Report on the Deliberation Results

March 3, 2021

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	(a) Lonasen Tablets 2 mg, (b) Lonasen Tablets 4 mg, (c) Lonasen Tablets 8 mg, (d) Lonasen Powder 2%
Non-proprietary Name	Blonanserin (JAN*)
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	May 28, 2020

Results of Deliberation

In its meeting held on February 25, 2021, the First Committee on New Drugs concluded that the partial change application for the products may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

February 3, 2021
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical products submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Lonasen Tablets 2 mg, (b) Lonasen Tablets 4 mg, (c) Lonasen Tablets 8 mg, (d) Lonasen Powder 2%
Non-proprietary Name	Blonanserin
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	May 28, 2020
Dosage Form/Strength	(a), (b), and (c): Each tablet contains 2, 4, or 8 mg of blonanserin. (d) Each 1 g of powder contains 20 mg of blonanserin.
Application Classification	Prescription drug (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the products have efficacy in the treatment of schizophrenia in children, and that the products have acceptable safety in view of their benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition.

Indication	Schizophrenia (No change)
Dosage and Administration	The usual adult starting dose is 4 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual adult maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be

adjusted according to the patient's age and symptoms. The daily dose should not exceed 24 mg.

The usual pediatric starting dose is 2 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual pediatric maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 16 mg.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

December 25, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Products Submitted for Approval

Brand Name	(a) Lonasen Tablets 2 mg, (b) Lonasen Tablets 4 mg, (c) Lonasen Tablets 8 mg, (d) Lonasen Powder 2%
Non-proprietary Name	Blonanserin
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	May 28, 2020
Dosage Form/Strength	(a), (b), and (c): Each tablet contains 2, 4, or 8 mg of blonanserin. (d) Each 1 g of powder contains 20 mg of blonanserin.
Proposed Indication	Schizophrenia

(No change)

Proposed Dosage and Administration

The usual adult starting dose is 4 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual adult maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 24 mg.

<u>The usual pediatric starting dose is 2 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual pediatric maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 16 mg.</u>

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Blonanserin, the active ingredient of Lonasen, is an atypical antipsychotic that exerts its antagonistic effects against dopamine D_2 receptors, dopamine D_3 receptors, and serotonin 5-HT_{2A} receptors. In Japan, Lonasen Tablets 2 mg, Lonasen Tablets 4 mg, and Lonasen Powder 2%[1)] were approved in January 2008 for the treatment of schizophrenia with an adult dosage, and a tape formulation of blonanserin was approved in June 2019 for the same indication with an adult dosage.

Outside Japan, blonanserin is approved for the treatment of schizophrenia in South Korea and China, as of November 2020; however, no pediatric dosage is approved in either of these countries.

In Japan, clinical studies in pediatric patients with schizophrenia aged ≥12 to ≤18 years were initiated in March 2012. Because these clinical studies demonstrated the efficacy and safety of blonanserin in the treatment of schizophrenia in children, the applicant has filed a partial change application for blonanserin.

Atypical antipsychotic drugs approved for the treatment of schizophrenia in Japan include risperidone, paliperidone and its palmitate, olanzapine, aripiprazole and its hydrate, quetiapine fumarate, asenapine maleate, brexpiprazole, and lurasidone. However, none of these have been approved for pediatric use.

2. Quality and Outline of the Review Conducted by PMDA

Because the present application is intended for a new dosage, no data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is intended for a new dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of blonanserin, and no new study data have been submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new dosage, the non-clinical pharmacokinetics data were previously evaluated for the initial approval of blonanserin, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application is intended for a new dosage, no data relating to toxicity have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Because blonanserin (approved drug products) was used in the clinical studies for the present application, no data relating to biopharmaceutic studies have been submitted.

[1)] Lonasen Tablets 8 mg were approved in December 2009.

Plasma blonanserin concentrations in human were quantified using liquid chromatography-tandem mass spectrometry. The lower limit of quantification was 0.01 ng/mL.

6.2 Clinical pharmacology

The applicant submitted the results from a phase III study (CTD 5.3.5.1.01, Study D4907001), a long-term treatment study (CTD 5.3.5.2.01, Study D4907002) in Japanese pediatric patients with schizophrenia, and the results of a population pharmacokinetics analysis (CTD 5.3.3.5.01, Analysis DSP5423-PPK-01), as evaluation data.

6.2.1 Studies in patients (CTD 5.3.5.1.01, Study D4907001; CTD 5.3.5.2.01, Study D4907002)

In Study D4907001, multiple doses of blonanserin were orally administered to Japanese pediatric patients ≥12 to ≤18 years of age diagnosed with schizophrenia twice daily after breakfast and dinner, at a dose of 4 mg/day at Week 1 and 8 mg/day for 5 weeks thereafter in the 8 mg/day group, or at a dose of 4 mg/day at Week 1, 8 mg/day at Week 2, and 16 mg/day for 4 weeks thereafter in the 16 mg/day group (the pharmacokinetic analysis set, 101 patients). Table 1 shows the plasma blonanserin concentrations (CTD 5.3.5.1.01, Study D4907001).

Table 1. Plasma blonanserin concentrations following multiple oral doses (Study D4907001)

Timepoint[a)]	Blonanserin 8 mg/day	Blonanserin 16 mg/day
Week 2	0.17 ± 0.08 (41)	0.16 ± 0.08 (42)
Week 6	0.25 ± 0.12 (38)	0.45 ± 0.19 (36)

Mean ± standard deviation (ng/mL) (n)
a) Blood samples for plasma blonanserin concentration measurement were collected at any timepoint during Weeks 2 and 6.

In Study D4907002, multiple doses of blonanserin was orally administered to Japanese pediatric patients with schizophrenia who had completed Study D4907001, twice daily after breakfast and dinner for 52 weeks (the pharmacokinetic analysis set, 103 patients). Treatment with blonanserin was started at a dose of 4 mg/day, which was then adjusted within the range of 4 to 24 mg/day, considering the efficacy and patient safety. Table 2 shows the plasma blonanserin concentrations (CTD 5.3.5.2.01, Study D4907002).

Table 2. Plasma blonanserin concentrations following multiple oral doses (Study D4907002)

Timepoint		Dose per administration[a)]					
		2 mg	4 mg	6 mg	8 mg	10 mg	12 mg
Week 28	2-4 hours postdose	0.27 ± 0.21 (11)	0.46 ± 0.26 (14)	0.39, 0.52[b)] (2)	0.79 ± 0.30 (7)	1.30[b)] (1)	1.22 ± 0.47 (3)
	Trough[c)]	0.12 ± 0.09 (10)	0.29 ± 0.13 (6)	0.25 ± 0.11 (7)	0.41 ± 0.48 (5)	0.31, 0.52[b)] (2)	0.56, 0.60[b)] (2)
Week 52	Trough[c)]	0.09 ± 0.06 (13)	0.19 ± 0.13 (21)	0.35 ± 0.24 (7)	0.51 ± 0.27 (12)	0.41 ± 0.19 (4)	0.15[b)] (1)

Mean ± standard deviation (ng/mL) (n)
a) Each dose represents the dose administered immediately before the blood sampling for plasma concentration measurement.
b) Concentration data from individual patients
c) Concentrations observed at ≥10 hours postdose

6.2.2 Population Pharmacokinetics (PPK) analysis (CTD 5.3.3.5.01, Analysis DSP5423-PPK-01)

A PPK analysis was performed based on the plasma blonanserin concentration data from the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) in pediatric patients with schizophrenia (132 patients, 347 timepoints). The pharmacokinetics of blonanserin was

described by a 2-compartment model with first-order absorption. A covariate analysis[2)] identified sex as a covariate for apparent volume of distribution, and body mass index (BMI) as a covariate for bioavailability. The population mean pharmacokinetic parameters estimated from the final model were 0.97 kL/h for apparent total body clearance, 17.9 kL for apparent central volume of distribution, 0.55 kL/h for apparent intercompartmental clearance, 111 kL for apparent peripheral volume of distribution, and 0.81 /h for the absorption rate constant.

6.R Outline of the review conducted by PMDA

6.R.1 Effects of age on the pharmacokinetics of blonanserin

As the proposed maintenance dose for pediatric patients is the same as the approved dose for adult patients, PMDA asked the applicant to explain the effects of age on the pharmacokinetics of blonanserin.

The applicant's explanation:

- Table 3 shows the plasma blonanserin concentrations in pediatric patients with schizophrenia by age category (<15 years and ≥15 years) in the phase III study (CTD 5.3.5.1.01, Study D4907001). There were no clear differences in the plasma blonanserin concentrations with age.

Table 3. Plasma blonanserin concentrations by age category (<15 years and ≥15 years) (Study D4907001)

Treatment	Timepoint[a)]	Age category	Plasma blonanserin concentration (ng/mL)
Blonanserin 8 mg/day	Week 2	≥12-<15 years	0.15 ± 0.07 (12)
		≥15-≤18 years	0.18 ± 0.08 (29)
	Week 6	≥12-<15 years	0.21 ± 0.07 (12)
		≥15-≤18 years	0.26 ± 0.13 (26)
Blonanserin 16 mg/day	Week 2	≥12-<15 years	0.16 ± 0.06 (12)
		≥15-≤18 years	0.16 ± 0.09 (30)
	Week 6	≥12-<15 years	0.43 ± 0.19 (11)
		≥15-≤18 years	0.46 ± 0.20 (25)

Mean ± standard deviation (n)
a) Blood samples for plasma blonanserin concentration measurement were collected at any timepoints during Weeks 2 and 6.

- Figure 1 shows the steady-state trough[3)] plasma concentrations of blonanserin[4)] administered as multiple oral doses of 8 mg/day or 16 mg/day by age category (<15 years, ≥15-≤18 years, and >18 years) in Study D4907001 and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) in pediatric patients with schizophrenia, and phase II studies as part of the clinical development program in adult patients >18 years of age with schizophrenia (CTD 5.3.5.2-1, Study AD5423-201-2 and CTD 5.3.5.2-2, Study AD5423-202-3 for the initial approval). The distribution of plasma blonanserin concentrations did not differ largely across the age categories.

2) The potential covariates in the PPK analysis were sex, body weight, age, BMI, and concomitant medications (etizolam, brotizolam, lorazepam, biperiden hydrochloride, triazolam, loxoprofen sodium hydrate, sodium picosulfate hydrate, paracetamol, sennoside A·B calcium, and fexofenadine hydrochloride).
3) Values observed at ≥10 hours postdose were handled as trough concentrations.
4) The analysis used the plasma blonanserin concentrations observed at Weeks 6 and 52 in Studies D4907001 and D4907002, respectively. The doses in Study D4907002 were based on the modal doses administered during the most recent 1 week before sampling.

