syndrome Scale (PANSS) scores, and was associated with a lower risk of hyperprolactinemia, but a higher risk of akathisia, agitation/excitement, and extrapyramidal symptoms (EPS), compared with a combination of risperidone and paliperidone [10].

Non-adherence to drug therapy is a serious unresolved issue for schizophrenia treatment. A positive attitude toward medication is one of the key factors needed to improve adherence, as patients' attitude is significantly associated with treatment adherence [11]. Dosage form also influences adherence to long-term drug therapy [12]. Commonly used atypical antipsychotics for long-term treatment of schizophrenia are mainly available in tablet formulation. When poor adherence is found, long-acting injections are also used.

The addition of a new dosage form is expected to be helpful for patients with schizophrenia who prefer not to use the current dose formulations, and this may be useful in increasing treatment adherence. We considered the main advantages of a transdermal patch formulation as follows: easy supervision by the medical staff or caregiver, providing stable blood concentrations over long periods, and avoiding first-pass metabolism that can affect plasma levels of oral agents [13].

Blonanserin is available as transdermal patches (20 mg and 40 mg), which is expected to provide a number of advantages over the tablet formulation. For example, transdermal patches can provide stable blood concentrations over long periods and avoid first-pass metabolism that can affect plasma levels of oral agents [14]. This may improve adherence and decrease the incidence of adverse events (AEs) that occur as a result of high

plasma concentrations immediately after administration. Of the long-acting antipsychotic formulations, transdermal systems have advantages over intramuscular injections because they are non-invasive and treatment can be stopped immediately, if needed, by removing the patch [14]. In a 6-week randomized, double-blind, multicenter, phase III study conducted in patients with acute-phase schizophrenia, blonanserin transdermal patches were well tolerated and significantly improved PANSS total scores compared with placebo [13].

The aim of this multicenter, open-label study was to evaluate the safety and efficacy of the blonanserin transdermal patches when used for 52 weeks in the treatment of patients with schizophrenia. The safety and efficacy of the blonanserin patches were also evaluated in patients who switched to the transdermal formulation from blonanserin tablets or other antipsychotic drugs.

2 Methods

2.1 Study Design

This 52-week multicenter, open-label study was conducted at 37 medical institutions in Japan from February 2015 to May 2017 (Clinical Study Registration No. NCT02335658).

Patients were eligible for inclusion if they were aged ≥ 18 years and met the diagnostic criteria for schizophrenia outlined in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). Premenopausal (fertile) women were required to have a negative pregnancy test result at the time of screening. All female patients had to agree to use appropriate contraceptives, as did all male patients with a potentially fertile sexual partner. For a full list of exclusion criteria, see supplementary Table S1 (see the electronic supplementary material [ESM]).

Eligible patients who provided written informed consent were enrolled in either cohort 1 (patients switched from blonanserin tablets to patch therapy) or cohort 2 (patients received continuous blonanserin patch therapy; Fig. 1), and then entered a dose reduction/observation period of ≤ 4 weeks, during which their previous antipsychotic treatment was withdrawn. The duration of the dose reduction/observation period depended on the dose of previous antipsychotic therapy, which had to be reduced to ≤ 12 mg haloperidol equivalents.

The objective of cohort 1 was to evaluate the safety and efficacy of the blonanserin patches in patients who received blonanserin tablets prior to the transdermal patches. Patients in cohort 1 received blonanserin tablets twice daily (after breakfast and dinner) for 6 weeks (tablet treatment phase), followed by blonanserin patches once daily for 52 weeks

(patch treatment phase) and a post-treatment follow-up period of 1–2 weeks (Fig. 1a). During the tablet treatment period, the initial dosage of blonanserin tablets was 8 mg/day, which was then adjusted according to predefined criteria (Table S2). At the end of the tablet treatment phase, patients could be receiving blonanserin tablets at a dosage of 8, 12, or 16 mg/day. The starting dose of blonanserin patches was determined by the final dose of oral blonanserin, i.e., patients who had received blonanserin tablets 8, 12, and 16 mg/day received 40, 60, and 80 mg/day patches, respectively (Table S3). This procedure means that patients started blonanserin patches from the comparable dose of tablets, which is one of the common situations in clinical settings. Patients applied 40–80 mg blonanserin transdermal patches to their back, chest, or abdomen by combining 20-mg or 40-mg patches. Blonanserin transdermal patch doses could be adjusted in a range between 40 mg and 80 mg by following the predefined criteria (Table S2) during the patch treatment phase.

The objective of cohort 2 was to evaluate the safety and efficacy of the blonanserin transdermal patches in patients, including those who had previously received any antipsychotic treatments or had not received a treatment for schizophrenia before. Patients entering cohort 2 received open-label treatment with blonanserin transdermal patches for 52 weeks, followed by a post-treatment follow-up period of 1–2 weeks (Fig. 1b). The cohort 2 study did not include an "oral tablet run-in" phase. All patients in cohort 2 started blonanserin transdermal patches from 40 mg, which is the minimum dose expected to be effective from the phase 2 trial result [15]. The conditions of the blonanserin transdermal patch treatment period were the same as those in cohort 1 (Table S2). Patients were enrolled in cohort 1 in order of entry, and enrollment in cohort 2 began after completion of cohort 1 enrollment.

This study was conducted in compliance with the ethical principles stated in the Declaration of Helsinki and with the Good Clinical Practice (GCP) guidelines and other relevant Japanese regulations. The study protocol was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all patients (and their legal guardian if the patient was < 20 years old or was hospitalized for medical care and protection) prior to the study.

