Development of Blonanserin Transdermal Patch, LONASEN® Tape

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Blonanserin is an atypical antipsychotic drug with a high affinity and selectivity for dopamine D_2, D_3 and serotonin 5-HT_{2A} receptors. Blonanserin transdermal patch, LONASEN Tape, is the first of its kind in the world for treatments indicating schizophrenia. Here, the authors report the background of starting development, patch formulation designs and results of clinical studies.

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Clinical aspects of schizophrenia and the current situation of schizophrenia treatment

Schizophrenia is a mental disorder whose cardinal symptoms are positive symptoms (i.e., hallucinations, delusions, and thought disorder), negative symptoms (i.e., blunted affect, autistic withdrawal, and loss of motivation), and cognitive impairment (i.e., poor memory, poor concentration, impaired executive functions, impaired attention, and impaired verbal fluency), which is caused by a long-term reduction in the ability to integrate thinking, behavior, and emotions. According to the 2017 Patient Survey in Japan, the total number of patients with "Schizophrenia, Schizotypal disorder, and Delusional disorder" is estimated to be 0.792 million (2017 Summary of Patient Survey, Ministry of Health, Labour and Welfare, March 1, 2019). Schizophrenia can follow a chronic course: it often develops during adolescence; it repeatedly worsens and improves in an advanced stage of illness, which is known as relapse and remission; and psychotic symptoms are less severe and become stable in the stable (residual) phase of schizophrenia.[1] Patients suffering from schizophrenia have trouble socializing, such as attending school and working, due to multiple psychotic symptoms. This disease has a long-term impact on these patients' lives.

Recovery*1 is an important therapeutic goal of schizophrenia. However, the proportion of patients who achieve recovery is estimated to be about 10%,[3),4)] and most patients usually experience relapse and recurrence of symptoms before recovery, thus making it difficult to achieve recovery. Antipsychotic drug treatment and psychosocial intervention play a significant role in the treatment of schizophrenia, and the combined use of these treatments is considered to be important,[5)] although the percentage of patients who continue treatment is low, which constitutes a major cause of relapse and recurrence of symptoms.[6),7)] Therefore, social function improvement greatly depends on the duration of both drug and psychosocial treatments, and it is key to the recovery in schizophrenia.

Effect, tolerability, and adherence*2 are, especially, reported as three important elements of continued drug treatment in patients with schizophrenia.[8)] Environment, drugs, and patients have been cited as influential factors of the third element, which is adherence. Besides these elements, dosage form has been recently emphasized.[9)] Since patients with schizophrenia

*1 Definition of recovery by Liberman *et al.*[2)]: (1) symptom remission, (2) at least half-time work or school, (3) independent management of funds and medications, and (4) socialization with peers; all of these should be maintained for at least two years.

*2 Adherence: Unlike "compliance," which is used to describe the administration of medication as directed by a doctor, it is a concept that patients are voluntarily involved in the decision of therapeutic strategy and proactively participate in the treatment.

characterized by a variety of symptoms are very particular about the details and have different preferences, adherence may be improved if the selected dosage form is comfortable for use by the patients to motivate them to receive treatment.[7),10)] Only oral and injectable formulations are now approved as antipsychotic drugs. Providing new treatment options other than these dosage forms will increase the chance of selecting the dosage form the patients want to use.

Shared decision making (SDM), which is defined as a collaborative work where healthcare staff, including doctors, and patients cooperate with making decisions on therapeutic strategy, has recently gained attention as a means of improving adherence in psychiatric treatment.[11)] If both patients and healthcare staff determine the treatment plan from various treatment options based on the idea of SDM, the patients will be encouraged to receive treatment, thus SDM can play useful role to improve adherence.[10),12)] The introduction of new dosage forms, namely, increased choices for formulations to be presented in the taking place of SDM, enables more tailored recommendations to patients according to their various preferences, which is expected to improve adherence.[13)]

In the light of these circumstances, the authors decided to develop blonanserin transdermal patch, LONASEN Tape (**Fig. 1**) to improve adherence and enhance treatment continuation by bringing a new dosage form the patients want to use in the healthcare settings.

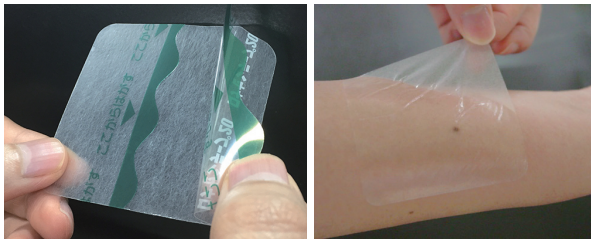


Fig. 1 Blonanserin transdermal patch, LONASEN Tape

Blonanserin

Blonanserin (**Fig. 2**) is an atypical antipsychotic drug developed by Sumitomo Dainippon Pharma Co., Ltd., and its oral formulation was approved in January 2008, with the indication for the treatment of schizophrenia: blonanserin tablets 2, 4, and 8 mg and blonanserin powders 2% are now marketed, named LONASEN as its bland name. With its antagonistic activity for dopamine D_2 and serotonin 5-HT_{2A} receptors (Ki values of 0.142 and 0.812 nmol/L, respectively), blonanserin antagonizes dopamine D_3 receptors (Ki value of 0.494 nmol/L), which is suggested to be involved in the improvement of negative symptoms, relief of extrapyramidal symptoms including akathisia,*3 and improvement of cognitive function.[14)–17)] Contrarily, blonanserin has negligible affinities for histamine H_1 receptors known to be associated with drowsiness and body weight gain and for muscarinic M_1 receptors related to thirst, gastrointestinal motility disorder, and memory impairment (Ki values of 765 and 100 nmol/L, respectively). It has also a relatively low affinity for serotonin 5-HT_{2C} and muscarinic M_3 receptors known to be associated with body weight gain and diabetes-like disorder and for adrenergic alpha-1 receptors that are potentially associated with sedative effects (Ki values of 26.4, 652, and 26.7 nmol/L, respectively). As described above, blonanserin with high specificity for receptors related to the improvement of symptoms of schizophrenia also has good pharmacological properties in terms of safety.

