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Prediction of Corresponding Dose of Transdermal Blonanserin to Oral Dose Based on Dopamine D_2 Receptor Occupancy

Unique Characteristics of Blonanserin Transdermal Patch

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Abstract:

Background/Purpose: Blonanserin is an atypical antipsychotic, a potent selective antagonist of dopamine D_2 receptor (D_2), prescribed as oral formulations in patients with schizophrenia. Blonanserin transdermal patch was developed to provide a new treatment option, but the corresponding dose to oral blonanserin was not clear. The aims of this study were to clarify the pharmacokinetic (PK)-pharmacodynamic characteristics of blonanserin after transdermal patch application and to evaluate the corresponding dose to oral formulation based on striatal D_2 occupancy.

Methods: The relationship between D_2 occupancy and plasma blonanserin concentration was analyzed using an E_{max} model based on data from positron emission tomography study with oral and transdermal blonanserin. D_2 occupancy was simulated using E_{max} models based on the observed plasma concentrations and the simulated plasma concentrations obtained from population PK model.

Results: Plasma blonanserin concentration levels after repeated patch applications were nearly stable throughout the day and no effect of sex, advanced age, or application site was detected. The concentration at half maximal D_2 occupancy during transdermal patch applications, 0.857 ng/mL, was higher than that after oral doses, 0.112 ng/mL, suggesting metabolite contribution after oral doses. The median predicted D_2 occupancy during blonanserin patch applications at doses of 40 and 80 mg/d was 48.7% and 62.5%, respectively, and the distribution of D_2 occupancy at these doses could cover most of that at oral doses of 8 to 24 mg/d.

Conclusions: Predicted D_2 occupancy suggested that a 40- to 80-mg/d blonanserin transdermal patch dose corresponds to an 8- to 24-mg/d oral dose for the treatment of schizophrenia.

Key Words: blonanserin, transdermal patch, dopamine D_2 receptor occupancy, corresponding dose, oral administration

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Blonanserin (Lonasen; Sumitomo Dainippon Pharma Co, Ltd, Osaka, Japan) is a unique atypical antipsychotic with high affinity to dopamine D_2, D_3, and serotonin 5-HT_{2A} receptors, but low affinity to dopamine $D_{1,4.2,5}$, 5-$HT_{1A,2B,2C,3-7}$, histaminic H_1, muscarinic M_1, and $\alpha_{1,2}$-/β-adrenergic receptors.[1] Blonanserin is prescribed in Japan, Korea, and China,[1–4] as oral formulations, tablets, and powder. Recently, transdermal patch of blonanserin has been developed and approved for the treatment of schizophrenia in Japan.[5]

Transdermal drug delivery has been used as a dosing route with various advantages, such as reduced dosing frequency, visual compliance checks, minimized first-pass metabolism, etc.[6] In schizophrenia treatment, discontinuation of drug treatment has been an issue causing exacerbation. Active patient participation in the shared treatment decision-making process would result in a greater commitment and adherence to the selected treatment regimen,[7–9] and dosage forms can provide choices and influence adherence to long-term drug therapy.[10]

In clinical development of blonanserin transdermal patch, a positron emission tomography (PET) study was conducted as a dose-finding study.[11] This was the first PET study in the world conducted as dose-finding study using striatal dopamine D_2 receptor (D_2) occupancy as primary end point, instead of placebo-controlled double blind study using change in Positive and Negative Syndrome Scale (PANSS) total score from baseline as the primary end point. The doses of 40 and 80 mg/d were selected for phase 3 studies by comparing D_2 occupancy with those of the oral doses of 8 and 16 mg/d.[11] Efficacy and safety at these doses were successfully confirmed in 2 phase 3 studies, a placebo-controlled double-blinded study (confirmatory study),[12] and a long-term study for 52 weeks.[13] As the highest approved oral blonanserin dose of 24 mg/d was not tested in this PET study, a question as to whether transdermal patch at 40 to 80 mg/d can cover 24 mg/d oral dose remained.

Striatal D_2 occupancy has been measured for various antipsychotics, including both typical and atypical, and has been an important predictor of response and adverse effects in antipsychotic treatment. Kapur et al[14] reported that the likelihood of clinical response and extrapyramidal adverse effects increased significantly as striatal D_2 occupancy exceeded 65% and 78%, respectively. On the other hand, observed D_2 occupancy during blonanserin transdermal patch applications at the doses of 40 and 60 mg/d in the PET study was lower than 65%.[11] As the efficacy of blonanserin transdermal patch at 40 mg/d has been confirmed,[12] a question as to which level of occupancy was required for blonanserin efficacy arose.

The aims of this study were (1) to analyze the relationship of D_2 occupancy to plasma blonanserin concentrations using PET study data, (2) to clarify the pharmacokinetic (PK)-pharmacodynamic characteristics of blonanserin transdermal patch, (3) to predict D_2 occupancy during blonanserin transdermal patch applications at the approved doses of 40 to 80 mg/d, and (4) to evaluate

the corresponding dose of transdermal patch to the oral formulations at the doses of 8 to 24 mg/d by comparing expected occupancy range.

METHODS

Major analysis processes were summarized in Figure 1. (1) D_2 occupancy and plasma blonanserin concentration from PET study[11] were analyzed with concentration-occupancy model. (2) Estimated parameters were compared with those of other antipsychotics. (3) Effect of various factors on plasma concentrations during patch applications were assessed. (4) and (5) Plasma concentration data for occupancy prediction were selected. (6) and (7) Occupancy was predicted using concentration-occupancy model based on observed blonanserin concentrations or simulated concentration using population PK model.[15] (8) Distribution of predicted occupancy was compared between formulations and (9) predicted occupancy-time profiles were compared between formulations for evaluation of corresponding doses.