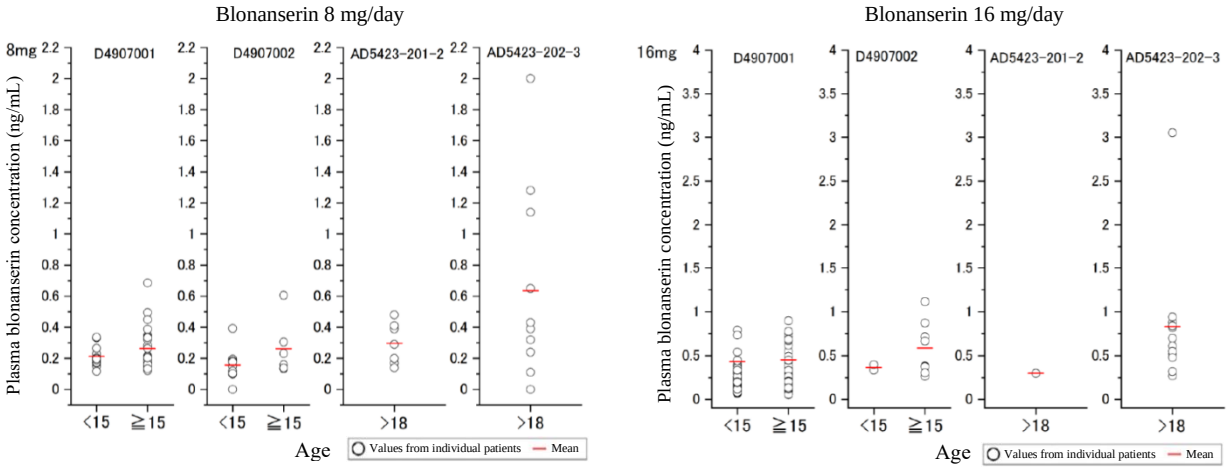

Figure 1. Trough plasma concentrations of blonanserin administered as multiple oral doses of 8 mg/day or 16 mg/day, by age category (<15 years, ≥15-≤18 years, and >18 years)

- A PPK analysis (CTD 5.3.3.5.01) based on the plasma blonanserin concentration data from Studies D4907001 and D4907002 revealed that the estimated apparent total clearance of blonanserin was similar, regardless of age, as presented in Table 4.

Table 4. Apparent total clearance (kL/h) by age estimated from a PPK analysis

12 years	13 years	14 years	15 years	16 years	17 years	18 years
0.784 (1)	1.12 [0.874, 1.36] (16)	1.08 [0.922, 1.23] (22)	1.05 [0.926, 1.17] (31)	0.961 [0.811, 1.11] (24)	1.07 [0.849, 1.29] (19)	1.04 [0.831, 1.26] (19)

Mean [95% CI] or values from individual patients (n)

- The above results indicate that the effect of age on the pharmacokinetic parameters of blonanserin is small, and that the pharmacokinetics of blonanserin is unlikely to substantially differ between adults and children ≥12 years of age.

PMDA's view:

Comparisons of plasma blonanserin concentration among age categories in Study D4907001, and between pediatric patients in Studies D4907001 and D4907002, and adult patients in phase II studies conducted as part of the clinical development program in adult patients revealed no tendency for plasma blonanserin concentrations to clearly differ depending on age category. In addition, the apparent total clearance estimated from the PPK analysis did not largely differ among pediatric patient groups of different ages, in the range from ≥12 to ≤18 years. In view of these results, the pharmacokinetics of blonanserin are unlikely to substantially differ between adults and children ≥12 years of age. The dosage regimen of blonanserin for pediatric patients with schizophrenia is discussed further in Section 7.R.5.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from Japanese clinical studies presented in Table 5.

Table 5. Summary of clinical efficacy and safety studies

Data category	Geographical location	Study identity CTD	Phase	Study population	N	Dosing regimen	Main endpoints
Evaluation	Japan	D4907001 5.3.5.1.01	III	Pediatric patients with schizophrenia aged ≥12 to ≤18 years	151	Placebo, or blonanserin 8 mg/day or 16 mg/day, administered orally twice daily after meals for 6 weeks	Efficacy Safety Pharmacokinetics
		D4907002 5.3.5.2.01	Long-term treatment	Patients who completed the 6-week treatment in Study D4907001	106	Blonanserin 4 to 24 mg/day, administered orally twice daily for 52 weeks	Safety Efficacy Pharmacokinetics

7.1 Phase III study

7.1.1 Phase III study (CTD 5.3.5.1.01, Study D4907001, March 2012 to March 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy, safety, and pharmacokinetics of blonanserin in Japanese children aged ≥12[5)] to ≤18 years at the time of informed consent, who were diagnosed with schizophrenia[6)] according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision (DSM-IV-TR) criteria[7)] (target sample size, 150 patients [50 per treatment group]) [see Section 6.2.1 for pharmacokinetics].

Patients received placebo, or blonanserin 8 mg/day or 16 mg/day orally twice daily after breakfast and dinner for 6 weeks. Treatment with blonanserin was started at a dose of 4 mg/day, and increased to 8 mg/day after 1 week in both the 8 mg/day and 16 mg/day groups. The dose in the 16 mg/day group was then further increased to 16 mg/day after another 1 week. Patients who entered the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) continued to receive the same dose of blonanserin for up to 2 weeks after the end of the 6-week study treatment in Study D4907001.

All 151 randomized patients (47 in the placebo group, 51 in the 8 mg/day group, and 53 in the 16 mg/day group) were included in the safety analysis set. Of these 151 patients, 1 patient in the 16 mg/day group had no baseline score on the Positive and Negative Syndrome Scale (PANSS), and the remaining 150 patients (47 in the placebo group, 51 in the 8 mg/day group, 52 in the 16 mg/day group) were included in the full analysis set (FAS). A total of 34 patients (7 in the placebo group, 12 in the 8 mg/day group, 15 in the 16 mg/day group) discontinued the study treatment. The main reasons for discontinuation were consent withdrawal (2 in the placebo group, 4 in the 8 mg/day group, 6 in the 16 mg/day group), deterioration of the primary disease (3 in the placebo group, 5 in the 8 mg/day group, 3 in the 16 mg/day group), and adverse events (1 in the placebo group, 3 in the 8 mg/day group, 5 in the 16 mg/day group).

Table 6 shows the primary endpoint of the change from baseline in PANSS total score to Week 6 in the FAS. A statistically significant difference was noted between the 16 mg/day group and the placebo group, but not between the 8 mg/day group and the placebo group.

5) The lower age limit of the target study population was changed from 13 years to 12 years of age, with protocol amendment Ver. 3, dated [redacted], 20[redacted].
6) Patients were required to have a PANSS total score of 60 to 120 at screening and before the start of study treatment, and a CGI-S score of ≥3 (mildly)
7) The Mini International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I.KID) was used as an aid for diagnosing schizophrenia.

Table 6. Change from baseline in PANSS total score to Week 6 (Study D4907001, FAS, MMRM)

Treatment	PANSS total score		Change from baseline[a)b)]	Difference from placebo[b)]	
	Baseline	Week 6		Between-group difference [95% CI]	*P*-value[c)]
Placebo	89.8 ± 10.41 (47)	74.3 ± 16.46 (41)	-10.6 ± 2.78		
Blonanserin 8 mg/day	86.5 ± 13.53 (51)	68.2 ± 16.55 (39)	-15.3 ± 2.76	-4.7 [-12.49, 3.03]	0.230
Blonanserin 16 mg/day	88.7 ± 13.81 (52)	66.2 ± 13.42 (39)	-20.5 ± 2.71	-9.9 [-17.61, -2.25]	0.012

Mean ± standard deviation (N)

a) Least-square mean ± standard error

b) This is based on the MMRM model with treatment as a fixed effect, and timepoint, baseline PANSS total score, and treatment-by-timepoint interaction as covariates (an unstructured covariance matrix was used for within-patient correlation).

c) As the first step, the placebo group and the combined blonanserin group (the 8 mg/day group and the 16 mg/day group combined) were compared with a 2-sided significance level of 0.05. If a significant difference was found, pairwise comparisons between each blonanserin group and the placebo group were performed with a 2-sided significance level of 0.05, as the second step. The *P*-value between the combined blonanserin group and the placebo group at the first step was 0.032.

The incidences of adverse events (including abnormal laboratory values) were 68.1% (32 of 47) of patients in the placebo group, 80.4% (41 of 51) of patients in the 8 mg/day group, and 92.5% (49 of 53) of patients in the 16 mg/day group. No patients died. Serious adverse events, other than deaths, were reported in 2.1% (1 of 47, schizophrenia) of patients in the placebo group and 2.0% (1 of 51, hyperventilation) of patients in the 8 mg/day group; a causal relationship to the study drug could not be ruled out for both of these events.

The incidences of adverse events (including abnormal laboratory values) for which a causal relationship to the study drug could not be ruled out were 25.5% (12 of 47) of patients in the placebo group, 54.9% (28 of 51) of patients in the 8 mg/day group, and 75.5% (40 of 53) of patients in the 16 mg/day group. Major adverse events were akathisia (2 patients, 7 patients, 17 patients), somnolence (1 patient, 7 patients, 9 patients), hyperprolactinaemia (1 patient, 5 patients, 9 patients), blood prolactin increased (1 patient, 3 patients, 7 patients), tremor (0 patients, 5 patients, 5 patients), dystonia (0 patients, 1 patient, 6 patients), nausea (3 patients, 2 patients, 2 patients), and schizophrenia (3 patients, 3 patients, 1 patient).

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature).

Clinically relevant electrocardiogram (ECG) changes reported in the study were PR interval prolonged[8)] (3 patients, 1 patient, 1 patient) and QRS complex prolonged[9)] (0 patients, 0 patients, 2 patients). Other ECG changes were QTcB high[10)] (1 patient, 4 patients, 1 patient), QTcB prolonged[11)] (1 patient, 0 patients, 1 patient), QTcF high[10)] (0 patients, 1 patient, 0 patients), and QTcF prolonged[11)] (1 patient, 0 patients, 1 patient).

7.1.2 Long-term treatment study (CTD 5.3.5.2.01, Study D4907002, April 2012 to March 2020)

An open-label, uncontrolled study was conducted to evaluate the safety, efficacy, and pharmacokinetics of long-term treatment with blonanserin in patients who had completed the 6-week study treatment in the phase III study (CTD 5.3.5.1.01, Study D4907001) (target sample size, ≤150 patients) [see Section 6.2.1 for pharmacokinetics].

8) Prolongation from baseline of >180 msec in patients aged ≥12 to <16 years, or of >200 msec in patients aged ≥16 years
9) Prolongation from baseline of >110 msec in patients aged ≥12 to <16 years, or of >120 msec in patients aged ≥16 years
10) A postdose value of >460 msec
11) Prolongation from baseline of ≥60 msec

Patients orally received blonanserin twice daily after breakfast and dinner for 52 weeks. Treatment with blonanserin was started at a dose of 4 mg/day, and the dose was adjusted[12)] within the range of 4 to 24 mg/day, considering the efficacy and patient safety.

All 106 treated patients were included in the safety analysis set. Of these 106 patients, 43 discontinued the study treatment. The main reasons for discontinuation were consent withdrawal in 26 patients, deterioration of the primary disease in 8 patients, and adverse events in 4 patients.

The mean dose (mean ± standard deviation) of blonanserin in the safety analysis was 8.9 ± 4.00 mg/day. The mean final dose was 4 to 8 mg/day in 60 patients (56.6%), 10 to 16 mg/day in 33 patients (31.1%), and 18 to 24 mg/day in 13 patients (12.3%).

Table 7 shows the change from baseline in PANSS total score to the last assessment in the safety analysis set, the primary endpoint.

Table 7. Change from baseline in PANSS total score to the last assessment (Study D4907002, safety analysis set, LOCF)

Treatment assigned in Study D4907001	N	PANSS total score		Change from baseline in Study D4907001	PANSS total score		Change from baseline in Study D4907002
		Baseline in Study D4907001	Last assessment		Baseline in Study D4907002	Last assessment	
Placebo	36	88.9±9.24	63.3±20.12	-25.6±21.71	73.1±15.48	63.3±20.12	-9.8±16.39
Blonanserin 8 mg/day	37	85.6±13.63	63.3±20.07	-22.3±21.54	68.2±17.46	63.3±20.07	-5.0±13.24
Blonanserin 16 mg/day	33	88.7±13.79	61.5±16.06	-27.2±19.04	64.3±13.96	61.8±16.18	-2.9±17.33
Overall study population	106	87.7±12.35	62.7±18.77	-24.9±20.76	68.7±16.01	62.9±18.82	-6.0±15.77

Mean ± standard deviation

The incidence of adverse events (including abnormal laboratory test results) was 90.6% (96 of 106) of patients. Two patients died (completed suicide in 2 patients); however, a causal relationship to blonanserin was denied for both deaths. Serious adverse events, other than deaths, were reported in 15 patients (schizophrenia in 10 patients, and pharyngitis streptococcal, toxicity to various agents, impulsive behaviour, suicidal ideation, and suicide attempt in 1 patient each). A causal relationship to blonanserin could not be ruled out for the schizophrenia in 1 patient.