2.2 Outcome Assessments

The safety endpoints included treatment-emergent AEs (TEAEs) and treatment-related AEs, extrapyramidal AEs (including the use of any concomitant antiparkinsonian drugs), skin-related AEs at the application site, and skin irritation assessment. TEAEs were defined as any untoward medical event that occurred during blonanserin transdermal patch use. Treatment-related AEs were defined as AEs for which a causal relation to blonanserin could not be ruled out.

a

b
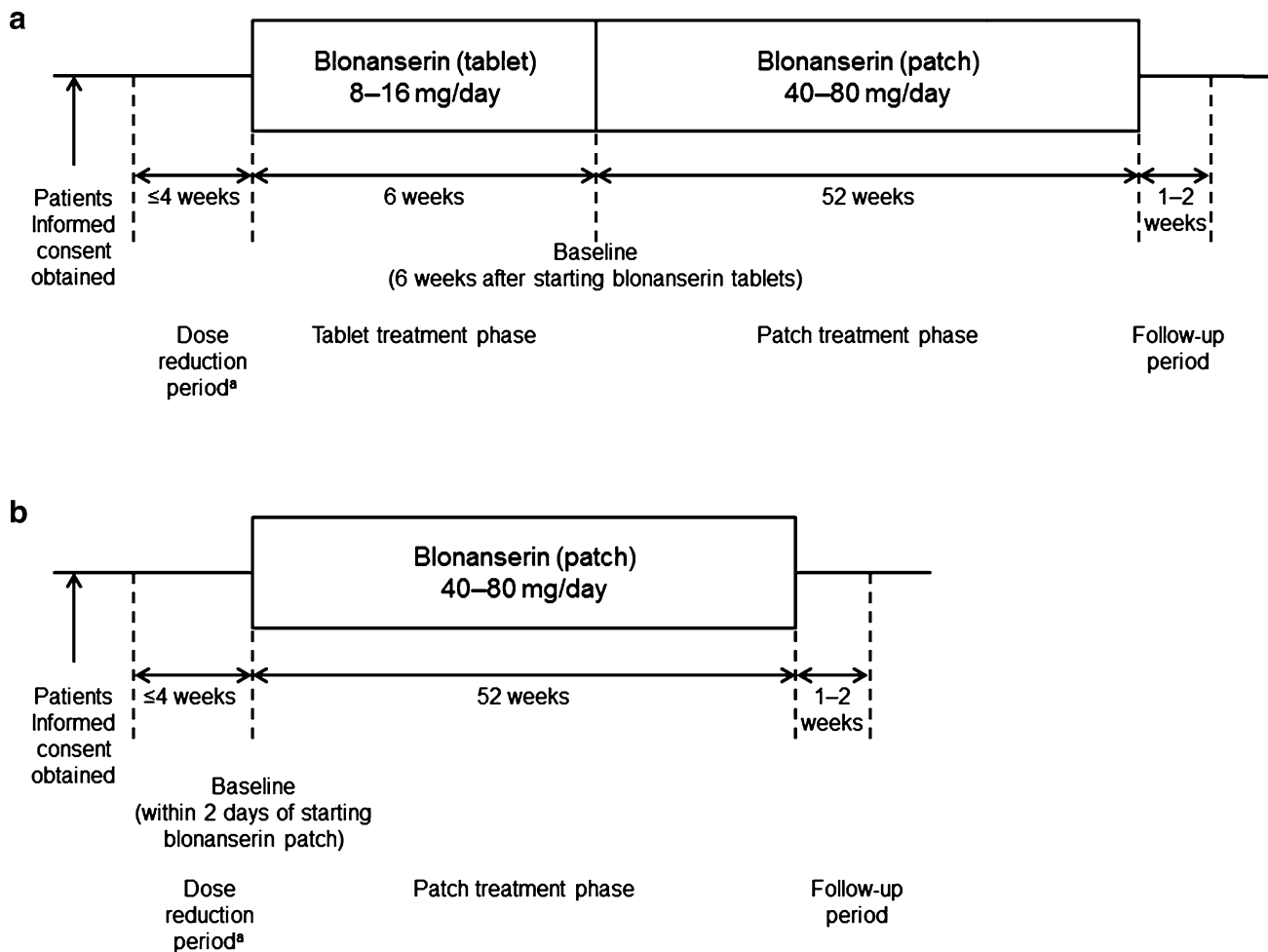
Fig. 1 Study design for **a** cohort 1 and **b** cohort 2. [a]There was a dose reduction/observation period for patients who had been previously treated with antipsychotics at the dosage of > 12.0 mg/day in haloperidol equivalents. Prior antipsychotics were first decreased to ≤ 12.0 mg/day and then gradually discontinued

AEs were recorded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. AEs that occurred more than once were counted only once in preferred term aggregation. Skin irritation was assessed on a 6-point scale (no reaction [−]; mild erythema [±]; erythema [+]; erythema/edema [++]; erythema/edema/papule, serous papule, vesicle [+++]; bulla [++++]) as described by Kawamura and colleagues [16]. The presence and severity of EPS were assessed using the change in Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) score [17] (total score not including overall severity and score for individual symptoms). Patients also underwent laboratory tests, including for serum prolactin concentration, and were assessed for vital signs, changes in body weight, and electrocardiographic (ECG) changes, specifically any changes in the corrected QT (QTc) interval. The potential for suicidal ideation was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) score [18]. The development of suicidal ideation or behavior was defined as patients who answered "No" to all the C-SSRS questions at baseline and answered "Yes" to any of the C-SSRS questions after starting blonanserin transdermal patch treatment.

Efficacy endpoints assessed in the present study included duration of blonanserin transdermal patch treatment, change in total PANSS score, change in total PANSS subscale score, change in total PANSS 5-factor score [19], and change in Clinical Global Impression-Severity (CGI-S) score from baseline to the end of the blonanserin transdermal patch treatment phase. Other endpoints included total Drug Attitude Inventory 10 (DAI-10) score [20] and EuroQol-5 Dimension (EQ-5D) effect value [21] and a patient questionnaire about the dosage form.

TEAEs, treatment-related AEs, extrapyramidal AEs, skin-related AEs, DIEPSS, C-SSRS, PANSS, and CGI-S were assessed at the baseline and at weeks 1, 2, 4, 6, 8, 12, 16, 20, 24, 28, 36, 44, and 52 or at the time of discontinuation of

the blonanserin transdermal patch treatment phase in cohort 1 and cohort 2. In addition, the DIEPSS, C-SSRS, PANSS, and CGI-S assessments were also performed at baseline and at weeks 1, 2, 4, and 6 of the blonanserin tablet treatment phase in cohort 1. DAI-10 was used to obtain information relating to patient adherence. DAI-10 and EQ-5D were assessed at baseline and at weeks 6, 28, and 52 of the blonanserin transdermal patch treatment phase, and a questionnaire about the dosage form was conducted at Week 52 of the blonanserin transdermal patch treatment phase in both cohorts. EQ-5D-5L was used with Japan tariff to obtain index scores [22]. The baseline of the patch treatment phase was defined as 6 weeks after starting treatment with blonanserin tablets in cohort 1 and within 2 days of blonanserin patch application in cohort 2.