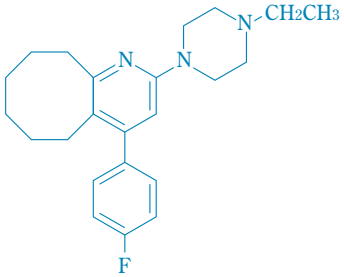


Fig. 2 Chemical structure of blonanserin

A systematic review and meta-analysis of blonanserin tablets have suggested that blonanserin tablets have similar efficacy to other antipsychotic drugs and are also well tolerated[18)] and that they have a lower risk of body weight gain than other antipsychotic drugs.[19)] Conversely, the systematic review and meta-analysis of blonanserin tablets have suggested that blonanserin tablets have a relatively higher risk of akathisia than other antipsychotic drugs.[18)]

*3 Akathisia: A condition that causes a feeling of restlessness in the lower limbs with an inability to sit still and stay still.

Changing the dosage form of blonanserin from an oral formulation to a transdermal patch formulation may offer the following four benefits: (1) a reduction in the dosage regimen from twice-daily administration after a meal to once-daily patch application; (2) smaller daily fluctuations in plasma concentrations of blonanserin and smaller changes in dopamine D_2 receptor occupancy, thereby making it easy to maintain the receptor occupancy in the therapeutic window for stable effects and reducing the incidence of adverse drug reactions, especially extrapyramidal symptoms, which are reported when exposed to a high dose of antipsychotics[20),21)]; (3) unlikely to be affected by interaction with drugs, etc. that inhibit or induce CYP3A4*4 because the drug is not absorbed by the gastrointestinal tract and not subject to the first-pass effect through the small intestine and liver; and (4) ease of checking and monitoring the application status (such as patch application and dose), bringing benefits to both patients and their family or healthcare staff. Thus, blonanserin transdermal patch might have properties different from those of blonanserin tablets and be able to reduce safety risk. Therefore, blonanserin transdermal patch holds promise for maximizing the drug efficacy of blonanserin tablets and being a new type of antipsychotic drug with fewer adverse drug reactions.

Characteristics of transdermal patches

Table 1 presents the general characteristics of transdermal patches.[22),23)]

Table 1 Potential advantages and disadvantages of patches

Advantages	• Avoids the first-pass metabolism • Avoids the gastrointestinal side effects • Stable plasma concentration without fluctuation • No food effect • Improves adherence • Visual reminder that the medication is taken
Disadvantages	• Possible skin irritation • Possibility to forget removal of patch • Varied absorption depending on the application site

Formulation designs of blonanserin transdermal patch[24)]

1. Technical hurdles on the design of transdermal patches

At present, only 16 drugs are marketed as systemic transdermal patches in Japan. This figure is not more than 25 drugs and is low worldwide.[25)] This is generally due to three technical hurdles ([1] skin permeability, [2] skin irritation, and [3] adhesiveness) on the design of transdermal patches.

The skin has a barrier function preventing the body fluids from leaking out of the body and blocking out external foreign substances; maintaining skin permeability is the first technical hurdle. If the drug has a low molecular mass, is highly lipophilic, and has a low melting point from a physical property standpoint, its skin permeability is said to be good; however, the target blood concentration is not often reached in many drugs having these properties only, and it is necessary to explore an optimal additive for enhanced drug permeability.

The second technical hurdle is the relief of skin irritation. Safety-oriented formulation designs should be considered to minimize skin damage. In general, some skin permeability enhancers are irritant, and it is necessary to design formulations with lesser irritant potential by adjusting the type and amount of additives.

The third technical hurdle is ensuring adhesiveness. To achieve a fixed dose level, patches must be kept in place without being peeled off and floated during treatment. Contrarily, no adhesive should remain on the skin when peeled off, and physical stimuli must be minimized.

As stated above, drugs should be absorbed across the skin barrier, have lesser irritant potential, must be kept in place during the treatment, and have less irritant when peeled off; these conflicting functions need to be balanced, making it difficult to develop transdermal patches.

2. Formulation design of blonanserin transdermal patch

The following are concrete descriptions of formulation of blonanserin transdermal patch intended to overcome these three technical hurdles ([1] skin permeability, [2] skin irritation, and [3] adhesiveness):

*4 CYP3A4: A protein that helps break down a drug. Blonanserin is primarily metabolized by CYP3A4.

(1) Improvement in skin permeability

To predict the degree of difficulty of skin permeability, the area of formulations necessary to reach an effective plasma concentration was first calculated on paper. Desktop calculations were performed using the Guy and Potts equation.[26] The molecular weight and log *P* were inputted to the equation to predict a skin permeability coefficient, and the necessary daily dose was calculated from the lowest maintenance dose of blonanserin tablets to predict the area of formulations.

Guy and Potts equation

$$\log Kp = 0.71 \log P - 0.0061\, MW - 6.3$$

Kp, permeability coefficient (cm/s);
log *P*, water-octanol partition coefficient;
MW, molecular weight

Generally, the body surface area is about 17,000 cm^2 in a man who is 170-cm tall and weighs 60 kg.[27] Therefore, it can be inferred that transdermal patches are difficult to make for drugs for which the area of formulations ≥ 1,000 cm^2 (about A3 size) is necessary when calculated on paper. The area of blonanserin was calculated to be about 330 cm^2 (about A5 size) on paper, and if permeability was improved by elaborating a method for formulation, its patch formulation could be realized with this figure.

Skin permeability needed to be improved on desktop calculations, and additives were explored to enhance the skin permeability. As a result, additive A, which markedly improved the skin permeability of blonanserin, was discovered among 50 or more additives.

Comparison of plasma concentration-time profiles of blonanserin following transdermal administration of patch in dogs revealed that additive A increased the plasma concentrations of blonanserin (**Fig. 3**).