The incidence of adverse events for which a causal relationship to blonanserin could not be ruled out was 65.1% (69 of 106) of patients. Major adverse events were akathisia in 19 patients, tremor in 17 patients, dystonia in 12 patients, and hyperprolactinaemia, weight increased, blood prolactin increased, and somnolence in 10 patients each.

12) In principle, dose adjustment was made at each assessment timepoint (Week 1, Week 2, every 4 weeks from Week 4 to Week 28, and every 8 weeks from Week 36 to Week 52). The dose was adjusted in increments or decrements of ≤4 mg/dose (8 mg/day), up to 12 mg/dose (24 mg/day). Once a dose adjustment was made, the dosage regimen was not changed for ≥1 week. In patients receiving a dose of <12 mg/dose (24 mg/day), the dose was increased in increments of 2 to 4 mg/dose (4 to 8 mg/day), if they had an inadequate improvement in CGI-I (i.e., CGI-I score of 3 [minimally improved] to 7 [very much worse]) at each assessment timepoint, as compared with baseline in the phase III study (CTD 5.3.5.1.01: Study D4907001) and the dose was well-tolerated. A dose adjustment was allowed outside of the scheduled assessment timepoints after PANSS, CGI-S, and CGI-I assessments, in cases where:
- An adverse event developed, and the investigator or subinvestigator determined that a dose reduction would be necessary.
- The investigator or subinvestigator determined that the patient had inadequate response to the study drug (CGI-I score of 3 [minimally improved] to 7 [very much worse]), and a dose increase would be necessary.

There were no clinically relevant changes in vital signs (blood pressure, pulse rate, and body temperature).

Clinically relevant ECG changes reported in the study were PR interval prolonged[8)] (2 patients) and QRS complex prolonged[9)] (2 patients). Other ECG changes were QTcB high[10)] (4 patients), QTcB prolonged[11)] (3 patients), QTcF high[10)] (2 patients), and QTcF prolonged[11)] (1 patient).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy endpoints

PMDA asked the applicant to explain the appropriateness of selecting PANSS, a rating scale to assess psychopathological severity in adults with mental disorders, as the primary endpoint in a phase III study in pediatric patients with schizophrenia aged ≥12 to ≤18 years (CTD 5.3.5.1.01, Study D4907001).

The applicant's explanation:

- Since the psychiatric symptoms characteristic of schizophrenia in adults are essentially also found in pediatric patients with schizophrenia, the same diagnostic criteria as those used in adults are applicable in children as well (*Japanese Journal of Clinical Medicine.* 2013;71:701-5), and childhood-onset schizophrenia shares the same clinical features with later-onset forms of the disorder (*Can J Psychiatry.* 2001;46:923-30). In reports from multiple foreign clinical studies in pediatric patients with schizophrenia, which were available at the planning of Study D4907001, patient's response was evaluated using PANSS (*Am J Psychiatry.* 2008;165:1432-41, *J Am Acad Child Adolesc Psychiatry.* 2009;48:60-70). In addition, in recently reported foreign clinical studies in pediatric patients with schizophrenia, PANSS is used to evaluate the efficacy of treatments (*J Child Adolesc Psychopharmacol.* 2017;27:516-25, *J Child Adolesc Psychopharmacol.* 2015;25:384-96, etc).
- On the basis of the above, the applicant believes that selecting PANSS as a rating scale of the primary endpoint in Study D4907001 in pediatric patients with schizophrenia aged ≥12 to ≤18 years was appropriate.

PMDA's view:

PMDA accepted the applicant's explanation. There were no particular problems with selecting the change from baseline in PANSS total score to Week 6 as the primary endpoint in Study D4907001.

7.R.1.2 Efficacy of blonanserin 8 mg/day

In the phase III study (CTD 5.3.5.1.01, Study D4907001), a comparison of the change from baseline in PANSS total score to Week 6, the primary endpoint, between the 16 mg/day group and the placebo group indicated a statistically significant difference, demonstrating the efficacy of blonanserin 16 mg/day. In contrast, as shown in Table 6, a comparison between the 8 mg/day group and the placebo group revealed no statistically significant difference. PMDA asked the applicant to explain the efficacy of blonanserin 8 mg/day in the treatment of schizophrenia in children.

The applicant's explanations about the factors that were responsible for the absence of a statistically significant difference between the 8 mg/day group and the placebo group in Study D4907001:

- The target sample size in Study D4907001 was set, assuming that the difference in the change from baseline in PANSS total score between the placebo group and the 8 or 16 mg/day group would be from 10 to 13, and that its standard deviation would be from 17 to 20, based on the results from Japanese clinical studies of blonanserin in patients with schizophrenia, conducted as part of the clinical development program in adult patients (CTD 5.3.5.1-1.1, Study AD5423-301-5[13] and CTD 5.3.5.1-2, Study AD5423-308-17,[14] for the initial approval), a Japanese placebo-controlled, double-blind, comparative study of paliperidone in adult patients with schizophrenia (*Japanese Journal of Clinical Psychopharmacology.* 2010;13:2077-103), and foreign placebo-controlled, double-blind, comparative studies[15] of antipsychotics[16] in pediatric patients with schizophrenia. However, the 8 mg/day group of Study D4907001 failed to yield the effect size that had been expected at the planning of the study.
- To investigate the factors that contributed to the unsuccessful achievement of the expected effect size in the 8 mg/day group of Study D4907001, which had a study design that did not differ substantially from that of any of the above studies, subgroup analyses by the demographic characteristics and disease data collected in Study D4907001 were conducted to identify the subgroups that affected the efficacy of blonanserin 8 mg/day. The subgroup analyses revealed that the difference between the 8 mg/day group and the placebo group tended to be small in patients with onset of schizophrenia at age <13 and patients who were hospitalized at the time of informed consent (Table 8).

Table 8. Change from baseline in PANSS total score to Week 6, by patient characteristics (Study D4907001, FAS, MMRM)

		Treatment	PANSS total score		Change from baseline[a) b)]	Difference from placebo [95% CI]
			Baseline	Week 6		
Age at onset	<13 years	Placebo	86.3 ± 6.65 (15)	73.2 ± 11.33 (15)	-12.3 ± 3.54	
		Blonanserin 8 mg/day	80.4 ± 11.37 (16)	68.3 ± 20.28 (13)	-10.7 ± 3.61	1.6 [-8.66, 11.80]
		Blonanserin 16 mg/day	83.3 ± 13.24 (21)	62.3 ± 13.01 (17)	-21.6 ± 3.09	-9.3 [-18.81, 0.14]
	≥13 years	Placebo	91.5 ± 11.49 (32)	74.9 ± 18.98 (26)	-9.6 ± 3.86	
		Blonanserin 8 mg/day	89.4 ± 13.63 (35)	68.2 ± 14.79 (26)	-18.1 ± 3.80	-8.5 [-19.33, 2.30]
		Blonanserin 16 mg/day	92.3 ± 13.16 (31)	69.2 ± 13.24 (22)	-19.6 ± 4.03	-10.0 [-21.18, 1.10]
Hospital status at the time of informed consent	Inpatient	Placebo	89.5 ± 10.03 (22)	71.2 ± 19.06 (20)	-15.1 ± 3.87	
		Blonanserin 8 mg/day	87.3 ± 13.47 (29)	71.0 ± 14.49 (23)	-11.5 ± 3.51	3.6 [-6.83, 14.06]
		Blonanserin 16 mg/day	87.8 ± 13.02 (27)	67.3 ± 15.02 (24)	-21.3 ± 3.45	-6.2 [-16.57, 4.17]
	Outpatient	Placebo	90.1 ± 10.94 (25)	77.3 ± 13.31 (21)	-6.4 ± 3.93	
		Blonanserin 8 mg/day	85.5 ± 13.85 (22)	64.3 ± 18.93 (16)	-20.4 ± 4.33	-13.9 [-25.77, -2.12]
		Blonanserin 16 mg/day	89.6 ± 14.83 (25)	64.3 ± 10.59 (15)	-20.4 ± 4.21	-14.0 [-25.62, -2.37]

Mean ± standard deviation (n)

a) Least-square mean ± standard error

b) This is based on the MMRM model with treatment as a fixed effect, and timepoint, baseline PANSS total score, and treatment-by-timepoint interaction as covariates (an unstructured covariance matrix was used for within-patient correlation).

- The number of patients or patient characteristics did not differ notably depending on the age at the onset of schizophrenia or hospital status (inpatient vs. outpatient).

[13] A phase III study using haloperidol as the comparator in patients aged ≥16 to ≤64 years. The enrolled patients comprised 3 patients aged <20 years and 118 patients aged ≥20 years.

[14] A phase III study using risperidone as the comparator in patients aged ≥15 years. The enrolled patients comprised 0 patients aged <20 years and 156 patients aged ≥20 years.

[15] *J Child Adolesc Psychopharmacol*. 2009;19:611-21, *Am J Psychiatry*. 2008;165:1432-41, *J Child Adolesc Psychopharmacol*. 2012;22:327-42, J *Am Acad Child Adolesc Psychiatry*. 2009;48:60-70

[16] Risperidone, aripiprazole, quetiapine, and olanzapine

- In general, the onset of schizophrenia in children <13 years represents a poor prognosis (*Can J Psychiatry*. 2001;46:923-30) and is often treatment-resistant (*Expert Opin Pharmacother*. 2008;9:459-65). This may be one reason why the efficacy of blonanserin 8 mg/day was suggested in patients with onset of schizophrenia at ≥13 years, whereas the change from baseline in PANSS total score to Week 6 in patients with onset of schizophrenia at <13 years did not differ between the 8 mg/day group and the placebo group in Study D4907001.
- The baseline PANSS total score did not differ largely between inpatients and outpatients at the time of informed consent. However, the change from baseline in PANSS total score in the 8 mg/day group was larger in outpatients than in inpatients, that in the 16 mg/day group was similar between inpatients and outpatients, and that in the placebo group tended to be larger in inpatients than in outpatients. The difference from the placebo group was smaller in inpatients than in outpatients, in both of the blonanserin 8 mg/day and 16 mg/day groups, and particularly in the 8 mg/day group. However, as described above, no notable differences in patient characteristics were found between the subgroups. Some patients with schizophrenia are admitted to a hospital at the request of the patients or their families, or for the purpose of social improvement, regardless of symptoms. In Study D4907001, information regarding the reason for hospitalization was not collected, and the details of hospitalization in individual patients were thus unknown, which precluded a precise evaluation of the reasons why the hospital status (inpatient vs. outpatient) at the time of informed consent affected the efficacy of blonanserin at 8 mg/day.

The applicant's explanation about the efficacy of blonanserin 8 mg/day:

- In Study D4907001, the percentages of PANSS responders[17] (Table 9) and the percent improvement in Clinical Global Impression of Global Improvement (CGI-I)[18] (Table 10), which were secondary endpoints, were consistently higher in the 8 mg/day group than in the placebo group. These improvement tendencies in the 8 mg/day group suggested the clinically significant efficacy of blonanserin 8 mg/day, as well as 16 mg/day.