Patient compliance with treatment was calculated from the physician-recorded patient's remainder of unused drugs and the number of prescriptions, without measuring blood blonanserin concentration.

2.3 Statistical Analysis

The sample size of the study was not statistically evaluated. However, assuming a drop-out rate of approximately 50%, it was estimated that a sample size of 200 would be required in order to assess 100 patients for 52 weeks in accordance with the Japanese guidelines (Pharmaceutical Affairs Bureau Notification No. 592).

The Kaplan–Meier method was used for the analysis of time to treatment discontinuation. Median treatment duration and 95% confidence intervals (CIs) were calculated by cohort. Patient demographics were summarized descriptively, as were efficacy, safety, pharmacokinetic, and other endpoints by cohort and study visit. All analyses were conducted in the safety analysis set, which included patients with at least one administration of blonanserin transdermal patches during the patch treatment phase. Missing data were not imputed, except for the Week 52 (LOCF) evaluation.

For repeated measurements, summary statistics for the observed value and change from baseline value (denoted by change) are based on subjects with both a baseline and target visit observation. The last observed score at Week 52 is shown as imputed data using the LOCF method.

3 Results

3.1 Patient Disposition and Baseline Characteristics

A total of 223 patients consented to participate in this study, 117 in cohort 1 (Fig. 2a) and 106 in cohort 2 (Fig. 2b). Of the 117 patients enrolled in cohort 1, 108 were treated with blonanserin tablets, and 97 went on to receive blonanserin patches and were included in the safety analysis set. Forty patients (41.2%) in cohort 1 discontinued treatment with blonanserin transdermal patches. The most common reason for discontinuation was AEs (18.6%). Overall, 103 of the 106 patients who entered cohort 2 were treated with blonanserin transdermal patches and were included in the safety analysis set. Forty-four patients (42.7%) discontinued treatment with blonanserin transdermal patches; the most common reason was withdrawal of consent (20.4%).

In the overall safety cohort ($n = 200$), 91 patients were male (45.5%) and the mean (SD) age of patients was 43.8 (13.50) years (Table 1). Patients had been diagnosed with schizophrenia a mean (SD) of 15.4 (12.15) years before study entry. The mean (SD) baseline PANSS total score was 67.0 (22.0), and approximately two-thirds ($n = 135$; 67.5%) had more negative than positive symptoms on the baseline PANSS assessment. Patient characteristics were similar in the two cohorts (Table 1).

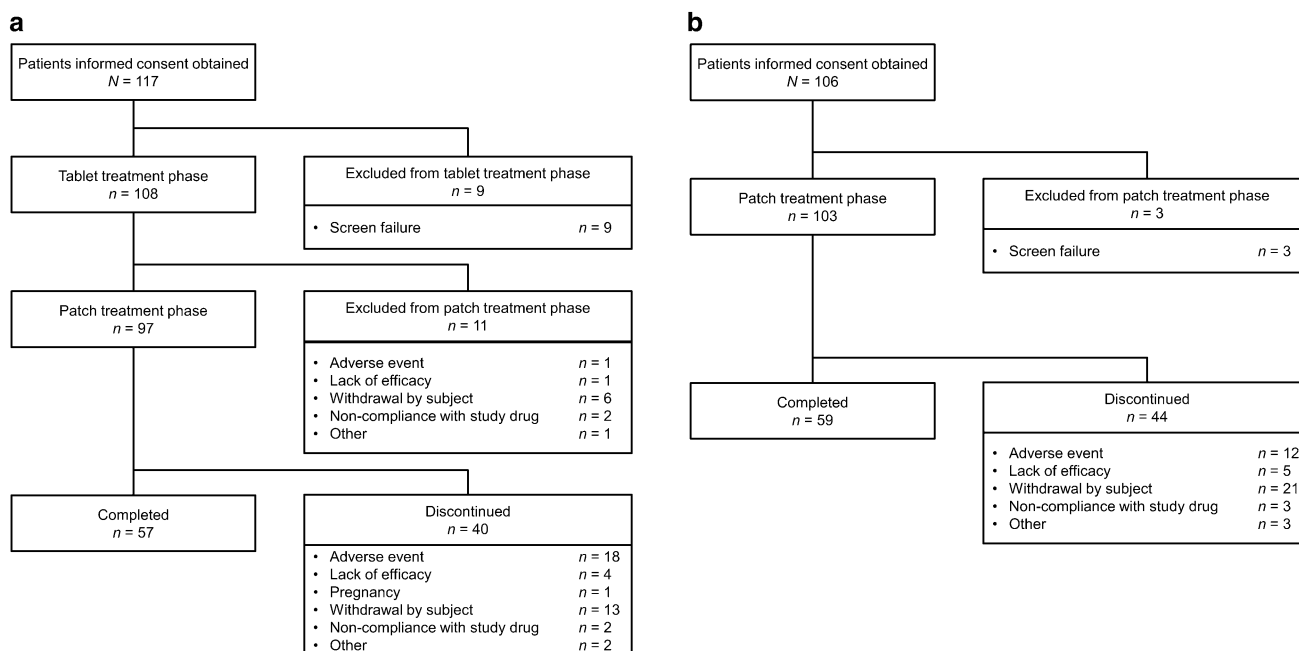## 3.2 Treatment Status and Continuation

The median duration of blonanserin transdermal patch treatment was 353 days (range 2–371) in cohort 1 and 350 days (range 4–378) in cohort 2. The mean (SD) daily blonanserin transdermal patch dosage was 55.2 (17.21) mg/day in cohort 1 and 56.0 (15.91) mg/day in cohort 2. At 28 weeks, 64.9% of patients (95% CI 54.6–73.5) in cohort 1 and 66.0% (95% CI 56.0–74.3) in cohort 2 were still using blonanserin transdermal patches. At 52 weeks, the treatment retention rate was 58.8% (95% CI 48.3–67.8) in cohort 1 and 57.3% (95% CI 47.2–66.2) in cohort 2 (Fig. S1; see the ESM).

Compliance with medication was 98.6% and 98.4% in cohort 1 and 2, respectively.