Clinical Study Data

The clinical studies from which blonanserin plasma concentration data were obtained are summarized in Table 1. D_2 occupancy and corresponding plasma concentration data after oral administrations and during subsequent transdermal patch applications were obtained from a PET study.[11] Positron emission tomography scans during the oral treatment period (2 times in each patient) were timed to correlate with trough and peak times associated with twice daily oral administration of blonanserin. Patch was applied every night and kept on for 24 hours, and PET scans (2 times in each patient) were performed at almost the same clock time as that for tablets. The blood samples were collected before and after PET scan and the average of these 2 concentrations was used as a corresponding plasma concentration at each PET scan (totally 4 PET scans in each patient). The details of the study have been reported separately.[11] Plasma blonanserin and its metabolite concentrations during transdermal patch applications were obtained from the studies in healthy volunteers and in patients with schizophrenia (Table 1).[11–13,16] Plasma blonanserin concentrations obtained from confirmatory study,[12] long-term study,[13] and long-term phase 3 studies on tablets[17,18] were used in the occupancy prediction. All studies were conducted in compliance with ethical principles based on the Declaration of Helsinki and approved by the respective institutional review board, and written informed consent was obtained before each study from all participants or proxies after provision of complete explanation of the study. A population PK model of transdermal blonanserin patch reported by Kitamura et al[15] was used for PK simulations. The details of blood sampling and plasma concentration measurements using validated liquid chromatography–tandem mass spectrometry methods were reported previously.[15]

Analysis of Dose Proportionality

Dose proportionality of plasma blonanserin concentrations during repeated transdermal patch applications was determined by performing a regression analysis of log(concentration) against log(dose) using Origin 2020b software (OriginLab Corporation, Northampton, Mass), based on the data obtained in the PET study[11] in the dose range of 10 to 80 mg/d. The estimated slope and its 95% confidence interval were used to judge the dose proportionality of plasma concentration.

Analysis of D_2 Occupancy-Concentration Relationship

D_2 occupancy measured for oral blonanserin or transdermal blonanserin in the PET study[11] was analyzed with an E_{max} model (Equation 1) separately, against corresponding plasma blonanserin concentration, using Origin 2020b.

$$\text{Occupancy}\ (\%) = \frac{B_{max} \times \text{Conc}}{C_{50} + \text{Conc}} \times 100 \quad \text{(Equation 1)},$$

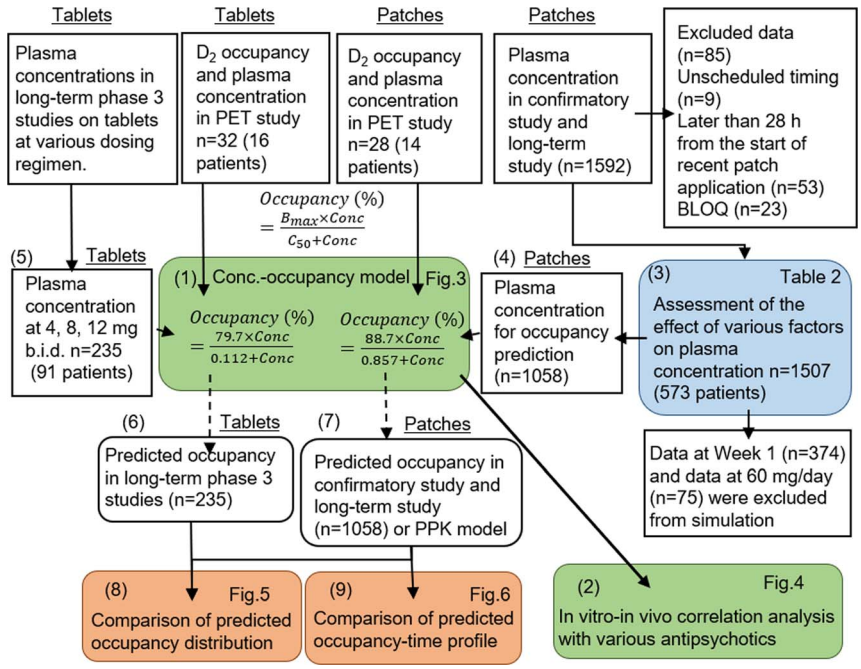

FIGURE 1. Scheme of the analysis flow. Bold arrow represents data flow and dashed arrow represents translation flow from plasma concentration to predicted occupancy. bid, bis in die (twice a day); BLOQ, below lower limit of quantitation; B_{max}, maximal occupancy; C_{50}, plasma concentration at half-maximal occupancy; n, number of observations.

TABLE 1. Summary of the Clinical Studies and D_2 Occupancy Data Used in This Analysis

Clinical Study	Population (n)	Oral Dose, mg/d	Transdermal Dose,* mg/d	D_2 Occupancy†	Reference
Multiple-application study for 10 d	Japanese healthy male volunteers (9)	—	64 (40)	—	[15]
PET study	Japanese patients with schizophrenia (16)‡	8, 16	10, 20, 40, 60, 80	Measured; twice on tablets, twice on patch	JapicCTI-121914 [11]
Multiple-application study for 2 wk	Japanese patients with schizophrenia (8)	—	80	—	JapicCTI-142423 [16]
Confirmatory study for 6 wk	Multinational patients with schizophrenia (377)	—	40, 80	Predicted	NCT02287584 JapicCTI-142688 [12]
Long-term study for 52 wk	Japanese patients with schizophrenia (196)	—	40, 60, 80	Predicted	NCT02335658 JapicCTI-152765 [13]
Long-term phase 3 studies on tablets§	Japanese patients with schizophrenia (91)	8, 16, 24	—	Predicted	[17,18]

*Transdermal doses with pilot formulation of 64 mg corresponded to the commercial formulation of 40 mg.

†Prediction of D_2 occupancy was conducted using plasma blonanserin concentrations in each clinical study and the relation obtained based on the PET study results (see Methods, Equation 1).