Table 9. Percentages of PANSS responders (Study D4907001, FAS, LOCF)

	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day
N	47	51	52
30% Responders	15 (31.9)	21 (41.2)	31 (59.6)
40% Responders	9 (19.1)	13 (25.5)	25 (48.1)
50% Responders	6 (12.8)	11 (21.6)	16 (30.8)

n (%)

Table 10. Percent improvement in CGI-I at Week 6 (Study D4907001, FAS, LOCF)

Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day
8/46 (17.4)	18/51 (35.3)	22/52 (42.3)

n/N (%)

- Table 11 shows the distribution of modal doses of blonanserin in the long-term treatment study (CTD 5.3.5.2.01, Study D4907002), by the treatment assigned in Study D4907001. In the long-term treatment study, the most common modal dose of blonanserin was 4 to 8 mg/day, regardless of the treatment assigned

[17] Patients who achieved a 30%, 40%, or 50% improvement in PANSS total score at Week 6 compared with baseline
[18] The proportion of patients who achieved a CGI-I score of 1 (very much improved) or 2 (much improved)

in Study D4907001. The modal dose (mean ± standard deviation) in each patient in Study D4907002 was 9.6 ± 5.12 mg/day, with a median of 8.0 mg/day. Thus, a majority of patients had a modal dose of 4 to 8 mg/day in Study D4907002, in which the dose of blonanserin was adjusted according to clinical decision, suggesting that most patients were able to maintain their responses to blonanserin at a dose of 4 to 8 mg/day.

Table 11. Distribution of the modal doses of blonanserin in Study D4907002, by the treatment assigned in Study D4907001 (safety analysis set)

Modal dose	Treatment assigned in Study D4907001 (N)			
	Placebo (36)	Blonanserin 8 mg/day (37)	Blonanserin 16 mg/day (33)	Total (106)
4 mg/day	8 (22.2)	10 (27.0)	5 (15.2)	23 (21.7)
6 mg/day	4 (11.1)	3 (8.1)	3 (9.1)	10 (9.4)
8 mg/day	12 (33.3)	11 (29.7)	12 (36.4)	35 (33.0)
4-8 mg/day	24 (66.7)	24 (64.9)	20 (66.6)	68 (64.2)
10-16 mg/day	9 (25.0)	10 (27.0)	11 (33.3)	30 (28.3)
18-24 mg/day	3 (8.3)	3 (8.1)	2 (6.1)	8 (7.5)

n (%)

On the basis of the above, the failure to demonstrate a statistically significant difference in the primary endpoint between the 8 mg/day group and the placebo group in Study D4907001 might be attributed to the small change in PANSS total score in patients with onset of schizophrenia at <13 years, which is prone to be intractable. However, the efficacy of blonanserin in the treatment of schizophrenia in children can be expected at a dose of 8 mg/day, as well, in view of the following study results: (a) The efficacy of blonanserin, as assessed by the primary endpoint, was suggested in patients with onset of schizophrenia at ≥13 years in the 8 mg/day group; (b) the percentages of responders based on PANSS total score and the percent improvement in CGI-I at Week 6, which were secondary endpoints, tended to be consistently higher in the 8 mg/day group than in the placebo group; and (c) the most common modal dose of blonanserin in Study D4907002 was 4 to 8 mg, regardless of the treatment assigned in Study D4907001.

PMDA's view:

- As the applicant explained, the failure to demonstrate a statistically significant difference in the primary endpoint between the 8 mg/day group and the placebo group in Study D4907001 might be attributed to the results from patients with onset of schizophrenia at <13 years, in view of the fact that such childhood-onset schizophrenia has been reported to be generally intractable. In addition, the change from baseline in PANSS total score to Week 6 in inpatients was larger than that in outpatients in the placebo group, and this greater improvement in inpatients of the placebo group might have affected the evaluation of the efficacy of blonanserin 8 mg/day. However, information regarding the reason for hospitalization, etc. was not collected in the study, which precluded a precise explanation of the effects of hospital status on the efficacy of blonanserin 8 mg/day.
- Nevertheless, the efficacy of blonanserin can be expected in the treatment of schizophrenia in children at a dose of 8 mg/day as well, in view of the following study results: (a) The results of Study D4907001 showed that the change from baseline in PANSS total score to Week 6, the primary endpoint, tended to be greater in the 8 mg/day group than in the placebo group (Table 6); (b) the percentages of PANSS responders and the percent improvement in CGI-I, which were secondary endpoints, tended to be consistently higher in the

8 mg/day group than in the placebo group; and, (c) the highest proportion of patients had a modal dose of blonanserin of 4 to 8 mg/day in Study D4907002, regardless of the treatment assigned in Study D4907001, suggesting that most patients were able to maintain their responses to blonanserin at a dose of 4 to 8 mg/day.

- On the basis of the efficacy of blonanserin 8 mg/day as discussed above, the dosage and administration, including the maintenance dose, for pediatric patients with schizophrenia is discussed further in Section 7.R.5

7.R.1.3 Factors that affect the efficacy of blonanserin

PMDA asked the applicant to explain the factors, other than age at onset and hospital status (inpatient vs. outpatient) at the time of informed consent [see Section 7.R.1.2], that affect the efficacy of blonanserin.

The applicant's explanation:

- Subgroup analyses of the change from baseline in PANSS total score to Week 6, the primary endpoint, in the phase III study (CTD 5.3.5.1.01, Study D4907001) by patient characteristics revealed that the difference between the placebo group and each blonanserin group tended to decrease in patients with prior antipsychotic therapy and patients with concomitant psychotherapy, as compared with those with no prior antipsychotic therapy and those with no concomitant psychotherapy, respectively (Table 12).

Table 12. Change from baseline in PANSS total score to Week 6, by patient characteristics (Study D4907001, FAS, MMRM)

		Treatment	PANSS total score		Change from baseline[a)b)]	Difference from placebo [95% CI]
			Baseline	Week 6		
Prior antipsychotic therapy	With	Placebo	89.4 ± 10.41 (29)	70.4 ± 16.97 (25)	-11.3 ± 3.84	
		Blonanserin 8 mg/day	84.6 ± 12.90 (30)	68.8 ± 14.85 (25)	-13.7 ± 3.83	-2.4 [-13.24, 8.44]
		Blonanserin 16 mg/day	85.8 ± 12.62 (34)	67.9 ± 13.74 (26)	-14.7 ± 3.60	-3.4 [-13.89, 7.14]
	Without	Placebo	90.5 ± 10.68 (18)	80.3 ± 14.08 (16)	-9.4 ± 3.54	
		Blonanserin 8 mg/day	89.3 ± 14.23 (21)	67.2 ± 19.80 (14)	-18.6 ± 3.56	-9.3 [-19.37, 0.87]
		Blonanserin 16 mg/day	94.1 ± 14.66 (18)	62.8 ± 12.56 (13)	-32.4 ± 3.73	-23.0 [-33.40, -12.67]
Concomitant psychotherapy	With	Placebo	88.5 ± 10.89 (11)	73.8 ± 19.98 (9)	-8.3 ± 6.00	
		Blonanserin 8 mg/day	87.9 ± 14.30 (17)	73.4 ± 19.02 (14)	-11.8 ± 4.54	-3.5 [-18.87, 11.88]
		Blonanserin 16 mg/day	81.2 ± 12.73 (14)	64.7 ± 13.03 (12)	-12.3 ± 5.15	-4.0 [-20.25, 12.25]
	Without	Placebo	90.2 ± 10.39 (36)	74.4 ± 15.70 (32)	-11.7 ± 3.05	
		Blonanserin 8 mg/day	85.9 ± 13.29 (34)	65.4 ± 14.62 (25)	-17.3 ± 3.37	-5.6 [-14.62, 3.49]
		Blonanserin 16 mg/day	91.4 ± 13.31 (38)	66.9 ± 13.78 (27)	-24.2 ± 3.11	-12.5 [-21.21, -3.86]

Mean ± standard deviation (n)
a) Least-square mean ± standard error
b) Change from baseline is based on the MMRM model with treatment as a fixed effect, and timepoint, baseline PANSS total score, and treatment-by-timepoint interaction as covariates (an unstructured covariance matrix was used for within-patient correlation).

- Although the baseline PANSS total score was not substantially different between subgroups of patients with and without prior antipsychotic therapy, the change from baseline in PANSS total score to Week 6 and the difference from placebo in each blonanserin group tended to be smaller in patients with prior antipsychotic therapy than in those without prior antipsychotic therapy. There were no notable differences in other patient characteristics between patients with and without prior antipsychotic therapy. As shown in Table 13 and Table 14, the percentages of PANSS responders and percent improvement in CGI-I of the secondary endpoints, tended to be higher in both blonanserin groups than in the placebo group, regardless of prior antipsychotic therapy, although the differences from placebo were smaller in patients with prior antipsychotic therapy than in those without prior antipsychotic therapy. The percentages of 30% responders

and 40% responders in patients with prior antipsychotic therapy in the 8 mg/day group were similar to those in patients with prior antipsychotic therapy in the placebo group, and were also similar to those in patients without prior antipsychotic therapy in the 8 mg/day group. Thus, the efficacy of blonanserin was suggested in the treatment of schizophrenia regardless of prior antipsychotic therapy, and the prior use of antipsychotic therapy is unlikely to have a clinically significant effect on the efficacy of blonanserin.

Table 13. Percentages of PANSS responders by prior use of antipsychotic therapy (Study D4907001, FAS, LOCF)

	With prior antipsychotic therapy			Without prior antipsychotic therapy		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day
N	29	30	34	18	21	18
30% Responders	12 (41.4)	12 (40.0)	18 (52.9)	3 (16.7)	9 (42.9)	13 (72.2)
40% Responders	7 (24.1)	7 (23.3)	13 (38.2)	2 (11.1)	6 (28.6)	12(66.7)
50% Responders	5 (17.2)	6 (20.0)	7 (20.6)	1 (5.6)	5 (23.8)	9 (50.0)

n (%)

Table 14. Percent improvement in CGI-I at Week 6, by prior use of antipsychotic therapy (Study D4907001, FAS, LOCF)

With prior antipsychotic therapy			Without prior antipsychotic therapy		
Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day
6/29 (20.7)	8/30 (26.7)	10/34 (29.4)	2/17 (11.8)	10/21 (47.6)	12/18 (66.7)

n/N (%)

- The baseline PANSS total score was not substantially different between subgroups of patients with and without concomitant psychotherapy in the placebo group and the 8 mg/day group, while the baseline PANSS total score was lower in patients with concomitant psychotherapy than in those without concomitant psychotherapy in the 16 mg/day group. The change from baseline in PANSS total score to Week 6 and its difference from placebo in each blonanserin group tended to be smaller in patients with concomitant psychotherapy than in those without concomitant psychotherapy. However, because a larger change was found in each blonanserin group than in the placebo group, the effect of concomitant psychotherapy on the efficacy of blonanserin is considered to be limited.
- As discussed above, no factors that may have a clinically significant effect on the efficacy of blonanserin have been identified.

PMDA's view:

In view of the results of the subgroup analyses of the primary endpoint and secondary endpoints in Study D4907001, the prior use of antipsychotic therapy or the concomitant use of psychotherapy is unlikely to have a clinically significant effect on the efficacy of blonanserin. PMDA accepted the applicant's explanation.

On the basis of the discussions presented in Sections 7.R.1.1 to 7.R.1.3, PMDA has concluded that there should be no major problems with the efficacy of blonanserin in the treatment of schizophrenia in children. The PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

7.R.2 Safety

7.R.2.1 Differences in the safety profile between children and adults

PMDA asked the applicant to explain whether any differences in the safety profile of blonanserin have been found between the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002), and the clinical studies conducted as part of the clinical development program in adult patients.