In terms of concomitant medications used in cohort 1 and cohort 2, 15.5% (15/97) and 21.4% (22/103) of patients used antipsychotics, 33.0% (32/97) and 22.3% (23/103) used antiparkinsonian drugs, 40.2% (39/97) and 40.8% (42/103) used psychotropics, and 69.1% (68/103) and 66.0% (67/97) used sleeping pills during treatment, respectively.

3.3 Safety

AEs were observed in 174 patients (87.0%), with a similar incidence in cohort 1 (84.5%) and cohort 2 (89.3%) (Table 2). Most AEs were mild or moderate in severity; seven patients (3.5%) developed severe AEs. A total of

a

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┌─────────────────────────────┐
│ Patients informed consent   │
│ obtained                    │
│ N = 117                     │
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Tablet treatment phase n = 108		Excluded from tablet treatment phase n = 9
		• Screen failure n = 9

Patch treatment phase n = 97		Excluded from patch treatment phase n = 11
		• Adverse event n = 1
		• Lack of efficacy n = 1
		• Withdrawal by subject n = 6
		• Non-compliance with study drug n = 2
		• Other n = 1

Completed n = 57		Discontinued n = 40
		• Adverse event n = 18
		• Lack of efficacy n = 4
		• Pregnancy n = 1
		• Withdrawal by subject n = 13
		• Non-compliance with study drug n = 2
		• Other n = 2

b

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┌─────────────────────────────┐
│ Patients informed consent   │
│ obtained                    │
│ N = 106                     │
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Patch treatment phase n = 103		Excluded from patch treatment phase n = 3
		• Screen failure n = 3

Completed n = 59		Discontinued n = 44
		• Adverse event n = 12
		• Lack of efficacy n = 5
		• Withdrawal by subject n = 21
		• Non-compliance with study drug n = 3
		• Other n = 3

Fig. 2 Patient flow for **a** cohort 1 and **b** cohort 2

Table 1 Patient background and clinical characteristics at study entry (prior to any blonanserin therapy)

	Cohort 1 $n = 97$	Cohort 2 $n = 103$	Overall $N = 200$
Male sex, n (%)	43 (44.3)	48 (46.6)	91 (45.5)
Mean (SD) age (years)	44.1 (14.43)	43.6 (12.63)	43.8 (13.50)
Mean (SD) weight (kg)	65.22 (17.637)	66.28 (15.145)	65.77 (16.368)
Mean (SD) BMI (kg/m²)	24.68 (5.429)	24.70 (4.857)	24.69 (5.129)
Hospitalization status at baseline, n (%)			
Inpatient	8 (8.2)	17 (16.5)	25 (12.5)
Outpatient	89 (91.8)	86 (83.5)	175 (87.5)
Patients with concomitant diseases, n (%)	87 (89.7)	79 (76.7)	166 (83.0)
Mean (SD) age at schizophrenia onset, years	29.1 (12.60)	27.8 (9.55)	28.4 (11.15)
Mean (SD) total schizophrenia episodes	1.9 (1.43)	1.8 (1.32)	1.8 (1.37)
Mean (SD) duration of illness[a], years	14.9 (12.72)	15.8 (11.63)	15.4 (12.15)
Mean (SD) duration of current episode[b], months	104.7 (108.87)	104.1 (93.38)	104.4 (100.89)
Mean (SD) PANSS total score	66.4 (22.73)	67.5 (21.34)	67.0 (21.98)
Positive > negative subscale score, n (%)	24 (24.7)	22 (21.4)	46 (23.0)
Positive = negative subscale score, n (%)	8 (8.2)	11 (10.7)	19 (9.5)
Positive < negative subscale score, n (%)	65 (67.0)	70 (68.0)	135 (67.5)
Mean (SD) CGI-S score	3.5 (1.07)	3.4 (1.11)	3.4 (1.09)
Mean (SD) DIEPSS total score[c]	0.6 (1.55)	0.8 (1.56)	0.7 (1.55)

BMI body mass index, *CGI-S* Clinical Global Impressions – Severity of Illness Scale, *DIEPSS* Drug-Induced Extrapyramidal Symptoms Scale, *PANSS* Positive and Negative Syndrome Scale, *SD* standard deviation

[a]Time from the initial episode of schizophrenia to provision of informed consent

[b]Time from the onset of the current episode to provision of informed consent

[c]Excludes overall severity

△ Adis

13 serious AEs occurred in 12 patients (6.0%), of which six occurred in cohort 1 and six occurred in cohort 2. Serious AEs were schizophrenia ($n=6$) and seven AEs ($n=6$), which included impulse-control disorder, fracture, epistaxis, asthma, pneumonia aspiration, pneumonia hemophilus, and pneumonia. No AEs were fatal. Discontinuation resulted from AEs in 18.6% (cohort 1) and 11.7% (cohort 2) of patients and from withdrawal of consent in 13.4% (cohort 1) and 20.4% (cohort 2) of patients. The most common AEs included nasopharyngitis ($n=62$, 31.0%), application site erythema ($n=45$, 22.5%), application site pruritus ($n=23$, 11.5%), and akathisia ($n=20$, 10.0%) (Table 3).

A total of 78 extrapyramidal AEs occurred in 51 patients (25.5%) in the overall patient population. The most frequent extrapyramidal AE was akathisia ($n=20$, 10.0%). None of the extrapyramidal AEs were serious. Among those who were not using antiparkinsonian drugs at study entry, 15.6% (12/77) in cohort 1 and 20.0% (20/100) in cohort 2 initiated antiparkinsonian drugs during the treatment period.

Skin-related TEAEs at the site of patch application were observed in 40.2% and 42.7% in cohort 1 and 2, respectively. Of these, 116 skin-related AEs in 78 patients (39.0%) were considered to be treatment-related. Skin-related AEs were mostly mild, and none were serious. Thirty-three percent of skin-related TEAEs occurred in week 1–13 and 7.9% in week 14–26. Skin-related TEAEs reported in $\geq 5\%$ of patients included application site erythema, pruritus, and dermatitis. Approximately 22% of skin-related AEs required treatment. Topical steroids and topical antihistamines were used by 7.2% and 13.6% of patients in cohorts 1 and 2, respectively. Among the patients who showed skin-related TEAEs ($n=83$), approximately half ($n=44$) received any treatment, including topical steroids ($n=21$), topical antihistamines ($n=7$), and others ($n=16$; e.g., moisturizer). Most patients with skin-related TEAEs recovered by the end of the trial. Seven patients discontinued the study due to skin-related TEAEs.