‡Patients who received oral doses at 8 mg/d were assigned to receive the patches at a dose of 10 or 20 mg/d, and patients who received oral doses at 16 mg/d were assigned to receive the patches at a dose of 40, 60, or 80 mg/d. PET data for 2 patients were for oral blonanserin at 16 mg/d only, as these patients completed oral dosing period but withdrew from the study before PET scans during patch application period.

§Only the data at the doses of 4, 8, and 12 mg twice daily were selected and used.

where B_{max} is the maximal occupancy, C_{50} is the concentration at half maximal occupancy, and Conc is the plasma blonanserin concentration. Two kinds of concentration-occupancy model were evaluated one with 2 parameter-estimation of B_{max} and C_{50} and the other with C_{50} estimation with fixed B_{max} at 100%. The goodness of fit was compared between models with Akaike information criteria (AIC) to select the better model.

In Vitro–In Vivo Correlation of D_2 Occupancy

In vivo C_{50} values reported for D_2 occupancy of asenapine,[19] clozapine,[20] haloperidol,[19,20] olanzapine,[19,20] ziprasidone,[19,20] transdermal blonanserin, and oral blonanserin were changed to unbound plasma concentration values, $C_{50,free}$, using protein binding ratio. In vitro Ki values were estimated by measuring human D_{2L} receptor binding activity of [^3H]-spiperone in the presence of each test compound (see Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A807, which summarizes the values of in vitro Ki, protein binding ratio, and in vivo C_{50}, together with the method of in vitro Ki value estimation). The $C_{50,free}$ values except clozapine and oral blonanserin were plotted on log-log scale against the corresponding in vitro Ki values and regression analysis was performed using Origin 2020b. The same procedures were conducted using the 2 sets of in vitro Ki values including clozapine in the literature[21,22] to check the interstudy variability and to confirm the robustness of the regression lines. The $C_{50,free}$ values for oral blonanserin with a known contribution of active metabolite were also plotted and compared with the regression line. Risperidone[19,20] was excluded from this analysis, because it is a substrate for P-glycoprotein.[23]

Evaluation of the Effect of Various Factors on Concentrations

Plasma concentrations during transdermal patch applications were measured at scheduled visits of 1, 2, and 6 weeks of treatment in the confirmatory study[12] and 6, 28, and 52 weeks of treatment in the long-term study.[13] These concentration data were logarithmically transformed and analyzed using mixed effect model with factors (study, dose, treatment period, sex, advanced age, country, and application site) as fixed effects and patient as a random variable, using SAS version 9.4 software (SAS Institute, Inc, Cary, NC). The effects of factors were evaluated as relative ratios to control condition. Concentration data obtained later than 28 hours from the start of the latest patch application (less than 3.4% of data) were excluded from the analysis, because the application duration was planned to be approximately 24 hours. The concentration data below the lower limit of quantitation were also excluded from the analysis.

Prediction of D_2 Occupancy

D_2 occupancy was predicted using Equation 1 (as deterministic occupancy simulation) based on plasma blonanserin concentrations: the individual concentrations from long-term phase 3 studies of tablets[17,18] at the doses of 8, 16, or 24 mg/d (4, 8, or 12 mg twice daily) and those from confirmatory study[12] and long-term study[13] for transdermal patch (Table 1). Frequency of predicted D_2 occupancy in transdermal patches of 40 and 80 mg/d was estimated for 20 bins with occupancy divided in 5% increments from 0% to 100%. In addition, median and 90% prediction intervals of D_2 occupancy-time profiles were predicted based on those of plasma blonanserin concentration-time profiles in Japanese patients with schizophrenia, which were predicted using the previously reported population PK model, considering interindividual variability.[15]

RESULTS

Plasma Concentration of Blonanserin

Dose proportionality of plasma blonanserin concentrations during repeated transdermal applications in the dose range of 10 to 80 mg/d was confirmed by regression analysis with the slope

of 0.961 (95% confidence interval, 0.743 to 1.18), the intercept of −1.36 (−1.70 to −1.02) and adjusted R^2 of 0.7504. Plasma blonanserin concentration time profiles after repeated transdermal patch applications are shown in Figures 2A and B, respectively, after adjusting the dose level to 40 mg/d based on the dose proportionality of plasma blonanserin concentration. During repeated transdermal patch applications (time 0 to 24 hours), the concentration was nearly stable and a slow elimination phase was observed after removing the patch at 24 hours. In contrast, plasma concentration after repeated oral administrations peaked approximately 2 hours after administration and decreased to nearly trough levels by approximately 8 hours (Figs. 2C, D). Plasma concentration of active metabolite M-1 was quite lower than blonanserin concentration during transdermal applications (Fig. 2A).

D_2 Occupancy-Concentration Relationship

Individual D_2 occupancy and corresponding plasma blonanserin concentration were analyzed using the E_{max} model (Equation 1). Estimated parameter sets of B_{max} and C_{50} with 95% confidence intervals were 79.7 (72.3% to 87.1%) and 0.112 (0.0568 to 0.168) ng/mL (adjusted R^2 = 0.466, AIC = 222.6) for oral formulation, as shown in Figure 3A, and 88.7 (74.8% to 102.7%) and 0.857 (0.461 to 1.25) ng/mL (adjusted R^2 = 0.771, AIC = 206.6) for transdermal patch, as shown in Figure 3B. If B_{max} was fixed to 100, C_{50} was 0.263 (0.218 to 0.308) ng/mL (adjusted R^2 = 0.0631, AIC = 239.7) for oral formulation, and 1.16 (0.962 to 1.36) ng/mL (adjusted R^2 = 0.759, AIC = 207.0) for transdermal patch. Larger R^2 and smaller AIC in the model with B_{max} estimation than in the model with fixed B_{max} suggested that the model with nonfixed B_{max} was adequate to explain the relationship.