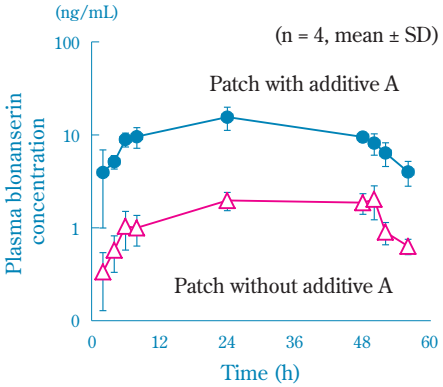


Fig. 3 Plasma concentration-time profile of blonanserin following transdermal administration of patch in dogs

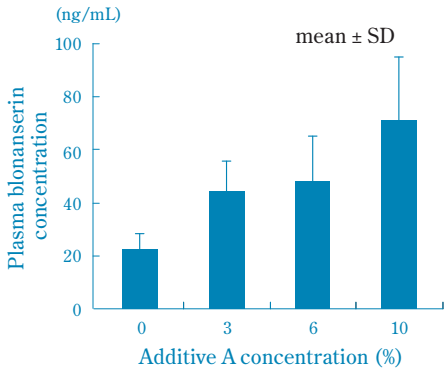
(2) Improvement in skin irritation

It turned out that additive A markedly improved skin permeability (**Fig. 4** a), whereas it aggravated skin irritation with increasing amount of the additive (**Fig. 4** b). Thus, we started to explore new additives for the reduction in skin irritation.

Additive A is essential for achieving the target plasma drug concentration. For this reason, we explored additives by taking the following three steps to reduce the skin irritation of additive A only without interfering with its permeability-enhancing effects.

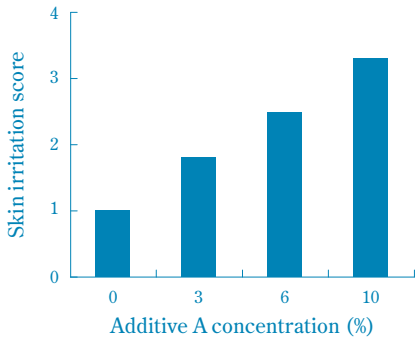
1) Exploring additives that act in synergy with additive A in an *in vitro* skin permeability test
2) Conducting a literature search, etc. for the additives discovered in 1) and extracting skin-protecting additives

(a)



Mean plasma concentration of blonanserin at 24 h after transdermal administration of patch formulation with additive A in rats

(b)



Skin irritation after transdermal administration of patch formulation with additive A in rabbits

Fig. 4 Effect of additive A

3) Evaluating the skin irritation and pharmacokinetics of patches containing the additives extracted in 2)

Then additive B, which did not decrease skin permeability (**Fig. 5** a) but reduced skin irritation only (**Fig. 5** b) as intended, was discovered.

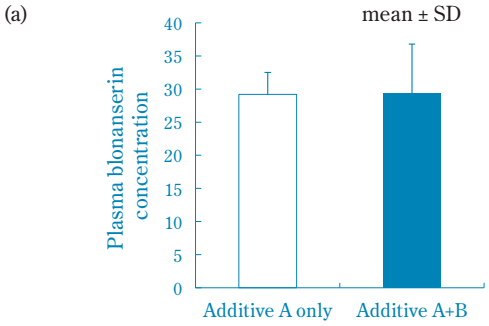
As presented in **Fig. 6**, the patches containing additives A and B increased skin irritation when applied to the same site on the back of rabbits every day, although the skin irritation score could be reduced to 2 or less by applying the patches to the same site in rotation every 4 days. This result suggested that the application of patches in rotation could also reduce skin irritation in the clinical practice.

(3) Improvement in adhesiveness

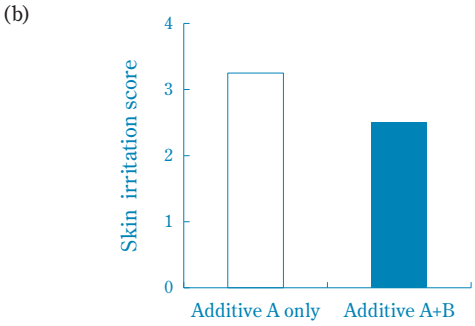
Keeping patches in place during treatment (i.e., do not peel off patches) is important for transdermal patches to ensure drug absorption. Additive A, which is essential for improving skin permeability, was found to reduce adhesiveness during sweating. Then, after rescreening additives, we discovered that additive C helped improve adhesiveness during sweating and determined a formulation for clinical studies by making fine adjustments to the amount of additives used. However, in spite of many elaborations and techniques applied, the formulations peeled off in subjects who sweated during phase 1 studies, underlying the necessity of modifying the formulations as soon as possible.

New additives had been explored for formulation modification to date. However, it took much time to explore new additives. Additional nonclinical studies might be required to ensure safety, and a substantial delay in the development schedule was anticipated.

Then, we attempted to improve adhesiveness based on the "counterintuitive idea" that the amount of additives used in formulations could be reduced. First, the amount of additive A was reduced to ensure the minimum skin permeability. Second, the additives inhibiting adhesiveness were removed. Third, the formulations were thinned to reduce the incidence of floating or peeling on the edge of the formulations, yielding a new formulation patch with improved adhesiveness during sweating.