None of the patients in the safety analysis set developed bullae during the blonanserin transdermal patch treatment phase according to the skin irritation assessment scores. The maximum scores were vesicle (+++) in two patients (1.0%), erythema/edema (++) in 12 (6.0%), erythema (+) in 48 (24.0%), and mild erythema (±) in 73 patients (36.5%).

There were no clinically significant changes in laboratory tests or examinations, including prolactin level, body weight, metabolism-related parameters, and QTc interval. The mean (SD) change in body weight was -0.04 (4.561) kg and -0.67 (6.841) kg in cohort 1 and cohort 2, respectively.

The mean (SD) change from baseline in total DIEPSS score at Week 52 (LOCF) was -0.1 (1.55), indicating no marked effect on EPS in patients who completed this assessment ($n=117$).

In total, 71 patients had a prior history of suicidal ideation and were excluded from the C-SSRS assessment. Of the patients who answered "No" to all C-SSRS categories at baseline ($n=129$), 13 patients (10.1%) were evaluated as having emergence of suicidal ideation. Among patients who answered "No" to all C-SSRS suicidal behavior categories at baseline ($n=172$), one (0.6%) was evaluated as having suicidal behavior during blonanserin transdermal patch treatment. No completed suicide was reported.

3.4 Efficacy

3.4.1 Cohort 1

In cohort 1, the PANSS total score decreased by a mean (SD) of 2.9 (7.2) points from the start of the tablet treatment until the last assessment before the switch to patches, and did not increase after switching treatment

Table 2 Summary of TEAEs

	Cohort 1 $n=97$		Cohort 2 $n=103$		Overall $N=200$	
	n (%)	Events	n (%)	Events	n (%)	Events
TEAE	82 (84.5)	306	92 (89.3)	442	174 (87.0)	748
Leading to death	0	0	0	0	0	0
Serious	6 (6.2)	6	6 (5.8)	7	12 (6.0)	13
Leading to treatment discontinuation	16 (16.5)	19	12 (11.7)	15	28 (14.0)	34
Severe	4 (4.1)	4	3 (2.9)	3	7 (3.5)	7
Extrapyramidal	21 (21.6)	27	30 (29.1)	51	51 (25.5)	78
Skin-related	39 (40.2)	51	44 (42.7)	72	83 (41.5)	123

TEAE treatment-emergent adverse event

Table 3 TEAEs that were reported in ≥2% of patients

	TEAE, n (%)		
	Cohort 1 n=97	Cohort 2 n=103	Overall N=200
Subjects with any TEAE	82 (84.5)	92 (89.3)	174 (87.0)
Endocrine disorders	7 (7.2)	7 (6.8)	14 (7.0)
Hyperprolactinemia	7 (7.2)	7 (6.8)	14 (7.0)
Gastrointestinal disorders	23 (23.7)	34 (33.0)	57 (28.5)
Dental caries	5 (5.2)	8 (7.8)	13 (6.5)
Diarrhea	5 (5.2)	5 (4.9)	10 (5.0)
Vomiting	7 (7.2)	3 (2.9)	10 (5.0)
Constipation	2 (2.1)	5 (4.9)	7 (3.5)
Nausea	3 (3.1)	3 (2.9)	6 (3.0)
Salivary hypersecretion	3 (3.1)	3 (2.9)	6 (3.0)
Stomatitis	0 (0.0)	4 (3.9)	4 (2.0)
General disorders and administration site conditions	42 (43.3)	49 (47.6)	91 (45.5)
Application site erythema	18 (18.6)	27 (26.2)	45 (22.5)
Application site pruritus	9 (9.3)	14 (13.6)	23 (11.5)
Application site dermatitis	8 (8.2)	2 (1.9)	10 (5.0)
Application site discoloration	4 (4.1)	2 (1.9)	6 (3.0)
Malaise	1 (1.0)	3 (2.9)	4 (2.0)
Infections and infestations	32 (33.0)	41 (39.8)	73 (36.5)
Nasopharyngitis	29 (29.9)	33 (32.0)	62 (31.0)
Pharyngitis	2 (2.1)	2 (1.9)	4 (2.0)
Injury, poisoning and procedural complications	12 (12.4)	13 (12.6)	25 (12.5)
Contusion	3 (3.1)	3 (2.9)	6 (3.0)
Excoriation	3 (3.1)	2 (1.9)	5 (2.5)
Ligament sprain	1 (1.0)	3 (2.9)	4 (2.0)
Investigations	10 (10.3)	28 (27.2)	38 (19.0)
Blood prolactin increased	2 (2.1)	12 (11.7)	14 (7.0)
Weight increased	3 (3.1)	7 (6.8)	10 (5.0)
Blood CPK increased	1 (1.0)	3 (2.9)	4 (2.0)
Musculoskeletal and connective tissue disorders	15 (15.5)	15 (14.6)	30 (15.0)
Back pain	8 (8.2)	5 (4.9)	13 (6.5)
Arthralgia	1 (1.0)	3 (2.9)	4 (2.0)
Muscle rigidity	1 (1.0)	3 (2.9)	4 (2.0)
Nervous system disorders	26 (26.8)	35 (34.0)	61 (30.5)
Akathisia	6 (6.2)	14 (13.6)	20 (10.0)
Tremor	4 (4.1)	10 (9.7)	14 (7.0)
Headache	6 (6.2)	1 (1.0)	7 (3.5)
Dizziness	3 (3.1)	3 (2.9)	6 (3.0)
Dyskinesia	2 (2.1)	4 (3.9)	6 (3.0)
Dystonia	4 (4.1)	2 (1.9)	6 (3.0)
Bradykinesia	2 (2.1)	3 (2.9)	5 (2.5)
Somnolence	1 (1.0)	4 (3.9)	5 (2.5)
Psychiatric disorders	25 (25.8)	28 (27.2)	53 (26.5)
Insomnia	7 (7.2)	11 (10.7)	18 (9.0)
Schizophrenia	9 (9.3)	9 (8.7)	18 (9.0)
Restlessness	4 (4.1)	2 (1.9)	6 (3.0)
Skin and subcutaneous tissue disorders	7 (7.2)	15 (14.6)	22 (11.0)
Eczema	3 (3.1)	2 (1.9)	5 (2.5)

CPK creatine phosphokinase, *TEAE* treatment-emergent adverse event

from blonanserin tablets to patches (Fig. 3a). The mean (SD) change from baseline in PANSS total score at Week 52 and Week 52 (LOCF) was − 3.5 (8.4) and − 0.1 (11.6), respectively. The PANSS subscale scores (Figs. S2–S4, see the ESM) and PANSS 5-factor scores (Figs. S5–S9) did not increase during the 52 weeks of the blonanserin transdermal patch treatment phase. The PANSS scores did not change after switching from tablets to patches.