In Vitro–In Vivo Correlation of D_2 Occupancy

Regression analysis of in vivo $C_{50,free}$ values of various antipsychotics against corresponding in vitro Ki values in log-log scale were conducted, using the 3 kinds of datasets of in vitro Ki (see Supplementary Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A807, which summarizes the values of in vitro Ki, protein binding ratio and in vivo C_{50}, together with the method of in vitro Ki value estimation). The 3 regression lines were almost parallel to each other, and 2 regression lines based on the datasets of in vitro Ki value in the literature[21,22] were almost within 1/3- to 3-fold range of the regression line based on the data

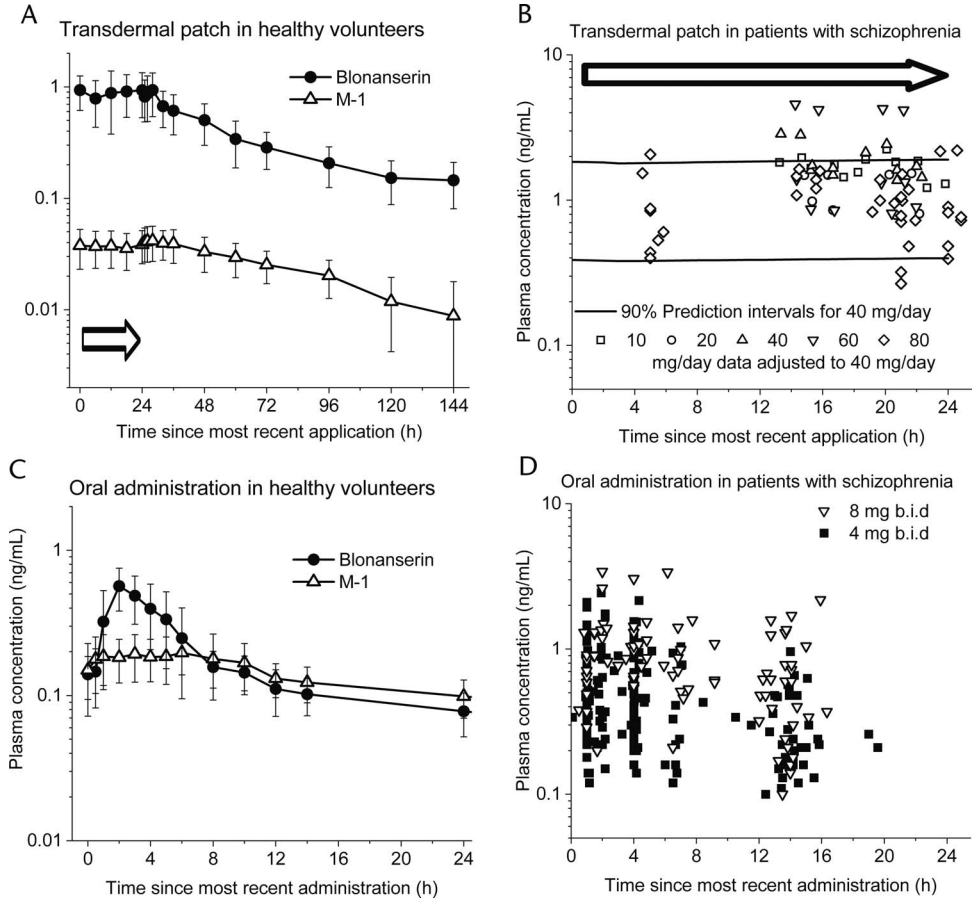

FIGURE 2. Plasma concentration–time profiles after repeated blonanserin transdermal patch applications (A, B) or oral administrations (C, D) in healthy volunteers (A, C) or patients with schizophrenia (B, D). A, Mean (±SD) concentrations of blonanserin and active metabolite M-1 after 10-day repeated transdermal patch applications at the dose of 64 mg/d of pilot formulation, which was comparable with the dose of 40 mg/d of the commercial formulation. B, Individual dose-adjusted blonanserin concentrations after 2-week repeated transdermal patch applications (adjusted to 40 mg/d). Lines represent 90% prediction interval obtained with population PK model. C, Mean (±SD) concentrations of blonanserin and metabolite M-1 after 10-day repeated oral administrations at 2 mg bid. D, Individual blonanserin concentrations after repeated oral administrations. White arrow represents the time of transdermal application for 24 hours. bid, bis in die (twice a day).

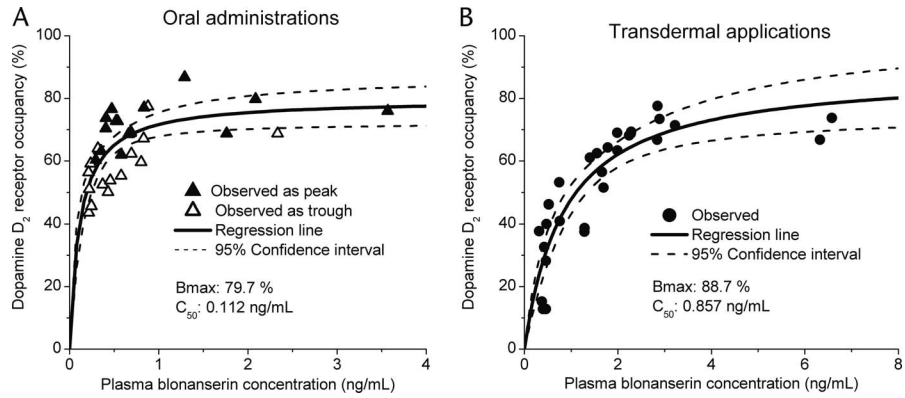

FIGURE 3. Relationship between D_2 occupancy and plasma blonanserin concentration after oral administrations (A) or transdermal patch applications (B). Symbols represent individual D_2 occupancy (32 data points for oral and 28 data points for transdermal administration). Regression lines were obtained with the equation of Occupancy (%) = B_{max} × Concentration / (C_{50} + Concentration).

set containing blonanserin transdermal patch, and almost all plots of the individual drugs distributed in the same range (Fig. 4), suggesting robustness of in vitro–in vivo relationship and small interstudy variability. In contrast, $C_{50,free}$ value of the oral blonanserin with a known contribution of active metabolite were far lower than the regression lines (Fig. 4).