The applicant's explanation:

- Table 15 shows the incidences of adverse events in Studies D4907001 and D4907002, and clinical studies in patients with schizophrenia conducted as part of the clinical development program in adult patients (CTD 5.3.5.1-1.1, Study AD5423-301-5;[13)] CTD 5.3.5.1-2, Study AD5423-308-17;[14)] CTD 5.3.5.2-5, Study AD5423-302-8;[19)] and CTD 5.3.5.2-6, Study AD5423-302-12,[20)] for the initial approval).
- The major adverse events reported with a higher incidence in children than in adults in double-blind, parallel-group studies included hyperprolactinaemia, dystonia, and schizophrenia, while those in open-label, uncontrolled studies included hyperprolactinaemia, skin abrasion, vomiting, schizophrenia, and acne. Most cases of hyperprolactinaemia reported in children were mild in severity, and the incidence of another "prolactin" event, blood prolactin increased, was high in adults. These results did not suggest that children are at an increased risk of "prolactin" events. All of the cases of dystonia, skin abrasion, vomiting, and acne reported in children were neither serious nor severe. With the exception of 1 patient who discontinued the study treatment due to vomiting (the 16 mg/day group of Study D4907001), none of the events led to drug discontinuation. Accordingly, these events were not considered to be clinically significant. Schizophrenia was reported only in children, and 10 patients in Study D4907002 reported serious schizophrenia. However, in the clinical studies conducted as part of the clinical development program in adult patients, it was prespecified that worsening of schizophrenia symptoms was not to be collected as an adverse event,[21)] thus precluding a precise comparison between children and adults.
- The above indicated that comparisons of the incidence of adverse events between children and adults are limited, due to differences in the designs of Studies D4907001 and D4907002 from those of the clinical studies conducted as part of the clinical development program in adult patients,[22)] and for other reasons. However, no clear differences in the safety profile of blonanserin have been found between children and adults.

[19)] A long-term treatment study (2) in patients aged ≥16 years. The lowest age of the patients actually enrolled in the study was 19 years old.
[20)] A long-term treatment study (3) in patients aged ≥16 years. The lowest age of the patients actually enrolled in the study was 16 years old.
[21)] Studies D4907001 and D4907002 had prespecified not to collect "lack of efficacy" as an adverse event, unless it exceeded the normal range. Studies AD5423-301-5, AD5423-302-8, and AD5423-302-12, which were conducted as part of the clinical development program in adult patients, had prespecified not to collect worsening of schizophrenia symptoms as adverse events while no particular specification was provided in Study AD5423-308-17.
[22)] Study D4907002 is an extension study from Study D4907001, whereas Studies AD5423-302-8 and AD5423-302-12, which were conducted as part of the clinical development program in adult patients, are not extension studies.

Table 15. Incidences of adverse events in clinical studies conducted as part of the clinical development programs in pediatric and adult patients with schizophrenia (safety analysis sets)

	Double-blind, parallel-group studies					Open-label, uncontrolled studies		
	Children			Adults		Children	Adults	
	Study D4907001			Study AD5423-301-5[a)]	Study AD5423-308-17[a)]	Study D4907002	Study AD5423-302-8[b)]	Study AD5423-302-12[b)]
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Blonanserin	Blonanserin			
N	47	51	53	129	156	106	61	321
All adverse events	32 (68.1)	41 (80.4)	49 (92.5)	120 (93.0)	153 (98.1)	96 (90.6)	59 (96.7)	311 (96.9)
Serious adverse events	1 (2.1)	1 (2.0)	0	3 (2.3)	3 (1.9)	17 (16.0)	6 (9.8)	19 (5.9)
Adverse events leading to drug discontinuation	3 (6.4)	5 (9.8)	6 (11.3)	19 (14.7)	33 (21.1)	9 (8.5)	10 (16.4)	35 (10.9)
Major adverse events								
Akathisia	2 (4.3)	7 (13.7)	17 (32.1)	35 (27.1)	45 (28.8)	19 (17.9)	21 (34.4)	60 (18.7)
Somnolence	1 (2.1)	8 (15.7)	10 (18.9)	20 (15.5)	32 (20.5)	10 (9.4)	24 (39.3)	77 (24.0)
Hyperprolactinaemia	1 (2.1)	5 (9.8)	9 (17.0)	1 (0.8)	1 (0.6)	10 (9.4)	3 (4.9)	4 (1.2)
Blood prolactin increased	1 (2.1)	3 (5.9)	7 (13.2)	10 (7.8)	72 (46.2)	10 (9.4)	18 (29.5)	91 (28.3)
Dystonia	0	1 (2.0)	7 (13.2)	11 (8.5)	7 (4.5)	12 (11.3)	6 (9.8)	11 (3.4)
Tremor	0	5 (9.8)	5 (9.4)	39 (30.2)	49 (31.4)	18 (17.0)	17 (27.9)	60 (18.7)
Headache	6 (12.8)	6 (11.8)	4 (7.5)	15 (11.6)	24 (15.4)	18 (17.0)	10 (16.4)	78 (24.3)
Nausea	4 (8.5)	5 (9.8)	4 (7.5)	14 (10.9)	16 (10.3)	9 (8.5)	8 (13.1)	61 (19.0)
Skin abrasion	3 (6.4)	2 (3.9)	4 (7.5)	0	9 (5.8)	11 (10.4)	1 (1.6)	14 (4.4)
Vomiting	2 (4.3)	1 (2.0)	4 (7.5)	11 (8.5)	13 (8.3)	15 (14.2)	4 (6.6)	33 (10.3)
Salivary hypersecretion	0	0	4 (7.5)	25 (19.4)	31 (19.9)	2 (1.9)	8 (13.1)	29 (9.0)
Contusion	2 (4.3)	2 (3.9)	3 (5.7)	0	9 (5.8)	6 (5.7)	1 (1.6)	19 (5.9)
Abdominal pain	2 (4.3)	1 (2.0)	3 (5.7)	3 (2.3)	2 (1.3)	9 (8.5)	3 (4.9)	11 (3.4)
Malaise	0	1 (2.0)	3 (5.7)	24 (18.6)	27 (17.3)	3 (2.8)	13 (21.3)	68 (21.2)
Constipation	0	0	3 (5.7)	20 (15.5)	16 (10.3)	11 (10.4)	12 (19.7)	74 (23.1)
Schizophrenia	3 (6.4)	4 (7.8)	2 (3.8)	0	0	21 (19.8)	0	0
Nasopharyngitis	9 (19.1)	1 (2.0)	2 (3.8)	8 (6.2)	27 (17.3)	38 (35.8)	17 (27.9)	116 (36.1)
Myalgia	1 (2.1)	1 (2.0)	1 (1.9)	1 (0.8)	4 (2.6)	8 (7.5)	1 (1.6)	5 (1.6)
Back pain	0	1 (2.0)	1 (1.9)	2 (1.6)	6 (3.8)	8 (7.5)	1 (1.6)	37 (11.5)
Blood creatine phosphokinase increased	1 (2.1)	1 (2.0)	1 (1.9)	10 (7.8)	23 (14.7)	6 (5.7)	6 (9.8)	34 (10.6)
Weight increased	0	2 (3.9)	0	3 (2.3)	1 (0.6)	15 (14.2)	5 (8.2)	23 (7.2)
Diarrhoea	0	1 (2.0)	0	5 (3.9)	12 (7.7)	10 (9.4)	11 (18.0)	63 (19.6)
Acne	0	0	0	0	0	15 (14.2)	0	1 (0.3)

n (%)
a) Dose, blonanserin 8-24 mg/day (twice daily); treatment duration, 8 weeks
b) Dose, blonanserin 8-24 mg/day (twice daily): treatment duration, ≤56 weeks

PMDA's view:

Although rigorous comparison is difficult due to differences in study design between Studies D4907001 and D4907002, and clinical studies conducted as part of the clinical development program in adult patients, no apparent differences in the safety profile of blonanserin have been found between children and adults.

The use of antipsychotics is associated with increased risks of some adverse drug reactions, including extrapyramidal symptoms, sedation, weight increased, and metabolic events, in pediatric patients compared with adult patients (*J Clin Psychiatry*. 2011;72:655-70). In view of this increased risk, "extrapyramidal syndrome," "sedation," "suicide," "weight increased," "glucose tolerance abnormal," "lipid metabolism disorder," "failure to thrive," and "hyperprolactinaemia" are individually investigated further, in the following subsections.

7.R.2.2 “Extrapyramidal syndrome” adverse events

PMDA asked the applicant to explain the incidence of “extrapyramidal syndrome” adverse events associated with blonanserin therapy.

The applicant’s explanation:

- Table 16 shows the incidences of “extrapyramidal syndrome” adverse events[23)] in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). In the blonanserin groups of Study D4907001, the incidence of such adverse events tended to increase in a dose-dependent manner. However, no serious events were reported. One patient in the 16 mg/day group of Study D4907001 discontinued the study treatment due to an “extrapyramidal syndrome” adverse event (akathisia).

Table 16. Incidences of “extrapyramidal syndrome” adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	2 (4.3)	13 (25.5)	27 (50.9)	17 (47.2)	24 (34.3)	41 (38.7)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	1 (1.9)	0	0	0
Major adverse events						
Akathisia	2 (4.3)	7 (13.7)	17 (32.1)	6 (16.7)	13 (18.6)	19 (17.9)
Dystonia	0	1 (2.0)	7 (13.2)	5 (13.9)	7 (10.0)	12 (11.3)
Tremor	0	5 (9.8)	5 (9.4)	9 (25.0)	9 (12.9)	18 (17.0)
Salivary hypersecretion	0	0	4 (7.5)	2 (5.6)	0	2 (1.9)
Dyskinesia	0	0	3 (5.7)	2 (5.6)	3 (4.3)	5 (4.7)
Oculogyric crisis	0	1 (2.0)	2 (3.8)	1 (2.8)	1 (1.4)	2 (1.9)
Bradykinesia	0	1 (2.0)	1 (1.9)	3 (8.3)	1 (1.4)	4 (3.8)
Extrapyramidal disorder	0	1 (2.0)	0	0	0	0
Myoclonus	0	1 (2.0)	0	0	1 (1.4)	1 (0.9)
Musculoskeletal stiffness	0	0	0	0	2 (2.9)	2 (1.9)
Muscle rigidity	0	0	0	1 (2.8)	0	1 (0.9)
Muscle tightness	0	0	0	1 (2.8)	0	1 (0.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 8,399 cases of “extrapyramidal syndrome” adverse drug reactions (24,425.6 cases per 100,000 patient-years, including 150 serious cases) collected as post-marketing adverse drug reaction reports.[24)] Of these 8,399 cases, 197 (including 5 serious cases) were reported in patients aged ≥12 to ≤18 years. Major adverse drug reactions were akathisia (69 cases, including 1 serious case), extrapyramidal disorder (27 cases, including 1 serious case), and tremor (21 cases, including no serious cases). The incidence of “extrapyramidal syndrome” adverse events in patients aged ≥12 to ≤18 years did not largely differ from that in patients aged >18 years. The incidences of “extrapyramidal syndrome” adverse drug reactions collected through the post-marketing

23) Events categorized into the standardized MedDRA query (SMQ) “extrapyramidal syndrome” or coded to the following preferred terms (PTs): Glabellar reflex abnormal, excessive eye blinking, salivary hypersecretion, gaze palsy, tongue paralysis, dysarthria, dyslalia, muscle contracture, myoclonus, periodic limb movement disorder, restless legs syndrome, nuchal rigidity, and intention tremor

24) The adverse events of Lonasen Tablets 2 mg, Lonasen Tablets 4 mg, Lonasen 8 mg, and Lonasen Powder 2%, as well as a tape formulation of blonanserin, entered in the safety information database from [redacted], 20[redacted] to [redacted], 20[redacted] were analyzed. The estimated total exposure was 34,386 patient-years. Patients whose ages are recorded as in the “10's,” and were not specified exactly were handled as patients aged from ≥12 to ≤18 years.

surveillance[25] were 11.4% (9 of 79) of patients aged ≤18 years and 10.9% (333 of 3,051) in patients aged >18 years in the general use-results survey, 18.8% (6 of 32 patients) and 15.5% (198 of 1,279 patients) in the general use-result survey (follow-up survey), 31.6% (6 of 19 patients) and 35.3% (47 of 133 patients) in the specified use-results survey (first episode), and 20.0% (1 of 5 patients) and 13.8% (157 of 1,139 patients) in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus tend to have no clearly higher incidence of "extrapyramidal syndrome" adverse drug reactions than those aged >18 years.