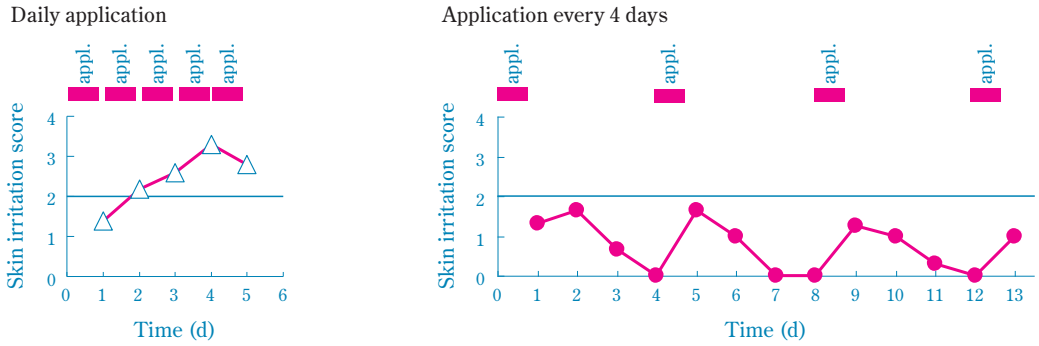


Mean plasma concentration of blonanserin at 24 h after transdermal administration of patch formulation with additive A or A+B in rats



Skin irritation after transdermal administration of patch formulation with additive A or A+B in rabbits

Fig. 5 Effect of additive B



Left panel : daily application at the same position.
Right panel : application every 4 days in rotation at the same position

Fig. 6 Skin irritation by patch administration in rabbits

The new formulation patch was found to follow the same time-course of plasma blonanserin concentrations as an old formulation patch (**Fig. 7**). Phase 2 and subsequent studies were conducted in Japan with this new formulation patch.

Adjusting the balance among skin permeability, skin irritation, and adhesiveness is very crucial to the design of transdermal patches. We, overcoming these technical challenges, succeeded in developing blonanserin transdermal patch.

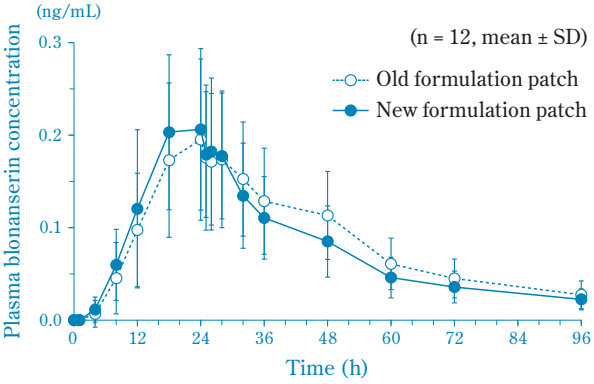


Fig. 7 Mean plasma concentration of blonanserin in comparative human PK*5 study

Clinical study results

1. Clinical pharmacology studies

(1) Single dose application study

Following the single dose application of one sheet of blonanserin transdermal patch 40 mg to the upper back of 12 healthy adult male subjects for 24 h, the plasma blonanserin concentration reached the maximum (C_{max}) about 25 h after the application and decreased gradually (**Fig. 8**). The C_{max} (mean ± SD) was 0.42 ± 0.09 ng/mL, $AUC_{0\text{-}last}$*6 (mean ± SD) was 13.16 ± 2.77 ng·h/mL, t_{max} (median [min–max]) was 25.3 (22.0–27.0) h, and $t_{1/2}$ (mean ± SD) was 41.9 ± 17.0 h.

(2) Multiple dose application study

Following the multiple dose application of dose equivalent to blonanserin transdermal patch 40 mg to the back of 9 healthy adult subjects once daily for 10 days, the mean plasma blonanserin concentration

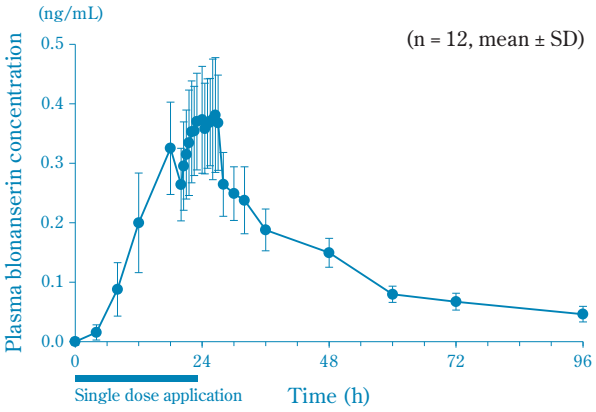
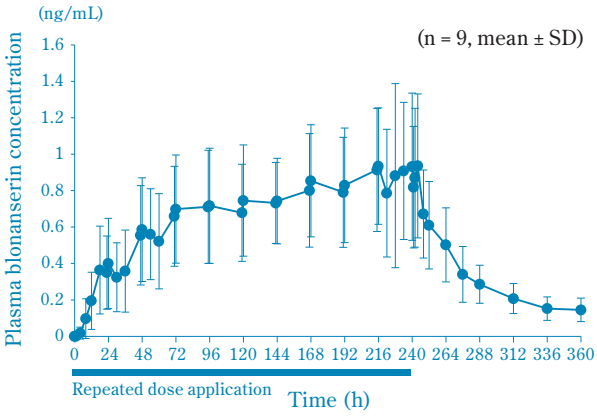


Fig. 8 Time-course of mean plasma blonanserin concentration



	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0\text{-}24}$ (ng·h/mL)	t_{max}* (h)	$t_{1/2}$ (h)
1st application	0.41±0.25	0.31±0.18	9.82±5.37	24.0(18-24)	-
10th application	0.96±0.41	0.78±0.36	21.05±9.40	24.0(18-28)	46.4±11.3

mean ± SD, *: median (min-max)

Fig. 9 Time-course of mean plasma blonanserin concentration

appeared to reach a steady state within 7 days of application (**Fig. 9**). The daily fluctuations in steady-state blonanserin concentrations were small, and the mean ratio of the maximum (C_{max}) and minimum (C_{min}) blonanserin concentrations at the final (10^{th}) application was 1.25.

2. Phase 2 study (PET study)

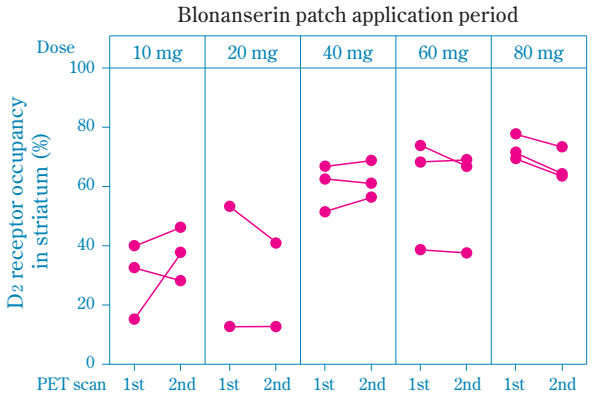
In the development of blonanserin transdermal patch, positron emission tomography (PET) was

*5 PK: Pharmacokinetics

*6 $AUC_{0\text{-}last}$: The area under the plasma drug concentration-time (x-axis) curve when it is assumed that infinite time has passed from administration, which is one of the indicators of drug exposure.

employed to compare dopamine D_2 receptor occupancy between blonanserin tablets and blonanserin transdermal patch for dose finding.