The CGI-S score decreased by a mean (SD) of 0.1 (0.41) from the start of the tablet treatment until the last assessment before the switch to patches, and the mean (SD) change from baseline in CGI-S score at Week 52 and Week 52 (LOCF) was − 0.1 (0.65) and 0 (0.76), respectively. The CGI-S score did not increase after switching treatment from blonanserin tablets to patches during 52 weeks of treatment (Fig. S10).

3.4.2 Cohort 2

In cohort 2, the PANSS total score decreased over the 52 weeks of treatment with the blonanserin transdermal patch (Fig. 3b). The mean (SD) change from baseline in PANSS total score at Week 52 and Week 52 (LOCF) was − 9.2 (15.1) and − 3.4 (15.3), respectively. The mean (SD) changes in the PANSS positive scores, negative scores, and general psychopathology subscale scores at Week 52 (LOCF) were −0.7 (4.55), −1.6 (4.35), and −1.1 (8.05), respectively. PANSS subscale scores (Figs. S2–S4) and 5-factor scores (Figs. S5–S9) showed small decreases over the first 6–8 weeks of treatment and then remained stable over the remainder of the assessment period. The PANSS total, subscale scores, and 5-factor scores showed gradual decrease throughout the treatment period.

The CGI-S score did not change throughout the blonanserin transdermal patch treatment (Fig. S10). The mean (SD)

Fig. 3 Mean (SD) PANSS total scores at each timepoint in **a** cohort 1 and **b** cohort 2. The PANSS score at each timepoint was shown as observed case using pairwise deletion analyses. *PANSS* Positive and Negative Syndrome Scale, *SD* standard deviation
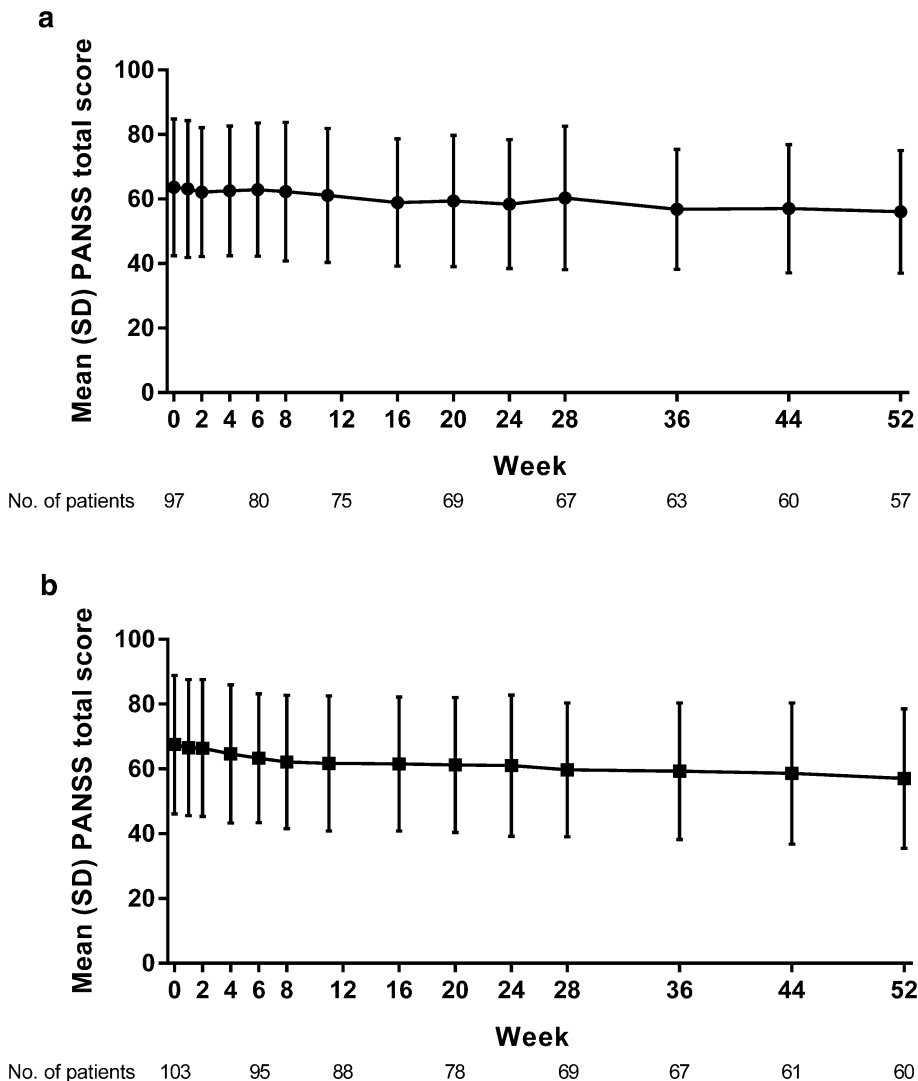
change from baseline in CGI-S score at Week 52 and Week 52 (LOCF) was −0.6 (0.83) and −0.2 (1.03), respectively.

3.5 Patient-Reported Outcomes

In patients who completed 52 weeks of blonanserin transdermal patch treatment ($n = 129$), the mean (SD) change in EQ-5D score from baseline to 52 weeks was −0.0172 (0.16968) for both cohorts combined. In the intention-to-treat population of the combined cohorts ($n = 200$), the mean (SD) change from baseline in EQ-5D score at the last assessment (either Week 52 or the last on-treatment assessment) was −0.0365 (0.17603).