- The package insert of blonanserin already includes cautionary statement regarding the development of "extrapyramidal syndrome" adverse events. In view of this, as well as the above clinical study results and post-marketing safety information in Japan, and because no new concerns have been identified in pediatric patients with schizophrenia aged ≥12 to ≤18 years, no further caution through the package insert will be needed.

PMDA's view:

Given that no safety concerns that require additional cautionary statement on the development of "extrapyramidal syndrome" adverse events have been identified in children aged ≥12 to ≤18 years who received blonanserin for schizophrenia, the applicant's explanation that no further caution through the package insert is needed at present, is acceptable. However, in light of the mechanism of action of blonanserin, the development of "extrapyramidal syndrome" adverse events associated with blonanserin therapy should be carefully monitored in children in the same manner as in adults. Because the incidence of such adverse events tended to increase in a dose-dependent manner, blonanserin should be adjusted to the required minimum dose for each patient, through careful monitoring.

7.R.2.3 "Sedation" adverse events

PMDA asked the applicant to explain the incidence of "sedation" adverse events associated with blonanserin therapy.

The applicant's explanation:

- Table 17 shows the incidence of "sedation" adverse events[26] in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). In Study D4907001, the incidence of these adverse events was higher in the blonanserin groups than in the placebo group; however, none of the reported events were serious. "Sedation" adverse events led to drug discontinuation in 3 patients (somnolence in 2 patients and malaise in 1 patient) in the 16 mg/day group and 1 patient (somnolence) in the 8 mg/day group of Study D4907001.

[25] The general use-results survey (survey period, October 2008 to June 2012; number of patients surveyed, 79 patients aged ≤18 years and 3,051 patients aged >18 years), the general use-result survey (follow-up survey) (survey period, October 2008 to June 2012; number of patients surveyed, 32 patients aged ≤18 years and 1,279 patients aged >18 years), the specified use-results survey (first episode) (survey period, April 2009 to December 2012; number of patients surveyed, 19 patients aged ≤18 years and 133 patients aged >18 years), and the specified use-results survey (acute exacerbation) (survey period, July 2014 to December 2015; number of patients surveyed, 5 patients aged ≤18 years and 1,139 patients aged >18 years). The surveys included no patients aged <12 years.

[26] Events coded to the following MedDRA PTs: Coma, depressed level of consciousness, fatigue, hypersomnia, sedation, somnolence, stupor, malaise, and sedation complication

Table 17. Incidences of "sedation" adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	1 (2.1)	9 (17.6)	13 (24.5)	7 (19.4)	7 (10.0)	14 (13.2)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	1 (2.0)	3 (5.7)	0	0	0
Major adverse events						
Somnolence	1 (2.1)	8 (15.7)	10 (18.9)	4 (11.1)	6 (8.6)	10 (9.4)
Malaise	0	1 (2.0)	3 (5.7)	3 (8.3)	0	3 (2.8)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 1,963 cases of "sedation" adverse drug reactions (5,708.7 cases per 100,000 person-years, including 16 serious reactions) collected as post-marketing adverse drug reaction reports.[24)] Among these 1,963 cases, 48 (including 0 serious cases) were reported in patients aged ≥12 to ≤18 years with somnolence (38 cases), malaise (7 cases), and sedation complication (3 case). The incidence of "sedation" adverse events in patients aged ≥12 to ≤18 years did not largely differ from that in patients aged >18 years. The incidences of "sedation" adverse drug reactions collected through the post-marketing surveillance[25)] were 5.1% (4 of 79) of patients aged ≤18 years and 2.3% (71 of 3,051) of patients aged >18 years in the general use-results survey, 3.1% (1 of 32) of patients and 2.5% (32 of 1,279) of patients in the general use-result survey (follow-up survey), 10.5% (2 of 19) of patients and 6.8% (9 of 133) of patients in the specified use-results survey (first episode), and 0% (0 of 5) of patients and 1.3% (15 of 1,139) of patients in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus tended to have no clearly higher incidence of "sedation" adverse drug reactions than those aged >18 years.
- The package insert of blonanserin already includes cautionary statement regarding the development of "sedation" adverse events. In view of the above clinical study results and post-marketing safety information in Japan, and because no new concerns have been identified in pediatric patients with schizophrenia aged ≥12 to ≤18 years, no further caution through the package insert will be needed.

PMDA's view:
PMDA accepted the applicant's explanation, considering that no safety issues, requiring additional cautionary statement, have been identified following treatments with blonanserin in pediatric patients with schizophrenia aged ≥12 to ≤18 years.

7.R.2.4 "Suicide" adverse events

PMDA asked the applicant to explain the incidence of "suicide" adverse events associated with blonanserin therapy.

The applicant's explanation:

- In the phase III study (CTD 5.3.5.1.01, Study D4907001), no "suicide" adverse events[27] were reported. Table 18 shows the incidence of "suicide" adverse events in the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). Two patients experienced completed suicide, for which a causal relationship to blonanserin was denied. Other than deaths, serious "suicide" adverse events included a suicide attempt and suicidal ideation in 1 patient each. The suicide attempt in 1 patient led to treatment discontinuation; however, a causal relationship to blonanserin was denied for both events. Three patients reported non-serious intentional self-injury, in 1 of whom a causal relationship to blonanserin could not be ruled out. In clinical studies conducted as part of the clinical development program in adult patients, "suicide" adverse events were reported in no patients in Study AD5423-301-5[13] (CTD 5.3.5.1-1.1 for the initial approval), 2 of 156 patients in Study AD5423-308-17[14] (CTD 5.3.5.1-2 for the initial approval), 1 of 61 patients in Study AD5423-302-8[19] (CTD 5.3.5.2-5 for the initial approval), and 2 of 321 patients in Study D5423-302-12[20] (CTD 5.3.5.2-6 for the initial approval). A "suicide" adverse event (completed suicide) resulted in death in 1 patient in Study AD5423-302-12. A causal relationship to blonanserin was denied for all of these events.

Table 18. Incidences of "suicide" adverse events (safety analysis set)

	Study D4907002		
	Placebo - blonanserin[a]	Blonanserin - blonanserin[b]	Overall study population
N	36	70	106
All adverse events	0	7 (10.0)	7 (6.6)
Deaths	0	2 (2.9)	2 (1.9)
Serious adverse events other than deaths	0	2 (2.9)	2 (1.9)
Adverse events leading to drug discontinuation	0	3 (4.3)	3 (2.8)
All adverse events			
Intentional self-injury	0	3 (4.3)	3 (2.8)
Completed suicide	0	2 (2.9)	2 (1.9)
Suicidal ideation	0	1 (1.4)	1 (0.9)
Suicide attempt	0	1 (1.4)	1 (0.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- One of the 2 patients reporting completed suicide in Study D4907002 was a [redacted] aged 1[redacted] years, who participated in Study D4907002 in an inpatient setting and experienced dose increases to 16 mg/day by Day 113 due to inadequate response, and committed suicide on Day 145 while on an outing. The investigator determined that the patient had been strongly reluctant to take the scheduled home visit due to a family conflict and had most likely committed suicide in an attempt to avoid the conflict. A causal relationship to blonanserin was therefore denied for the suicide. The other patient was a [redacted] aged 1[redacted] years, who participated in Study D4907002 in an outpatient setting and experienced dose increases to 12 mg/day by Day 89 due to inadequate response, and committed suicide on Day 114. The investigator determined that the patient stopped blonanserin therapy by self-judgment on Day 109, and the suicide was not drug-induced. A causal relationship to blonanserin was therefore denied.

[27] Events categorized into "Suicide/self-injury (SMQ)"

- In Studies D4907001 and D4907002, suicidal ideation was monitored using the Clinical Global Impression of Suicide Severity (CGI-SS). The percent deterioration in CGI-SS[28] at the last assessment (last observation carried forward [LOCF]) in Study D4907001 was 4.3% (2 of 47) of patients in the placebo group, 0% (0 of 51) of patients in the 8 mg/day group, and 1.9% (1 of 52) of patients in the 16 mg/day group, indicating no tendency of the blonanserin groups to have a higher percent deterioration than the placebo group. The percent deterioration in CGI-SS in the overall population of Study D4907002, based on the highest score observed during the 52-week treatment period, was 3.8% (4 of 104) of patients.
- The available post-marketing safety information for blonanserin in Japan includes 46 cases of "suicide" adverse drug reactions (133.8 cases per 100,000 patient-years, including 21 serious cases) collected as post-marketing adverse drug reaction reports.[24] Among these 46 cases, 1 (non-serious) was reported in patients aged ≥12 to ≤18 years. "Suicide" adverse drug reactions were reported in a total of 5 patients through the post-marketing surveillance[25] (the general use-results survey, the general use-result survey [follow-up survey], the specified use-results survey [first episode], and the specified use-results survey [acute exacerbation]). However, all of the reports were from patients aged >18 years, with no reports from patients aged ≤18 years.
- The incidences of "suicide" adverse events associated with other antipsychotics,[29] in foreign clinical studies in pediatric patients with schizophrenia are as follows: In short-term studies (6-week treatment),[30] no completed suicide was reported in patients receiving any antipsychotic, whereas intentional self-injury and suicidal ideation were reported as serious adverse events in 1 patient each, in those receiving quetiapine. In long-term studies (6-month or 2-year treatment), "suicide" adverse events occurred in 9.3% of patients receiving paliperidone (*J Child Adolesc Psychopharmacol*. 2015;25:548-57), in no patients receiving aripiprazole (52-week treatment) (*J Am Acad Child Adolesc Psychiatry*. 2017;56:784-92), and in 4.9% (19 of 390 patients) of patients receiving risperidone (6- or 12-month treatment) (*Child Adolesc Psychiatry Ment Health.* 2012;6:23). Adverse events reported with a ≥10% incidence in patients receiving olanzapine (44-week treatment) included no "suicide" adverse events (*J Am Acad Child Adolesc Psychiatry*. 2010;49:583-94).
- As shown above, the incidences of "suicide" adverse events associated with blonanserin therapy tended to be slightly higher in Study D4907002 than in the clinical studies conducted as part of the clinical development program in adult patients. However, a causal relationship to blonanserin was denied for all of the events reported in Study D4907002, except for non-serious intentional self-injury in 1 patient. In addition, the available post-marketing safety information for blonanserin in Japan has revealed no tendency for patients aged ≤18 years to be at a clearly increased risk of "suicide" adverse events, compared with patients aged >18 years. Further, "suicide" adverse events were also reported at a certain frequency in foreign long-term treatment studies of other antipsychotics in pediatric patients with schizophrenia, and the risk of "suicide" adverse events associated with blonanserin therapy is not particularly higher than that associated with other antipsychotics. The above indicated that blonanserin has not been shown to pose an evident risk of "suicide" adverse events to pediatric patients with schizophrenia aged ≥12 to <18 years. The

[28] The proportion of patients whose suicidality, as compared with baseline, was rated at 6 (much worse) or 7 (very much worse) on the CGI-SS
[29] Paliperidone, aripiprazole, risperidone, olanzapine, quetiapine, and lurasidone
[30] *Biol Psychiatry*. 2011;70:1179-87, *Am J Psychiatry.* 2008;165:1432-41, *J Child Adolesc Psychopharmacol.* 2009;19:611-21, *J Am Acad Child Adolesc Psychiatry*. 2009;48:60-70, *J Child Adolesc Psychopharmacol*. 2012;22:327-42, and *J Child Adolesc Psychopharmacol.* 2017;27:516-25

package insert of blonanserin already includes a cautionary statement that blonanserin may exacerbate symptoms in patients with a history of suicide attempt or with suicidal ideation, in the "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" section. In view of this, along with the above clinical study results, the post-marketing safety information in Japan, and available publications, no further caution through the package insert will be needed.