After blonanserin tablets were administered to patients with schizophrenia at a dose of 8 or 16 mg/day twice daily for 2 weeks (up to 4 weeks), blonanserin transdermal patch was applied at a dose of 10, 20, 40, 60, or 80 mg/day once daily for 2 weeks (up to 4 weeks), and the dopamine D_2 receptor occupancy in the striatum 2 weeks after the start of treatment with blonanserin tablets (two time points corresponding to the trough and peak plasma blonanserin concentrations) and 2 weeks after the start of blonanserin transdermal patch application (two time points near the t_{min} and t_{max} of the plasma blonanserin concentration) were evaluated by PET. The plasma blonanserin concentrations and dopamine D_2 receptor occupancy in the striatum were calculated. As a result, the dose of blonanserin transdermal patch expected to provide the same clinical efficacy as was achieved by the clinical dose of blonanserin tablets 8 and 16 mg/day was estimated to be 40 and 80 mg/day, respectively. Among the patients to whom blonanserin transdermal patch was applied, 2 of 3 in the 40 mg/day group, 2 of 3 in the 60 mg/day group, and all 3 patients in the 80 mg/day group exhibited >60% dopamine D_2 receptor occupancy in the striatum, although none of them exhibited >80% occupancy at doses up to 80 mg/day (**Fig. 10**). From the above results, the dose to be used in the confirmatory study was set at 40 and 80 mg/day.



n = 14 Plot for individual value

Fig. 10 D_2 receptor occupancy in striatum

3. Phase 3 studies

(1) Global phase 3 study (confirmatory study)

A global phase 3 study, consisted of four phases, i.e., the washout phase (1 week), double-blind treatment phase (6 weeks), open-label treatment phase (52 weeks in Japan and 28 weeks outside Japan), and follow-up phase (1 to 2 weeks), was conducted in patients with acute exacerbated schizophrenia (**Fig. 11**). During the double-blind treatment phase, the primary endpoint was to evaluate the efficacy of blonanserin patch (40 or 80 mg/day) compared with placebo*7 by assessing the

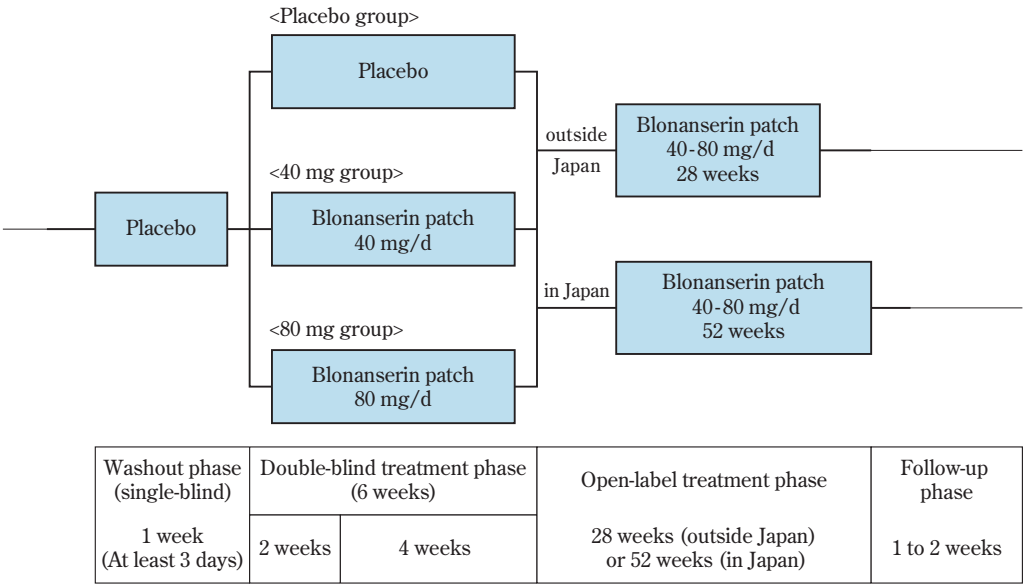


Fig. 11 Study schematic of global phase 3 study

*7 Placebo: A dummy, which looks like blonanserin patch but contains no active ingredient.

mean change in Positive and Negative Syndrome Scale (PANSS) total scores from baseline at Week 6. In addition, the safety, effectiveness, and pharmacokinetics of long-term application of blonanserin patch were evaluated.