After 52 weeks of blonanserin transdermal patch treatment, the total DAI-10 score increased or remained unchanged compared with baseline in 82 of the 129 patients (63.6%) for whom these data were available. As a positive DAI-10 score is associated with improved adherence [23], we set the minimum positive score value of 2 as the cut-off score between positive and negative attitude toward treatment, because 2 is the smallest positive number. DAI-10 scores have been maintained during the study (Table 4); however, in 165 patients who had a DAI-10 score ≥ 2 at baseline, 30 (18.2%) reverted to a score of < 2 at Week 52 (LOCF), whereas 48.6% (17/35) of patients with a score of < 2 at baseline reported a score ≥ 2 at Week 52 (LOCF). In the patient questionnaire about dosage form, most patients indicated that it would be better if patch formulations of any treatment were available ($n = 135$, 69.6%; Table 5). Approximately one-third of patients indicated that, compared with taking tablets, continuing treatment with patches would be easier ($n = 62$, 32.0%) or at least as easy ($n = 69$, 35.6%). Forty-one percent of patients indicated that they would use blonanserin transdermal patches in the future ($n = 79$, 40.7%).

4 Discussion

This was the first study to evaluate the long-term safety and efficacy of blonanserin transdermal patches in Japanese patients with schizophrenia and showed that blonanserin

transdermal patches are well tolerated and maintain efficacy in the long-term treatment of schizophrenia.

As expected, the long-term safety profile of blonanserin patches was similar to, or better than, that of blonanserin tablets. The incidence of treatment-related AEs observed in the present study (68.5%) was similar to that reported in the previous long-term studies of blonanserin tablets (72.1% and 68.5%) [5, 7]. The incidence of extrapyramidal AEs, such as akathisia and tremor, was lower in the present study (10.0% and 7.0%, respectively) than in the long-term studies of blonanserin tablets (akathisia 17.1%–32.8%, tremor 15.9%–21.3%) [5, 7]. This lower incidence of overall AEs or

Table 4 Number of patients with total DAI-10 score < 2 or ≥ 2 before and after the blonanserin transdermal patch treatment phase

	Number of patients (%)	
	DAI-10 score < 2	DAI-10 score ≥ 2
Before the treatment baseline	35 (17.5)	165 (82.5)
Week 52 (LOCF)	48 (24.0)	152 (76.0)

DAI-10 Drug Attitude Inventory-10, *LOCF* last observation carried forward

Table 5 Dosage form questionnaire

		Cohort 1 $n = 97$	Cohort 2 $n = 103$	Overall $N = 200$
Question 1. Would you like the patch dosage form to be available?				
Completed	n	57	59	116
	Yes	42 (73.7)	52 (88.1)	94 (81.0)
	No	15 (26.3)	7 (11.9)	22 (19.0)
Discontinued	n	39	39	78
	Yes	22 (56.4)	19 (48.7)	41 (52.6)
	No	17 (43.6)	20 (51.3)	37 (47.4)
Overall	n	96	98	194
	Yes	64 (66.7)	71 (72.4)	135 (69.6)
	No	32 (33.3)	27 (27.6)	59 (30.4)
Question 2. Is it easy for you to continue treatment with patches compared with tablets?				
Completed	n	57	59	116
	Yes	19 (33.3)	27 (45.8)	46 (39.7)
	Equal	24 (42.1)	21 (35.6)	45 (38.8)
	No	14 (24.6)	11 (18.6)	25 (21.6)
Discontinued	n	39	39	78
	Yes	10 (25.6)	6 (15.4)	16 (20.5)
	Equal	9 (23.1)	15 (38.5)	24 (30.8)
	No	20 (51.3)	18 (46.2)	38 (48.7)
Overall	n	96	98	194
	Yes	29 (30.2)	33 (33.7)	62 (32.0)
	Equal	33 (34.4)	36 (36.7)	69 (35.6)
	No	34 (35.4)	29 (29.6)	63 (32.5)
Question 3. Would you like to use the patches that you used during this study in the future?				
Completed	n	57	59	116
	Yes	25 (43.9)	36 (61.0)	61 (52.6)
	No	32 (56.1)	23 (39.0)	55 (47.4)
Discontinued	n	39	39	78
	Yes	10 (25.6)	8 (20.5)	18 (23.1)
	No	29 (74.4)	31 (79.5)	60 (76.9)
Overall	n	96	98	194
	Yes	35 (36.5)	44 (44.9)	79 (40.7)
	No	61 (63.5)	54 (55.1)	115 (59.3)

extrapyramidal TEAEs could possibly be due to a less rapid increase and stable transition in plasma blonanserin levels with the transdermal patches compared with the oral formulation. When plasma drug concentrations antagonizing dopamine D_2 receptors are maintained stably, maximum blood concentration (C_{max})-dependent AEs could be suppressed. Hyperprolactinemia was observed in 7.0% of patients in the present study, which was less than that previously observed with blonanserin tablets (34.4% and 29.6%) [5, 7]. Weight gain was observed in 5.0% of patients in this study and 8.2% and 7.2% in the previous studies with blonanserin tablets [5, 7].

In long-term studies conducted in patients with schizophrenia treated with other antipsychotics approved in Japan, the overall incidence of AEs at 48 or 52 weeks was between 84 and 97% [24–27], and our study showed similar safety findings (87%). The overall incidence of extrapyramidal AEs was 25.5% in this study, which was lower than that found with blonanserin tablets (35.8%) [7] and lower than (32.9%) [24] or similar to (22.2%) [25] that of other antipsychotics approved in Japan. The proportion of patients who were administered antiparkinsonian drugs was 18% (32/177) in this study, which was lower than that reported in the previous studies with other antipsychotics approved in Japan (93%, 25%, and 81%) [7, 24, 25].

Skin-related AEs are characteristic of patch formulations. In the present study, skin-related AEs were observed in 41.5% of patients, which was higher than that reported in the short-term phase III, placebo-controlled study of blonanserin transdermal patches (13.3%–18.6%) [13]. In this study, the substrate and the drug substance were not distinguished during the collection of AEs. It should be noted, however, that in the short-term phase III study, the incidence of AEs at the application site was higher in the active patch group than in the placebo patch group. Although the number of cases increased due to the long duration of treatment, all skin-related AEs observed in the present study were mild or moderate in severity. They tended to occur early in treatment and were appropriately managed with topical therapies. Two patients discontinued the study because of skin-related AEs; however, the proportion of patients who used treatment for skin-related AEs was similar to that of the phase III study [13].