PMDA's view:

Although a rigorous comparison is difficult, the incidence of "suicide" adverse events in Study D4907002 tended to be slightly higher than that in the clinical studies conducted as part of the clinical development program in adult patients, and completed suicide, for which a causal relationship to blonanserin was denied, was reported in 2 patients in Study D4907002. In view of these facts, the development of "suicide" adverse events should be carefully monitored in pediatric patients aged ≥12 to ≤18 years who are treated with blonanserin for schizophrenia in the same manner as in adult patients. The above applicant's explanation that no further caution through the package insert is needed at present, is acceptable. However, the applicant should continue to carefully observe the incidence of "suicide" adverse events in the post-marketing setting.

7.R.2.5 Weight increased, glucose tolerance abnormal, and lipid metabolism disorder

7.R.2.5.1 Weight increased

PMDA asked the applicant to explain the effects of blonanserin on body weight.

The applicant's explanation:

- Table 19 shows the percentages of patients in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002), by the change from baseline in body weight in Study D4907001. Body weight did not tend to increase in the blonanserin groups compared with the placebo group in Study D4907001, and did not tend to significantly increase due to long-term treatment with blonanserin in Study D4907002.

Table 19. Percentages of patients by the change from baseline in body weight in Study D4907001 to the last assessment (LOCF) (safety analysis set)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
≥7% increase	1 (2.1)	2 (4.0)	2 (3.8)	11 (30.6)	20 (28.6)	31 (29.2)
>0%-<7% increase	25 (53.2)	23 (46.0)	20 (38.5)	12 (33.3)	30 (42.9)	42 (39.6)
0%	1 (2.1)	0	2 (3.8)	0	0	0
>0%-<7% decrease	17 (36.2)	23 (46.0)	25 (48.1	11 (30.6)	16 (22.9)	27 (25.5)
≥7% decrease	3 (6.4)	2 (4.0)	3 (5.8)	2 (5.6)	4 (5.7)	6 (5.7)

n (%)

a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002

b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- Table 20 shows the incidence of "weight increased" adverse events[31] in Studies D4907001 and D4907002. The incidence of such adverse events did not tend to increase in the blonanserin groups compared with the placebo group in Study D4907001, and no "weight increased" adverse events were serious or led to drug discontinuation in either Study D4907001 or D4907002.

Table 20. Incidences of "weight increased" adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	1 (2.1)	2 (3.9)	0	6 (16.7)	12 (17.1)	18 (17.0)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	0	0	0	0
Major adverse events						
Weight increased	0	2 (3.9)	0	4 (11.1)	11 (15.7)	15 (14.2)
Increased appetite	1 (2.1)	0	0	2 (5.6)	0	2 (1.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 294 cases of "weight increased" adverse drug reactions (855.0 cases per 100,000 patient-years, including 2 serious cases) collected as post-marketing adverse drug reaction reports.[24)] Among these 294 cases, 11 (including 0 serious cases) were reported in patients aged ≥12 to ≤18 years, including 9 cases of weight increased, 1 case of obesity, and 1 case of increased appetite. The incidence of "weight increased" adverse drug reactions in patients aged ≥12 to ≤18 years did not tend to largely differ from that in patients aged >18 years. The incidences of "weight increased" adverse drug reactions collected through the post-marketing surveillance[25)] were 1.3% (1 of 79) of patients aged ≤18 years and 0.7% (20 of 3,051) of patients aged >18 years in the general use-results survey, 6.3% (2 of 32) and 1.4% (18 of 1,279) of patients in the general use-result survey (follow-up survey), 0% (0 of 19) and 0% (0 of 133) of patients in the specified use-results survey (first episode), and 0% (0 of 5) and 0.5% (6 of 1,139) of patients in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus tended to have no clearly higher incidence of "weight increased" adverse drug reactions than those aged >18 years.
- The package insert of blonanserin already includes cautionary statement regarding the development of "weight increased" adverse events. In view of the above clinical study results and post-marketing safety information in Japan, and because no new concerns have been identified in pediatric patients aged ≥12 to ≤18 years who received blonanserin for schizophrenia, no further caution through the package insert will be needed.

7.R.2.5.2 Glucose tolerance abnormal

PMDA asked the applicant to explain the incidence of "glucose tolerance abnormal" adverse events associated with blonanserin therapy.

[31)] Events coded to the following MedDRA PTs: Binge eating, body mass index increased, eating disorder, fat tissue increased, compulsive hoarding, hunger, hyperphagia, increased appetite, obesity, overweight, weight increased, weight fluctuation, weight loss poor, weight control, metabolic syndrome, body fat disorder, food craving, metabolic disorder, appetite disorder, eating disorder symptom, waist circumference increased, and central obesity

The applicant's explanation:

- In both the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002), all of the patients had blood glucose levels within the normal range at baseline and had no abnormally low (<65 mg/dL) or high (≥126 mg/dL) levels. In addition, after the start of the study treatment, most of the patients had neither abnormally low nor high levels of blood glucose, with the exception of 1 patient in the 8 mg/day group of Study D4907001, who had an abnormally low level.
- Table 21 shows the incidence of "glucose tolerance abnormal" adverse events[32)] in Studies D4907001 and D4907002. The incidence of such adverse events did not tend to increase in the blonanserin groups, compared with the placebo group in Study D4907001, and no "glucose tolerance abnormal" adverse events were serious or led to drug discontinuation in either Study D4907001 or Study D4907002.

Table 21. Incidences of "glucose tolerance abnormal" adverse events (safety analysis sets)

	Study D4907001[a)]			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	3 (6.4)	4 (7.8)	2 (3.8)	6 (16.7)	13 (18.6)	19 (17.9)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	0	0	0	0
Major adverse events						
Thirst	1 (2.1)	1 (2.0)	1 (1.9)	0	1 (1.4)	1 (0.9)
Dehydration	0	0	1 (1.9)	0	2 (2.9)	2 (1.9)
Weight increased	0	2 (3.9)	0	4 (11.1)	11 (15.7)	15 (14.2)
Hypertriglyceridaemia	0	1 (2.0)	0	0	0	0

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 750 cases of "glucose tolerance abnormal" adverse drug reactions (2,181.1 cases per 100,000 person-years, including 36 serious reactions), collected as post-marketing adverse drug reaction reports.[24)] Of these 750 cases, 14 (including 0 serious cases) were reported in patients aged ≥12 to ≤18 years, including 9 cases of weight increased, and 1 case each of obesity, increased appetite, blood triglycerides increased, polydipsia, and thirst. The incidence of "glucose tolerance abnormal" adverse drug reactions in patients aged ≥12 to ≤18 years did not tend to clearly differ from that in patients aged >18 years. The incidences of "glucose tolerance abnormal" adverse drug reactions collected through the post-marketing surveillance[25)] were 3.8% (3 of 79) of patients aged ≤18 years and 3.1% (94 of 3,051) of patients aged >18 years in the general use-results survey, 9.4% (3 of 32) of patients and 5.1% (65 of 1,279) of patients in the general use-result survey (follow-up survey), 0% (0 of 19) of patients and 0.8% (1 of 133) of patients in the specified use-results survey (first episode), and 0% (0 of 5) of patients and 1.3% (15 of 1,139) of patients in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus had no tendency toward a clearly higher incidence of "glucose tolerance abnormal" adverse drug reactions than those aged >18 years.

[32)] Events categorized into the MedDRA "hyperglycaemia/new onset diabetes mellitus (SMQ)"

- The package insert of blonanserin already includes cautionary statement regarding the development of "glucose tolerance abnormal" adverse events. In view of the above clinical study results and post-marketing safety information in Japan, and because no new concerns have been identified in pediatric patients aged ≥12 to ≤18 years who received blonanserin for schizophrenia, no further caution through the package insert will be needed.

7.R.2.5.3 Lipid metabolism disorder

PMDA asked the applicant to explain the incidence of "lipid metabolism disorder" adverse events associated with blonanserin therapy.

The applicant's explanation:

- Table 22 shows the incidences of "lipid metabolism disorder" adverse events[33] in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). In Study D4907001, the incidence of these adverse events did not tend to increase in each blonanserin group, compared with the placebo group, and none of the events were serious or led to drug discontinuation in either Study D4907001 or Study D4907002.

Table 22. Incidences of "lipid metabolism disorder" adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	0	2 (3.9)	0	0	4 (5.7)	4 (3.8)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	0	0	0	0
Major adverse events						
Dyslipidaemia	0	1 (2.0)	0	0	1 (1.4)	1 (0.9)
Hypertriglyceridaemia	0	1 (2.0)	0	0	0	0
Hyperlipidaemia	0	0	0	0	2 (2.9)	2 (1.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 121 cases of "lipid metabolism disorder" adverse drug reactions (351.9 cases per 100,000 patient-years, including 1 serious case), collected as post-marketing adverse drug reaction reports.[24)] Of these 121 cases, only 1 case of blood triglycerides increased (non-serious) was reported in patients aged ≥12 to ≤18 years. The incidences of "lipid metabolism disorder" adverse drug reactions collected through the post-marketing surveillance[25)] were 1.3% (1 of 79) of patients aged ≤18 years and 2.0% (62 of 3,051) of patients aged >18 years in the general use-results survey, 3.1% (1 of 32) and 3.6% (46 of 1,279) of patients in the general use-result survey (follow-up survey), 0% (0 of 19) and 1.5% (2 of 133) of patients in the specified use-results survey (first episode), and 0% (0 of 5) and 0.4% (4 of 1,139) of patients in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus tended to have no tendency toward a clearly higher incidence of "lipid metabolism disorder" adverse drug reactions than those aged >18 years.

[33)] Events categorized into the following MedDRA High Level Group Terms (HLGTs): "Lipid metabolism disorders" and "lipid analyses"

- The package insert of blonanserin already includes cautionary statement regarding the development of "lipid metabolism disorder" adverse events. In view of the above clinical study results and post-marketing safety information in Japan, and because no new concerns have been identified in pediatric patients aged ≥12 to ≤18 years who received blonanserin for schizophrenia, no further caution through the package insert will be needed.

PMDA's view:

In view of the applicant's explanations in Sections 7.R.2.5.1 to 7.R.2.5.3, no safety problems requiring new cautionary statement have been identified in children aged ≥12 to ≤18 years who are treated with blonanserin for schizophrenia in the clinical studies. The applicant's explanations are thus acceptable.

7.R.2.6 Failure to thrive

PMDA asked the applicant to explain the potential for failure to thrive associated with blonanserin therapy.