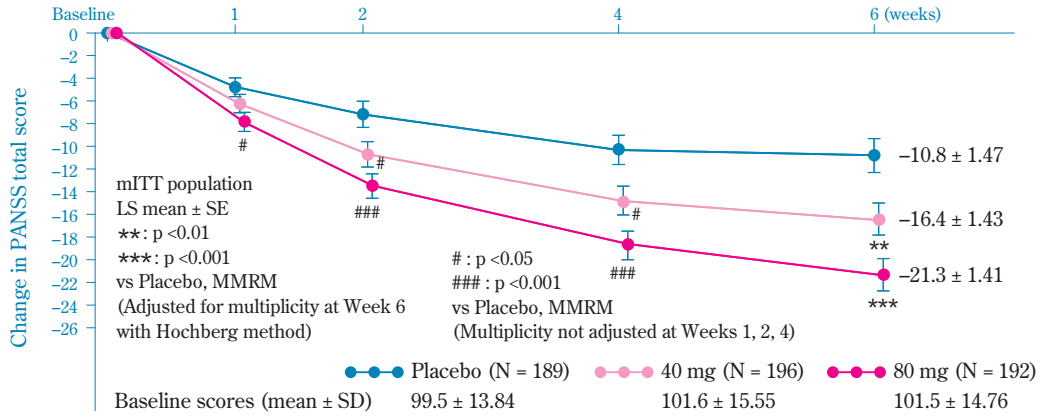
(i) Double-blind treatment phase

The least square (LS) mean difference in the change in PANSS total score at Week 6 versus placebo was −5.6 (95% CI −9.6, −1.6) for blonanserin patch 40 mg group and −10.4 (95% CI −14.4, −6.4) for blonanserin patch 80 mg group, demonstrating the superiority of both blonanserin patch 40 mg and 80 mg to placebo (adjusted p=0.007 for blonanserin patch 40 mg group and adjusted p<0.001 for the blonanserin patch 80 mg group; MMRM*8 [Hochberg procedure]).

The effect size was 0.297 in the 40 mg group and 0.555 in the 80 mg group. The LS mean differences in the change in PANSS total scores versus placebo during the double-blind treatment phase were −3.5 (95% CI −6.5, −0.4) at Week 2 in the 40 mg group and −3.1 (95% CI −5.3, −0.9) at Week 1 in the 80 mg group, which were greater than those reported in the placebo group. These differences increased over time (**Fig. 12**). These results indicated that blonanserin patch 40 to 80 mg/day would be effective for the treatment of acute symptoms and take effect at an early stage after application.

During the double-blind treatment phase, blonanserin patch 40 or 80 mg/day was applied on the first application day without dose titration. No difference was observed in the incidence of all adverse events early at application between the 40 mg group and the 80 mg group. The overall incidence of adverse events during the double-blind treatment phase was 60.0% (114/190), 62.8% (123/196), and 67.0% (130/194), respectively, in the placebo group, 40 mg group, and 80 mg group (hereinafter listed in the same order as presented here). No difference was observed in the incidence of severe or serious adverse events among these groups, and blonanserin patch did not cause any safety concerns at doses up to 80 mg/day. No significant difference was observed in the number of subjects with adverse events leading to discontinuation and episodes of such events and their incidence among these groups either.

The adverse events that reported with an incidence of 5% or higher in the 40 mg group or the 80 mg group were application site erythema (1.6%, 5.6%, and 9.3%), application site pruritus (0.5%, 5.1%, and 7.2%), akathisia (1.1%, 5.6%, and 9.8%), tremor*9 (2.6%, 4.1%, and 8.8%), insomnia (4.7%, 5.1%, and 5.2%), and schizophrenia (7.4%, 5.1%, and 1.5%). No difference was observed in the safety between the 40 mg group and the 80 mg group, indicating that the patients could start using blonanserin patch at the maximum dose, 80 mg/day, without the need for dose titration and that the drug would be suitable for the treatment of acute symptoms that should be improved in the early stage of drug therapy.



Display represents model LS mean estimate for change from baseline +/− SE
N: Number of subjects in the population

Fig. 12 Change from Baseline in PANSS total score (Double-blind treatment phase, MMRM)

*8 MMRM: A statistical model for analyzing repeated measures without imputing missing values (linear mixed-effect model).
*9 Tremor: An involuntary shaking movement.

(ii) Open-label treatment phase

The numbers of subjects who completed the double-blind treatment phase and entered to the open-label treatment phase were 131, 143, and 157 in the placebo group, 40 mg/day group, and 80 mg/day group, respectively (hereinafter listed in the same order as presented here), in the double-blind treatment phase. The PANSS total scores (mean ± SD; hereinafter the same shall apply) at the start of the open-label treatment phase were 84.6 ± 19.98, 80.1 ± 19.23, and 78.1 ± 20.28, respectively. The PANSS total scores at Week 52 (only Japanese subjects) and Week 52 (last observation carried forward [LOCF*10]) were 67.2 ± 23.98 and 69.8 ± 25.55, 71.4 ± 19.90 and 69.0 ± 24.21, and 77.7 ± 21.01 and 67.0 ± 23.21, respectively. The PANSS total scores decreased compared with those measured at the start of the open-label treatment phase at any time points, and they did not worsen and were stable during the open-label treatment. The obtained results revealed that blonanserin patch improved acute symptoms, and subsequent long-term blonanserin patch application had a sustained effect on these symptoms.

(2) Japan long-term phase 3 study

An open-label, 52-week, long-term study was conducted in Japanese patients with schizophrenia by switching directly to blonanserin patch (once-daily flexible-dose of 40, 60, or 80 mg). The study consisted of two cohorts*11 (Cohort 1 where blonanserin patch was applied after the administration of blonanserin tablets alone for 6 weeks (**Fig. 13** a) and Cohort 2 where blonanserin patch was applied from the beginning (**Fig. 13** b), and its primary objective was to investigate the safety of blonanserin patch applied to schizophrenic patients at a dose of 40–80 mg/day for 52 weeks. The secondary objectives of the study were to investigate the safety and effectiveness of switching from blonanserin tablet administration to blonanserin patch and to investigate the effectiveness and pharmacokinetics of DSP-5423P at a dose of 40–80 mg/day for 52 weeks. The subjects were also asked to answer a questionnaire about dosage form preference for the examination of the clinical position of transdermal patches.

The PANSS total scores at Week 52 (LOCF) and Week 52 decreased compared with those measured before the start of blonanserin patch application in both cohorts. The Japan long-term phase 3 study, which enrolled many patients with relatively stable symptoms, indicated the sustained long-term effectiveness of blonanserin patch without worsening of stable symptoms (**Fig. 14**).