The rate of treatment discontinuation observed with blonanserin transdermal patches in the present study was similar to rates reported in long-term studies of other antipsychotic drugs conducted in Japan [24–27]. No marked increase in treatment discontinuation was observed after switching from tablets to patches in cohort 1. In the phase III study, patients in the 80-mg treatment group switched from their prior treatment without tapering, and no special AEs that were possibly due to switching were observed [13]. Taken together, these data suggest that the blonanserin patches are well tolerated when switching from blonanserin tablets or from other antipsychotic drugs, although further study is warranted.

Suicidal ideation is an important parameter to assess in the treatment of patients with schizophrenia. However, it was difficult to compare the results of the present study with those of other studies, because none of them assessed suicidal ideation or behavior using the C-SSRS [24–27]. In the phase III study of blonanserin transdermal patches, the incidence of suicidal ideation evaluated using the C-SSRS was 5.6% with 40 mg and 3.1% with 80 mg blonanserin transdermal patches [13], which was lower than the incidence observed in the present study (10.1%). Further research, such as a study in the real-world clinical setting, is warranted to evaluate the influence of blonanserin transdermal patch therapy on suicidal thoughts and behavior.

The PANSS and CGI-S scores remained relatively stable throughout the study, and no apparent increases were noted. In addition, both the positive and negative symptoms of schizophrenia were stabilized with blonanserin transdermal patches. Continuous control of symptoms is one of the main goals of long-term pharmacotherapy in schizophrenia. Considering the fact that relapse or worsening of symptoms during treatment is one of the risk factors for non-adherence to treatment [28], sustained efficacy over an extended period could help to maintain a patient's long-term engagement with treatment. In addition, many of the patients enrolled in this study were considered to have chronic schizophrenia based on the mean duration of disease and of the current episode, and the study included a high proportion of patients with higher negative than positive PANSS symptom scores [29]. Over 98% of patients had been treated with antipsychotics, which are generally more effective in reducing positive symptoms than negative symptoms [30]. These factors could have influenced the effectiveness of blonanserin transdermal patches in the present study. The 6-week, randomized, phase III study of blonanserin transdermal patches showed efficacy in patients with acute phase schizophrenia. In this long-term study, similar efficacy was shown in patients with chronic schizophrenia. Taken together, it is expected that blonanserin transdermal patch therapy may be effective for patients in either acute or chronic phases of schizophrenia.

Continuous drug therapy is important to control schizophrenia, particularly in the maintenance/stable phase. Although poor treatment adherence increases the risk of rehospitalization, patients with schizophrenia often stop taking their medication [31]. While there are a number of reasons for treatment discontinuation, one key factor is patients' low willingness to participate in the treatment process [32]. Shared decision making (SDM) that includes patients and medical staff, as well as physicians, is a method of improving treatment adherence, for example, by presenting patients with a choice of treatment options or deciding on a specific treatment based on the patient's intentions or preferences.

SDM decreases the frequency of re-hospitalizations in patients with schizophrenia [33]. To support SDM, it is important to include patient-reported outcomes and measures of patients' attitude to treatment, such as DAI-10 scores [34], in the evaluation of treatment [11]. In particular, positive DAI-10 scores are associated with improved treatment adherence [23].

Based on the DAI-10 scores, patients' attitudes towards blonanserin transdermal patches were generally positive. Most patients with a DAI-10 score ≥ 2 at baseline had the same DAI-10 score after 52 weeks of treatment, with 18.2% reverting to a score of < 2 at Week 52 (LOCF). Among patients with a score of < 2 at baseline, 48.6% reported a score ≥ 2 at Week 52 (LOCF). In addition, no marked changes in the EQ-5D scores were observed, indicating maintenance of stable quality of life.

In the patient questionnaire asking specifically about blonanserin transdermal patch treatment, 60% of patients indicated that they would not use blonanserin transdermal patches in the future, but this included patients who had discontinued treatment. In patients who completed the study, more than half (52.6%) said they would like to use the patches. In addition, the majority of patients (69.6%) would prefer to have transdermal patches available as a potential treatment option.

Taken together, these DAI-10 scores and results from a questionnaire indicate that the positive attitude toward blonanserin transdermal patch treatment held by a certain proportion of patients did not change during long-term treatment. As the patient's positive attitude is critical for improving treatment adherence, the use of the patch formulation of blonanserin may help patients to achieve a positive treatment outcome.

Limitations of this study include its open-label, uncontrolled design and the absence of statistical evaluation of efficacy endpoints. As this is an open-label study without an active or placebo comparator, it is unclear if the same cohort would have improved similarly with an alternate treatment regimen or no treatment at all. In addition, the number of patients who had been previously treated with blonanserin was higher than in previous clinical studies, suggesting that recruitment may have been biased. Further, it is difficult to determine whether positive results shown in this study were related to improved adherence. Although the patients in this study showed good compliance to treatment, adherence should be evaluated according to patient's attitude toward the treatment. For supporting information, we used DAI-10 score and an original questionnaire; however, additional data to analyze patient's adherence is needed. In addition, it is also unclear whether improvement was related to longer time on an antipsychotic medication or other characteristics of

the medication or formulation. Further studies with a controlled design may help answer these questions.

5 Conclusion

This study demonstrates the safety and efficacy of blonanserin transdermal patches in the long-term treatment of patients with schizophrenia, including after switching from blonanserin tablets. The long-term safety profile of blonanserin transdermal patches was similar to, or better than, that of blonanserin tablets. The majority of skin-related AEs, which were mild or moderate in severity, occurred early in treatment and were appropriately managed with topical therapies. Efficacy measures did not worsen during treatment with blonanserin transdermal patches. In addition, patients' attitudes to blonanserin transdermal patch therapy were generally positive, and these positive attitudes did not decrease during long-term treatment.

chida, Otsuka, Sumitomo Dainippon, Mitsubishi Tanabe, Eli Lilly, and Takeda outside the submitted work. IN, MM, YK, and HN are employees of Sumitomo Dainippon Pharma Co., Ltd.

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