Effect of Various Factors on Concentration

From the whole obtained concentration data in phase 3 studies of transdermal patch,[12,13] 85 data points (5.3% of total amount of data) were excluded from the analysis (Fig. 1). Analysis with mixed effect model detected no significant effect of study, sex, advanced age, or application site and the impact of each factor was estimated as the concentration ratio and its 90% confidence interval to control condition (Table 2). The concentration ratios at the doses of 60 and 80 mg/d corresponded to the dose ratios to 40 mg/d. Concentration ratio at 1 week was 0.624, suggesting that the steady state has not been achieved by 1 week after the start of treatment, and the ratios at 28 and 52 weeks to 6 weeks were almost 1, suggesting that the steady state was achieved before 6 weeks. The concentration ratio and its 90% confidence interval at each application site against back were included in the range of 0.8 to 1.25, suggesting the bioequivalence among application sites (back, chest, and abdomen). Considering these results, data at 1 week were excluded from the prediction of D_2 occupancy.

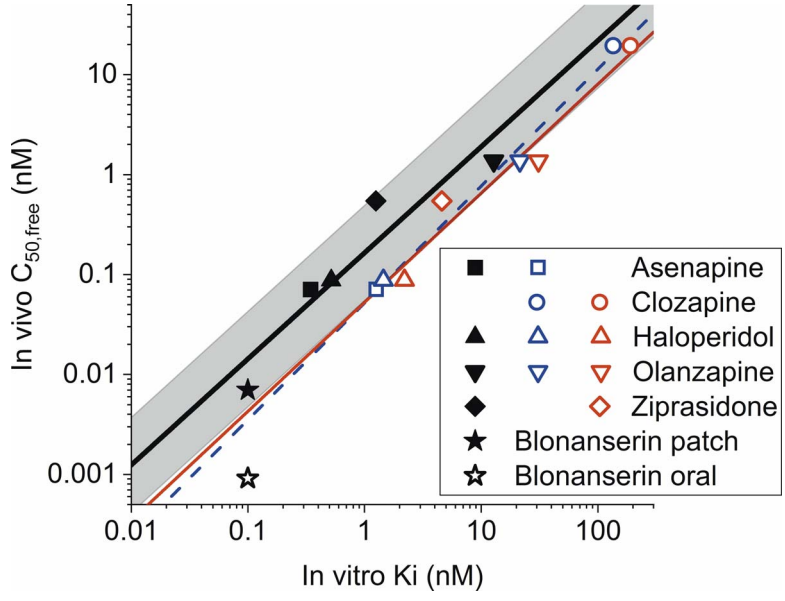

FIGURE 4. Correlation between in vitro Ki and in vivo $C_{50,free}$ values for D_2 occupancy of various drugs for schizophrenia. Regression analysis was performed on each of the 3 data sets containing in vitro Ki values measured in different organizations. Filled symbols and bold black line represent the plots against in vitro Ki values containing blonanserin patch and derived regression line with the slope (SE) of 1.06 (0.22) and the intercept of –0.781 (0.155) with adjusted R^2 of 0.851. Shaded area represents the range from 1/3-to 3-fold times the regression line. Unfilled blue symbols and blue dashed line represent the plots against in vitro Ki values from other source[21] and derived regression line with the slope (SE) of 1.17 (0.07) and the intercept of –1.28 (0.09) with adjusted R^2 of 0.990. Unfilled red symbols and red thin line represent the plots against in vitro Ki values reported by Schotte et al[22] and derived regression line with the slope (SE) of 1.09 (0.19) and the intercept of –1.28 (0. 26) with adjusted R^2 of 0.916. Unfilled star symbol represents in vivo $C_{50,free}$ value of oral blonanserin derived from the same PET study as blonanserin patch plotted against the same in vitro Ki value as blonanserin. $C_{50,free}$, protein unbound plasma drug concentration at half-maximal occupancy; SE, standard error.

TABLE 2. Effect of Various Factors on Plasma Blonanserin Concentration During Transdermal Applications

				Least Square Mean Ratio		
				Estimate	90% Confidence Interval	
Factors		No. Patients	No. Measurements		Lower	Upper
Study	Confirmatory*†	377	1045	1	—	—
	Long term‡	196	462	1.01	0.865	1.18
Dose	40 mg/d*	305	756	1	—	—
	60 mg/d	50	75	1.65	1.43	1.91
	80 mg/d	262	676	2.05	1.87	2.25
Treatment period	1 wk	374	374	0.624	0.587	0.662
	2 wk	351	352	0.830	0.781	0.883
	6 wk*	512	512	1	—	—
	28 wk	149	149	0.981	0.898	1.07
	52 wk	120	120	1.02	0.923	1.12
Sex	Male *	312	833	1	—	—
	Female	261	674	1.01	0.913	1.11
Age	<65 y*	532	1404	1	—	—
	≥65 y	41	103	0.838	0.689	1.02
Country	Japan	305	754	1.29	1.12	1.47
	Except Japan *§	268	753	1	—	—
Application site	Back*	418	803	1	—	—
	Abdomen	292	435	0.970	0.909	1.04
	Chest	198	269	0.906	0.842	0.975

Least square mean ratio to control condition was estimated by the analysis of log-transformed blonanserin concentration with mixed effect model.

*Used as control condition in each factor and the ratio to control condition was estimated.

†Confirmatory study (for 6 weeks, NCT02287584, JapicCTI-142688).[12]

‡Long-term study (for 52 weeks, NCT02335658, JapicCTI-152765).[13]

§China, Korea, Taiwan, Malaysia, Philippine, Russia, and Ukraine.