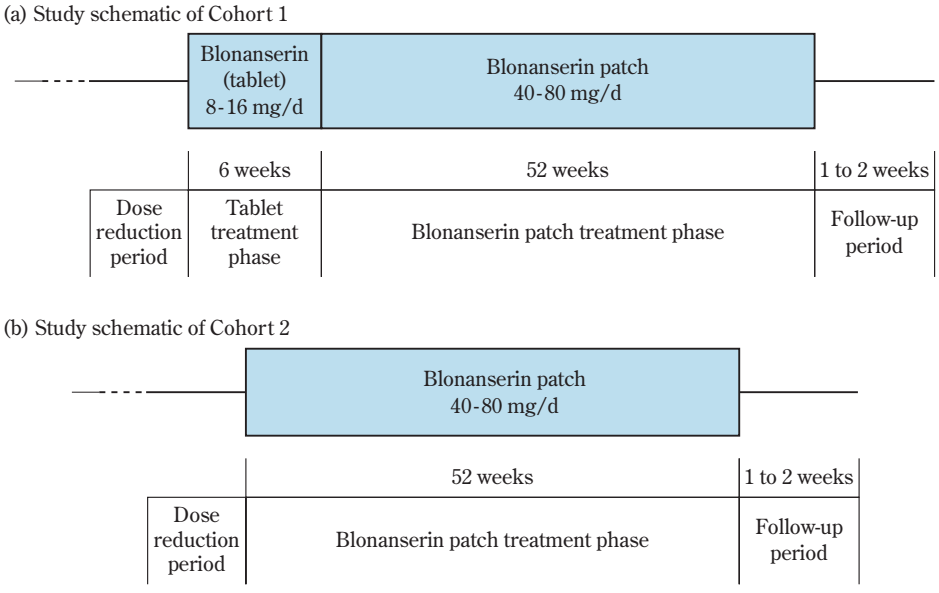


Fig. 13 Study schematic of Japan long-term phase 3 study

*10 LOCF: A method of imputing a missing value with one value. The missing value is imputed by using the last observed data.
*11 Cohort: A group of subjects who share a common characteristic and are to be observed.

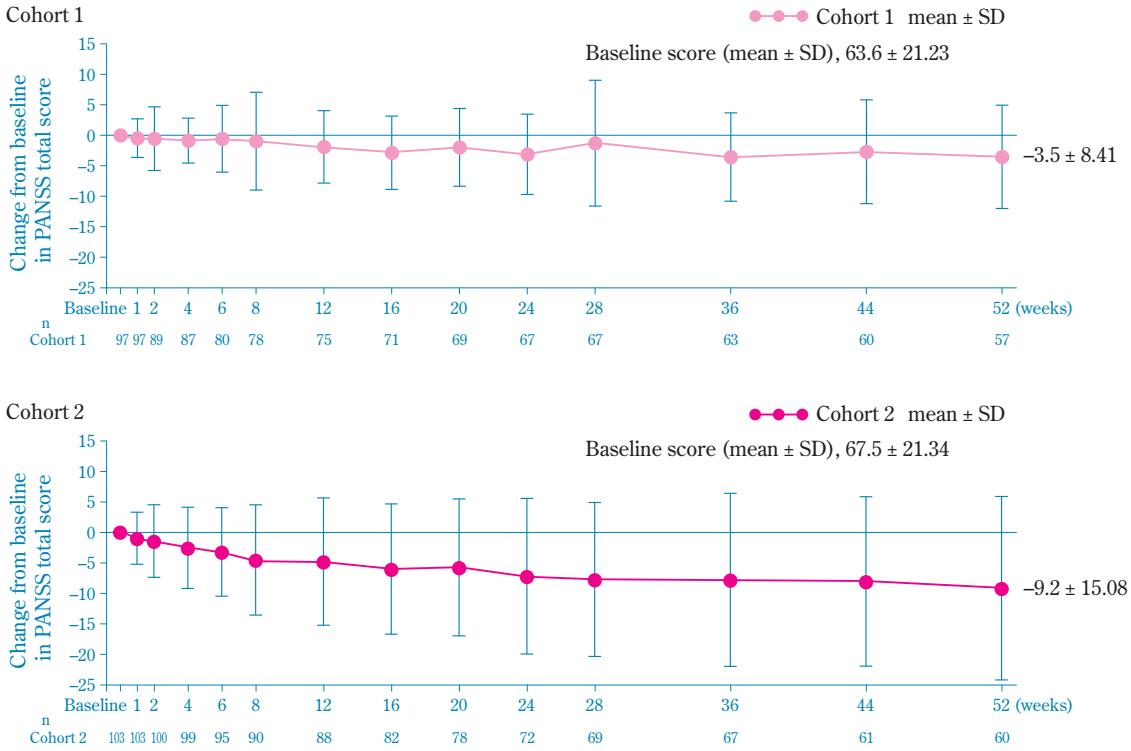


Fig. 14 PANSS total score – Blonanserin patch treatment phase

There was no worsening of scores for efficacy assessments associated with switching from oral antipsychotic drugs, including blonanserin tablets, to blonanserin patch.

The percentages of patients who continued treatment during blonanserin patch treatment phase in Cohorts 1 and 2 (95% CI; hereinafter the same shall apply) were 64.9% (54.6, 73.5) and 66.0% (56.0, 74.3), respectively, at Week 28 and 58.8% (48.3, 67.8) and 57.3% (47.2, 66.2), respectively, at Week 52. Over half of all subjects continued to receive treatment for 52 weeks. The comparison of the percentage of subjects who continue to participate in the clinical study between antipsychotic drugs recently approved in Japan[28)–30)] and blonanserin patch indicates that blonanserin patch, a new dosage form called transdermal patches, will have a percentage of subjects who continue treatment equal to or greater than that of oral formulations.

The percentages of respondents who answered Yes to the question “Would you like the patch dosage form to be available?” in the questionnaire survey on dosage form preference (the sum of all cohorts; hereinafter the same shall apply) were 81.0% in “completed subjects” who completed the 52-week application and 52.6% even in “discontinued subjects” who dropped out of the study. The percentages of respondents who answered Yes to the question “Is it easy for you to continue treatment with patches compared with tablets” were 39.7% in the completed subjects and 20.5% in the discontinued subjects. When the percentage of subjects who answered “No difference” was added, the percentages were increased to 78.4% in the completed subjects and 51.3% in the discontinued subjects. Over half of all subjects found it easier to keep using patches than tablets or felt that there was not much difference between patches and tablets in terms of treatment continuation. The percentages of respondents who answered Yes to the question “Would you like to use the patches that you used during this study in the future?” were 52.6% in the completed subjects and 23.1% in the discontinued subjects and 40.7% overall. These results suggested that there was a group of patients who wanted to use transdermal patches as one of the treatment options and that many patients wished to use blonanserin patch. Blonanserin patch can be considered as a dosage form favored by patients and that it can be one of the new treatment options for schizophrenia.