Comparison of Distribution of Predicted D_2 Occupancy

Distributions of the predicted individual occupancy for oral formulations are shown as histograms by dose together with the frequency of the predicted occupancy for transdermal patch in Figure 5. The predicted occupancy for oral administrations at 8 mg/d was covered by that for transdermal application at 40 mg/d and that at 80 mg/d (Fig. 5A). The predicted occupancy for oral administrations at 16 mg/d was covered by that for transdermal application at 80 mg/d (Fig. 5B). The predicted occupancy for oral administrations at 24 mg/d (Fig. 5B) was slightly higher than that at 16 mg/d and mostly covered by that for transdermal applications at 80 mg/d (Fig. 5B).

Comparison of Predicted D_2 Occupancy-Time Profiles

The individual occupancy values during repeated oral administrations and median and 90% prediction intervals of occupancy during transdermal patch applications were predicted and plotted against time as shown in Figure 6. The predicted occupancy during transdermal applications showed small within-day fluctuation, while that during oral administrations showed a peak approximately 2 to 6 hours and fluctuation was larger than transdermal patch, especially at the lower dose. At the oral dose of 8 or 16 mg/d, the predicted occupancy distributed approximately 60% or 70% at the peak time and approximately 50% or 65% at trough, respectively, and within the 90% prediction intervals of D_2 occupancy during transdermal application at 40 or 80 mg/d, respectively, except around peak values at 8 mg/d.

DISCUSSION

In this study, the relationship between striatal D_2 occupancy and plasma blonanserin concentration was analyzed for oral doses and for transdermal patch, which was the first transdermal formulation approved for the treatment of schizophrenia in the world. The doses of transdermal patch corresponding to the therapeutic oral doses were then estimated based on D_2 occupancy.

Striatal D_2 occupancy is a good predictor of the efficacy and safety of antipsychotics.[14] Given that blonanserin is a potent antagonist of dopamine D_2 receptor and the therapeutic doses of oral formulations were known, a PET study using both oral and transdermal blonanserin formulations was conducted to explore the doses of transdermal patch for a confirmatory study.[11] The relationship of D_2 occupancy with plasma blonanserin concentration after oral doses has been previously reported.[24] The C_{50} value for striatal D_2 occupancy was 0.17 ng/mL, with mean striatal occupancy of 60.8%, 73.4%, and 79.7% at oral doses of 8, 16, and 24 mg/d, respectively.[24] Based on current analysis, the C_{50} (95% confidence interval) value for oral tablets was estimated to be 0.112 (0.0568–0.168) ng/mL (Fig. 3A) and the mean peak occupancy at the oral doses of 8 and 16 mg/d was 65.5% and 74.5%, respectively, consistent with the previous results.[24] These results agreed with the previous review by Uchida et al[20] that D_2 occupancy could be estimated with a high degree of accuracy using plasma concentrations and E_{max} model parameters for each drug.

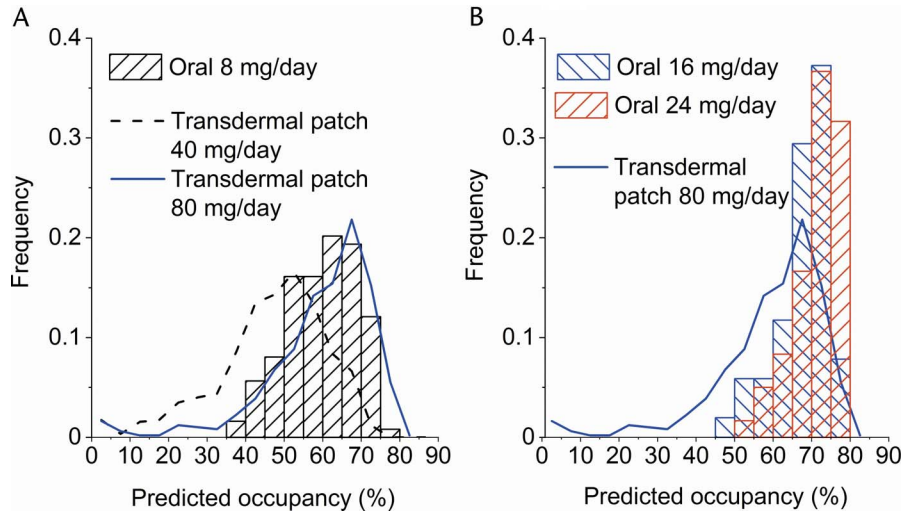

FIGURE 5. Distribution of predicted D_2 occupancy after oral administrations or transdermal patch applications of blonanserin in phase 3 studies. Frequency of predicted occupancy during blonanserin transdermal patch applications at the dose of 40 (n = 572, median occupancy = 48.7%; A) or 80 mg/d (n = 486, median occupancy = 62.5%; A, B) was overlaid on the histogram of predicted occupancy after oral administrations at the dose of 8 mg/d (4 mg bid, n = 124; A), 16 mg/d (8 mg bid, n = 51), and 24 mg/d (12 mg bid, n = 60; B). bid, bis in die (twice a day).

However, with the transdermal patch (Fig. 3B), the estimated C_{50} (with 95% confidence interval) was 0.857 (0.461–1.25) ng/mL, 7.65 times higher than after oral administrations.

Pharmacokinetic property of blonanserin transdermal patch can add an explanation to such discrepancy. As blonanserin is predominantly metabolized by CYP3A during first pass after oral administrations, transdermal route is effective to avoid first-pass metabolism and related drug-drug interactions.[25] The plasma concentration ratio of the active metabolite M-1/blonanserin was 0.8 during oral administrations[26] and 0.04 during transdermal applications.[27] The in vitro Ki of M-1 for dopamine D_2 receptor is 1.38, approximately 10 times less inhibitory potential than of blonanserin[5] and free fraction of M-1 from plasma protein binding is 0.007, about twice that of blonanserin.[26] These data suggest partial contribution of M-1 to efficacy during oral administrations and negligible contribution during transdermal applications. Comparing with the regression lines of in vivo $C_{50,free}$ against in vitro Ki values in log-log scale (Fig. 4), the in vivo $C_{50,free}$ values for oral blonanserin were clearly lower, which would be reasonable considering the contribution of occupancy by the active metabolite. These results suggested that the in vivo $C_{50,free}$ observed for transdermal blonanserin is the actual value of the unchanged blonanserin. The parameters for oral blonanserin are those of the empirical model that describes the apparent relationship between unchanged blonanserin concentration and D_2 occupancy.

In the present analysis, B_{max} values were estimated separately for patients on tablets or patches treatment, 79.7% and 88.7%, respectively (Fig. 3). With the previous PET data obtained after oral blonanserin administrations,[24] B_{max} could be 84.1%, if estimated without fixing to 100%, suggesting the similar B_{max} in these PET studies in patients with schizophrenia. In the PET study in healthy White participants with single oral blonanserin administration at 2 to 40 mg or multiple oral administrations at 5 to 15 mg/d in fasting condition, the highest observed individual D_2 occupancy was 97.5% with plasma blonanserin concentration of 3.09 ng/mL,[26] suggesting that B_{max} was close to 100%. Observed occupancy in the range of plasma blonanserin concentrations greater than 1 ng/mL were 68.8% to 86.8% in patients with

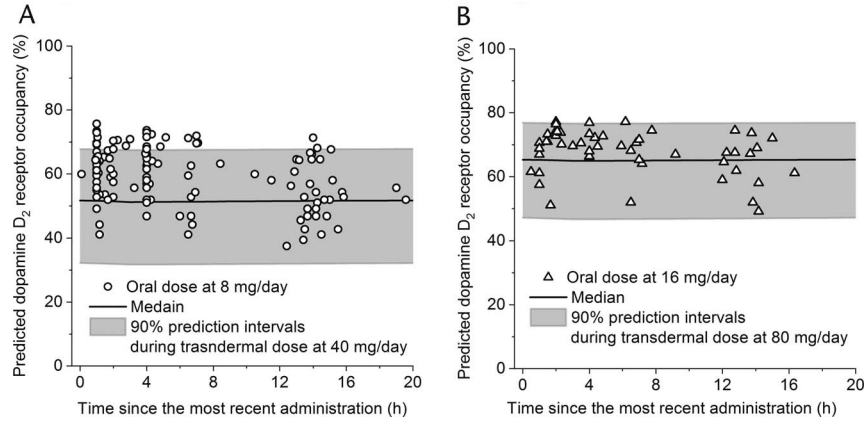

FIGURE 6. Predicted D_2 occupancy at various time points after oral administrations and during transdermal patch applications of blonanserin. Prediction interval of occupancy-time profile at steady state during application of blonanserin transdermal patch at the dose of 40 (A) or 80 mg/d (B) was overlaid on the plots of individual predicted occupancy during oral administration of blonanserin at the dose of 8 mg/d (4 mg bid, n = 124; A) and 16 mg/d (8 mg bid, n = 51; B). bid, bis in die (twice a day).

schizophrenia (n = 8)[11,24] and 85.7% to 97.5% in healthy volunteers (n = 5),[26] suggesting that lower observed occupancy in higher plasma blonanserin concentration range resulted in lower estimated B_{max} in patients. Differences in study design and populations may have contributed to such differences in occupancy and estimated B_{max} values.

These results indicated that plasma concentration–D_2 occupancy relationship for transdermal patch should be analyzed separately from oral formulations, and D_2 occupancy prediction for evaluation of corresponding doses should be conducted based on the respective model parameters. Considering the limited data for each formulation, interindividual variability could not be estimated for the model parameters and deterministic simulations based on observed concentrations or predicted concentrations were conducted to predict D_2 occupancy for patients on each formulation.

Significant efficacy of blonanserin transdermal patch against placebo in 6-week treatment at the doses of 40 and 80 mg/d was confirmed,[12] and a long-term study supported continuous efficacy and safety of blonanserin patch for 1 year at the same dose range.[13] Given the small amount of data for blonanserin transdermal patch in the PET study,[11] D_2 occupancy was predicted based on plasma concentrations measured in the confirmatory study[12] and the long term study[13]. These predicted occupancy was compared with that of tablets (Fig. 5). Distribution of the observed values of D_2 occupancy after oral doses in PET study[11] (52.9%–65.5% and 58.8%–73.8% from trough to peak at 8 and 16 mg/d, respectively) and those in the previous PET study[24] (56.9%–63.6%, 67.2%–79.5%, and 78.2%–83.7% around peak time at 8, 16, and 24 mg/d, respectively) were similar to the predicted values shown in Fig. 5. Distribution of the observed values during transdermal treatment in the PET study[11] (51.5%–68.7% and 63.4%–77.6% at 40 and 80 mg/d, respectively) were comparable with the predicted values (Fig. 5). These results suggested that the predicted D_2 occupancy based on the large-scale studies for each formulation are acceptable to explore the corresponding doses of transdermal patch to oral dose. The predicted occupancy in patients on transdermal patch at 40 mg/d was slightly lower than that in patients on oral doses at 8 mg/d but that for transdermal patch at 80 mg/d could cover the higher range of occupancy at 8 mg/d (Fig. 5A). The predicted occupancy in patients on transdermal patch at 80 mg/d could cover that in patients on oral doses at 16 and 24 mg/d except for the occupancy greater than 75% (Fig. 5B). These results suggested that blonanserin patch at 40 to 80 mg/d could cover most patients with oral blonanserin at 8 to 24 mg/d. Considering that higher occupancy approximately 78% or greater should be avoided for safety reasons,[14] not covering the occupancy of 75% and greater, which were mainly observed with tablets at 24 mg/d, would be desirable characteristics of the patch. These results suggested that 80 mg/d blonanserin transdermal patch is a good alternative for patients with 24 mg/d oral blonanserin.