As for the safety, the incidence of adverse events was 87.0% (174/200, the sum of all cohorts; hereinafter the same shall apply). Overall, the adverse events that occurred with an incidence of 5% or more were nasopharyngitis (31.0%), application site erythema (22.5%), application site pruritus (11.5%), akathisia

(10.0%), insomnia (9.0%), schizophrenia (9.0%), blood prolactin increased (7.0%), hyperprolactinemia (7.0%), tremor (7.0%), back pain (6.5%), dental caries (6.5%), application site dermatitis (5.0%), weight increased (5.0%), diarrhoea (5.0%), and vomiting (5.0%). The incidence of extrapyramidal adverse events was lower for blonanserin patch than for blonanserin tablets 6 weeks after the start of application (23.1% [25/108] during blonanserin tablets treatment phase [6 weeks] in Cohort 1 versus 16.5% [17/103] during blonanserin patch application phase [up to 6 weeks after the start of application] in Cohort 2). Despite the fact that no definitive comparison of long-term application could be performed, their incidence was also likely to be lower in subjects treated with blonanserin patch than in those receiving blonanserin tablets. Blonanserin patch could help maintain a more stable blood concentration compared with blonanserin tablets (see the multiple application study), suggesting the possibility that subjects treated with blonanserin patch had a lower incidence of extrapyramidal adverse events.

No clinical issues were observed in the safety of long-term blonanserin patch application and the safety of switching from oral antipsychotic drugs, including blonanserin tablets, to blonanserin patch.

Conclusion

Blonanserin patch, LONASEN Tape, is the world's first antipsychotic transdermal patch. Based on the obtained clinical findings, blonanserin patch is expected to provide favorable treatment outcomes, improve the tolerability of blonanserin tablets, and bring about more improvement in adherence compared with existing therapeutic drugs; therefore, blonanserin patch can greatly contribute to treatment continuation. The introduction of new dosage forms to treatment options for schizophrenia in the process of SDM will also enable more tailored treatment recommendations to patients according to their preferences, which may significantly contribute to the achievement of patient recovery.

Reference

1) Supervised by the Staff Meeting of the Department of Psychiatry (M. Sato *et al.*, Editors), "Tougousittyoushouchiryougaidorainn (Treatment Guideline for Schizophrenia)", Second Edition, Igaku-Shoin Ltd. (2008), p.1.
2) R. P. Liberman and A. Kopelowicz, Psychiatr. Serv., 56, 735 (2005).
3) D. G. Robinson *et al.*, Am. J. Psychiatry, 161, 473 (2004).
4) E. Jääskeläinen *et al.*, Schizophr. Bull., 39, 1296 (2013).
5) E. Ikebuchi, Igaku no Ayumi, 213, 677 (2005).
6) T. Koyama *et al.*, Jpn J Clin Psychopharmacol, 11, 729 (2008).
7) S. Nanko, Jpn J Clin Psychopharmacol, 13, 1448 (2010).
8) K. Watanabe, Jpn J Clin Psychopharmacol, 13, 1425 (2010).
9) N. Sawada and K. Watanabe, Jpn J Clin Psychopharmacol, 11, 1633 (2008).
10) T. Higuchi, Jpn J Clin Psychopharmacol, 11, 491 (2008).
11) S. Yamaguchi *et al.*, Japanese Journal of Psychiatric Rehabilitation, 17 (2), 182 (2013).
12) J. Hamann (K. Watanabe, Translator), Jpn J Clin Psychopharmacol, 14, 678 (2011).
13) T. Yoshio, Jpn J Clin Psychopharmacol, 10, 2142 (2007).
14) P. Sokoloff and B. Le Foll, Eur. J. Neurosci., 45, 2 (2017).
15) S. Nakajima *et al.*, Eur. Neuropsychopharmacol., 23, 799 (2013).
16) J. C. Neill *et al.*, Eur. Neuropsychopharmacol., 26, 3 (2016).
17) G. Gross and K. Drescher (M. A. Geyer and G. Gross, Editors), "Novel Antischizophrenia Treatments", Heidelberg. Springer (2012), p.167-210.
18) T. Kishi *et al.*, J. Psychiatr. Res., 47, 149 (2013).
19) T. Kishi *et al.*, PLoS One, 9 (2), e88049 (2014).
20) S. Kapur *et al.*, Am. J. Psychiatry, 157, 514 (2000).
21) H. Kimura *et al.*, J. Psychopharmacology, 30, 795 (2016).
22) W. Oertel *et al.*, Neurology, 69 (4 Suppl.1), S4 (2007).
23) C. Kawano *et al.*, J. Practical pharmacy, 64, 3243 (2013).
24) M. Tanaka *et al.*, J. New Rem & Clin, 69 (2), 103 (2020).
25) M. Igawa, "Sekainohifugaiyouyakusijou 2019 (Global Market for External Preparations for the Skin 2019)", TPC marketing research corp. (2019), p.8-9, p.27-29.
26) R. O. Potts and R. H. Guy, Pharm. Res., 9, 663 (1992).

27) D. Du Bois and E. F. Du Bois, Arch. Intern. Med., 17, 863 (1916).
28) Y. Hirayasu *et al.*, Jpn J Clin Psychopharmacol, 13, 2105 (2010).
29) T. Kinoshita *et al.*, Jpn J Clin Psychopharmacol, 19, 753 (2016).
30) T. Kinoshita *et al.*, Jpn J Clin Psychopharmacol, 19, 771 (2016).

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