The blonanserin plasma concentration-time profile after transdermal application was significantly different from that after oral administration. During repeated applications of blonanserin transdermal patches, plasma concentrations remained almost constant, without fluctuation (Figs. 2A, B), while approximately 5-fold difference was observed between peak and trough (approximately 12 hours) concentrations after repeated twice daily oral administrations (Figs. 2C, D) with larger variability in patients (Fig. 2D).[15] In the PET study,[11] peak D_2 occupancy during oral administrations was higher than at trough, with mean (minimum, maximum) difference of 13.5% (7.2%, 27.1%), while the difference during transdermal patch applications was small, 2.1% (−5.0%, 7.1%). Considering the fluctuation of occupancy with oral doses, the predicted occupancy was plotted against the time since the most recent dose and compared with the 90% intervals of the predicted occupancy for blonanserin transdermal patch (Fig. 6). Occupancy during transdermal applications was nearly constant and did not cover the highest occupancy at the peak time during oral administration at the corresponding doses. These properties would make transdermal patch a valuable option for avoiding adverse effects at higher occupancy range.

The predicted median occupancy during blonanserin transdermal patch applications at the doses of 40 and 80 mg/d in phase 3 studies were 48.7% and 62.5%, respectively, which were lower than previously reported effective values. Kapur et al[14] reported that the likelihood of clinical response increased significantly as D_2 occupancy exceeded 65%, based on the data of 22 patients with baseline PANSS positive score of 20.9 ± 3.8 and negative score of 15.9 ± 6.5 (mean ± SD). In the case of the confirmatory study of blonanserin transdermal patch, the baseline PANSS was 25.7 to 26.3 in positive score, 25.4 to 26.3 in negative score, and significant efficacy with the effect size of 0.297 at 40 mg/d[27] and 0.555 at 80 mg/d was observed,[12] suggesting that blonanserin transdermal patch could show moderate effect size in acute phase treatment at moderate occupancy levels without high peak occupancy.

Recently, the efficacy of a preferential D_3 antagonist, F17464, that improves the symptoms of acute exacerbation of schizophrenia, has been reported,[28] suggesting that D_3 receptor can be a target of action. A PET study of F17464 revealed that D_2 occupancy was very low (24% or lower) compared with D_3 occupancy (79% or higher).[29] Blonanserin has an affinity for the D_3 receptor in addition to the D_2 receptor and has similar in vitro Ki values.[30] The C_{50} after oral dose was also similar between D_2-rich brain region and D_3-rich brain region in healthy volunteers (0.39 and 0.40 ng/mL, respectively)[31] and in patients with schizophrenia (0.30 and 0.70 ng/mL, respectively),[32] suggesting contribution of D_3 occupancy to efficacy of blonanserin. This could be one of the reasons for the lower D_2 occupancy at therapeutic doses of blonanserin transdermal patches compared with the previously reported values in other antipsychotics. Even if the maximum occupancy of D_2 receptors falls below the reported upper limit (78%), subjective unpleasant experiences such as depressive symptoms are in association with inhibition of D_2 receptors.[33,34] Considering this, it is a preferable property of the transdermal patch of blonanserin as an antipsychotic that efficacy can be obtained even at a low D_2 occupancy rate together with the possible contribution of the D_3 occupancy. For oral blonanserin, a postmarketing surveillance in which data were collected from 1357 patients over a 1-year data collection period showed that the average daily dose for patients treated with blonanserin alone (145 patients) at 12 weeks, 6 months, and 1 year (last evaluation) treatment was 11.4, 11.6, and 11.9 mg/d, respectively.[35] These results suggested that patients who could be treated with blonanserin monotherapy seem to maintain relatively lower doses of oral blonanserin in real clinical settings compared with the previously reported dose range (12.9–22.1 mg/d) estimated based on the therapeutic window of striatal D_2 occupancy.[24] It is considered that the D_3 receptor inhibitory potential of blonanserin may explain this dose difference mentioned above, and may contribute to its clinical efficacy.

There were several limitations in this study. First, only 33 and 28 occupancy data points were obtained in the PET study for oral and transdermal blonanserin, respectively, and the participants had used oral blonanserin before their entry in the study.[11] Therefore, patients in need of higher doses might have been included in the 16 mg/d group, resulting in possible bias in the occupancy-concentration relationship. However, such bias can be excluded from the C_{50} comparison, because occupancy during oral dosing and transdermal applications was measured in the same patients. Second, the analysis used Equation 1, which assumes that plasma concentration and D_2 occupancy were in rapid equilibrium, without lag time. As blonanserin is a highly permeable lipophilic compound, lag time should be negligible, except during peak hours

after oral administrations. Thus, predicted peak occupancy after oral administration was excluded from the occupancy range to be covered by the corresponding transdermal dose, not only to avoid possible adverse effects but also to exclude possibly biased peak values. Third, action of blonanserin on nonstriatal brain regions (eg, limbic system) and on receptors other than dopamine D_2 receptors (eg, dopamine D_3, serotonin 5-HT_{2A}) have not been examined in blonanserin transdermal patch. Therefore, in this study, striatal D_2 occupancy, which has been commonly used as an indicator of clinical efficacy, was used as a predictor of clinical efficacy of blonanserin.

CONCLUSIONS

Blonanserin plasma concentration at the half-maximal D_2 occupancy under the blonanserin transdermal patch treatment was 0.857 ng/mL. Lower D_2 occupancy with transdermal blonanserin (median values of 48.7 and 62.5% at the doses of 40 and 80 mg/d) compared with commonly reported values for various antipsychotics (65%–78%) was enough to achieve a therapeutic effect in patients with schizophrenia. The predicted D_2 occupancy supports that a 40- to 80-mg/d dose of blonanserin transdermal patch is the corresponding dose of an oral dose of 8 to 24 mg/d for the schizophrenia treatment.

DATA AVAILABILITY STATEMENT

Sumitomo Dainippon Pharma Co, Ltd, policy on data sharing can be found on the Web site (https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Sunovion.aspx).

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AUTHOR DISCLOSURE INFORMATION

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