The applicant's explanation:

- Table 23 shows the change in height and body weight percentiles, which were calculated using the standard data in general Japanese children (School Health Statistics Research FY2017, the Ministry of Education, Culture, Sports, Science and Technology), in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). The changes in height and body weight in pediatric patients enrolled in the clinical studies did not largely differ from the average changes in general Japanese children.

Table 23. Height and body weight percentiles in pediatric patients in Studies D4907001 and D4907002, relative to the standard values in general Japanese children (safety analysis sets)

		Treatment assigned in Study D4907001	n	Percentile	
				Baseline[a)]	Last assessment[b)]
Height	<15 years	Placebo	9	66.8 ± 32.98	74.5 ± 32.05
		Blonanserin	21	55.4 ± 27.71	62.8 ± 28.54
		Overall study population	30	58.9 ± 29.29	66.3 ± 29.58
	≥15 years	Placebo	27	48.4 ± 29.60	51.3 ± 30.49
		Blonanserin	49	55.5 ± 29.76	56.8 ± 30.05
		Overall study population	76	53.0 ± 29.71	54.9 ± 30.12
Body weight	<15 years	Placebo	9	64.2 ± 24.57	75.7 ± 26.98
		Blonanserin	21	68.4 ± 24.58	78.3 ± 19.17
		Overall study population	30	67.2 ± 24.23	77.5 ± 21.35
	≥15 years	Placebo	27	42.4 ± 28.04	47.7 ± 29.90
		Blonanserin	49	59.3 ± 34.83	61.9 ± 34.13
		Overall study population	76	53.3 ± 33.40	56.9 ± 33.20

Mean ± standard deviation
a) Baseline in Study D4907001
b) LOCF

- Table 24 shows the incidences of "failure to thrive" adverse events[34)] in Studies D4907001 and D4907002. The incidence of these adverse events did not tend to increase in the blonanserin groups, compared with the placebo group in Study D4907001, and no "failure to thrive" adverse events were serious or led to drug discontinuation in either Study D4907001 or Study D4907002.

Table 24. Incidences of "failure to thrive" adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	1 (2.1)	2 (3.9)	0	4 (11.1)	11 (15.7)	15 (14.2)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	0	0	0	0
All adverse events						
Weight increased	0	2 (3.9)	0	4 (11.1)	11 (15.7)	15 (14.2)
Weight decreased	1 (2.1)	0	0	1 (2.8)	0	1 (0.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- In view of the above clinical study results, no particular concerns regarding the development of "failure to thrive" adverse events associated with blonanserin therapy have been identified in pediatric patients aged ≥12 to ≤18 years. Therefore, no further caution through the package insert will be needed.

PMDA's view:

Given the number of patients assessed in Studies D4907001 and D4907002, and the individual variation in normal growth or development in the age range from ≥12 to ≤18 years, a rigorous evaluation of the risk of "failure to thrive" adverse events associated with blonanserin therapy is difficult. However, the submitted clinical study results showed no marked deviations from the standard height or body weight values, or the development of clinically relevant adverse events. The applicant's explanation that no additional caution through the package insert is needed at present, is thus acceptable.

7.R.2.7 Hyperprolactinaemia

PMDA asked the applicant to explain the incidence of "prolactin" adverse events associated with blonanserin therapy.

[34)] Events coded to the following MedDRA PTs: Abnormal loss of weight, abnormal weight gain, blood growth hormone abnormal, blood growth hormone decreased, blood growth hormone increased, body mass index decreased, body mass index increased, developmental delay, dwarfism, epiphyses delayed fusion, epiphyses premature fusion, growth disorder, growth accelerated, growth hormone-producing pituitary tumour, overweight, weight decreased, weight gain poor, weight increased, underweight, weight fluctuation, weight loss poor, growth retardation, growth hormone deficiency, body height above normal, body height below normal, body height decreased, body height increased, weight abnormal, body height abnormal, and blood growth hormone releasing hormone increased

The applicant's explanation:

- Table 25 shows the change from baseline in blood prolactin level[35)] and the percentages of patients with an abnormally high level of blood prolactin[36)] in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002). In Study D4907001, the change from baseline in blood prolactin level in female patients tended to increase in a dose-dependent manner. In Study D4907002, many male and female patients had abnormally high levels of blood prolactin.

Table 25. Change from baseline in blood prolactin level and percentages of patients with an abnormally high level of blood prolactin (safety analysis sets)

		Study D4907001			Study D4907002		
		Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
Male	Baseline[c)]	17.1 ± 22.55 (20)	22.2 ± 18.75 (20)	30.0 ± 29.20 (23)	13.3 ± 9.37 (14)	29.6 ± 26.43 (31)	24.6 ± 23.68 (45)
	Last assessment (LOCF)	11.1 ± 4.16 (20)	21.7 ± 12.59 (21)	24.7 ± 13.47 (23)	21.4 ± 16.94 (14)	19.8 ± 15.55 (30)	20.3 ± 15.82 (44)
	Change from baseline	-6.0 ± 23.27	-0.4 ± 17.80	-5.3 ± 36.57	8.1 ± 20.56	-10.2 ± 31.28	-4.4 ± 29.37
	Patients with an abnormally high level[d)]	7 (35.0)	18 (85.7)	21 (91.3)	14 (100.0)	27 (90.0)	41 (93.2)
Female	Baseline[c)]	30.9 ± 33.59 (27)	34.8 ± 37.04 (29)	35.4 ± 34.38 (29)	35.3 ± 35.77 (22)	29.8 ± 29.04 (38)	31.9 ± 31.48 (60)
	Last assessment (LOCF)	21.5 ± 15.17 (27)	29.5 ± 16.80 (28)	44.2 ± 27.14 (30)	24.7 ± 17.00 (22)	28.2 ± 23.67 (38)	26.9 ± 19.97 (60)
	Change from baseline	-9.4 ± 36.25	0.6 ± 28.65	8.2 ± 47.39	-10.6 ± 37.73	-1.6 ± 36.6[e)]	-4.9 ± 36.94[f)]
	Patients with an abnormally high level[d)]	7 (25.9)	19 (67.9)	20 (66.7)	17 (77.3)	30 (78.9)	47 (78.3)

Mean ± standard deviation (ng/mL) (N)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002
c) Baseline in Study D4907001
d) n (%)
e) n = 37
f) n = 59

- Table 26 shows the incidences of "prolactin" adverse events[37)] in Studies D4907001 and D4907002. Although the incidence of such adverse events tended to increase in a dose-dependent manner in the blonanserin groups of Study D4907001, no "prolactin" adverse events were serious or severe in either Study D4907001 or Study D4907002. One patient in the 16 mg/day group of Study D4907001 discontinued the study treatment due to blood prolactin increased. No patients reported sexual maturation-related adverse events, such as delayed menstruation or delayed puberty, indicating the presence of no evident effects on sexual maturation due to the increase in prolactin level.

35) The serum prolactin analysis instrument used in Study D4907001 was faulty and did not dispense the desired amount of samples. Accordingly, the measured plasma serum prolactin levels in some samples might be lower than the true levels. For this reason, 9 measured levels that might be lower than the true levels were excluded from the analysis. However, an analysis not excluding the 9 measured levels was also performed. The descriptions in the Review Report (1) are based on the results from the analysis that excluded the 9 measured levels.

36) Values beyond the upper limit of normal (13.69 ng/mL for men, 29.32 ng/mL for women)

37) Events coded to the following MedDRA PTs: amenorrhoea, anorgasmia, blood prolactin, blood prolactin abnormal, blood prolactin increased, breast discharge, breast enlargement, breast pain, breast swelling, breast tenderness, ejaculation disorder, galactorrhoea, gynaecomastia, hirsutism, hyperprolactinaemia, hypomenorrhoea, libido decreased, loss of libido, menstrual disorder, menstruation delayed, menstruation irregular, metrorrhagia, oligomenorrhoea, orgasm abnormal, prolactin-producing pituitary tumour, sexual dysfunction, orgasmic sensation decreased, female sexual dysfunction, male sexual dysfunction, libido disorder, erectile dysfunction, amenorrhoea-galactorrhoea syndrome

Table 26. Incidences of "prolactin" adverse events (safety analysis sets)

	Study D4907001			Study D4907002		
	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Placebo - blonanserin[a)]	Blonanserin - blonanserin[b)]	Overall study population
N	47	51	53	36	70	106
All adverse events	2 (4.3)	8 (15.7)	17 (32.1)	9 (25.0)	15 (21.4)	24 (22.6)
Serious adverse events	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	0	1 (1.9)	0	0	0
Major adverse events						
Hyperprolactinaemia	1 (2.1)	5 (9.8)	9 (17.0)	4 (11.1)	6 (8.6)	10 (9.4)
Blood prolactin increased	1 (2.1)	3 (5.9)	7 (13.2)	4 (11.1)	6 (8.6)	10 (9.4)
Galactorrhoea	0	0	1 (1.9)	0	1 (1.4)	1 (0.9)
Menstruation irregular	0	0	0	1 (2.8)	1 (1.4)	2 (1.9)

n (%)
a) Patients who were assigned to placebo in Study D4907001 and then enrolled in Study D4907002
b) Patients who were assigned to blonanserin in Study D4907001 and then enrolled in Study D4907002

- The available post-marketing safety information for blonanserin in Japan includes 1,252 cases of "prolactin" adverse drug reactions (3,641.0 cases per 100,000 person-years, including 9 serious cases), collected as post-marketing adverse drug reaction reports.[24)] Of these 1,252 cases, 60 (including 1 serious case) were reported in patients aged ≥12 to ≤18 years. Major adverse drug reactions reported in this patient population included 18 cases of blood prolactin increased (including 0 serious cases), 16 cases of galactorrhoea (including 0 serious cases), 10 cases of hyperprolactinaemia (including 0 serious cases), and 8 cases of menstruation irregular (including 1 serious case). The incidence of "prolactin" adverse drug reactions in patients aged ≥12 to ≤18 years did not tend to largely differ from that in patients aged >18 years. The incidences of "prolactin" adverse drug reactions collected through the post-marketing surveillance[25)] were 7.6% (6 of 79) of patients aged ≤18 years and 3.4% (104 of 3,051) of patients aged >18 years in the general use-results survey, 9.4% (3 of 32) and 5.6% (71 of 1,279) of patients in the general use-result survey (follow-up survey), 0% (0 of 19) and 0.8% (1 of 133) of patients in the specified use-results survey (first episode), and 0% (0 of 5) of patients and 2.1% (24 of 1,139) of patients in the specified use-results survey (acute exacerbation). Patients aged ≥12 to ≤18 years thus tended to have no clearly higher incidence of "prolactin" adverse drug reactions than those aged >18 years.
- In a foreign long-term treatment (6 or 12 months) study of risperidone in pediatric patients with schizophrenia, the development of sexual maturation as well as the progression from baseline in Tanner stage were observed in both boys and girls (*Child Adolesc Psychiatry Ment Health.* 2012;6:23). In a long-term (2-year) treatment study of paliperidone in pediatric patients with schizophrenia, Tanner stage increased from <4 at baseline to 4 or 5 at the end of the study in patients aged 12 or 13 years, suggesting that the patients had normal sexual maturation *(J Child Adolesc Psychopharmacol.* 2015;25:548-57). A pooled analysis of 5 foreign clinical studies in which patients aged 5 to 15 years with disruptive behavioral disorder received risperidone for 1 year revealed that the transient increase in blood prolactin level did not affect sexual maturation, indicating no correlation between blood prolactin level and sexual maturation (*Am J Psychiatry.* 2004;161:918-20).
- Similarly, although the results of the clinical studies and available post-marketing safety information for blonanserin in Japan have shown that blonanserin increases blood prolactin in children as well as adults, the results from Studies D4907001 and D4907002 revealed neither serious or severe "prolactin" adverse

events, nor sexual maturation-related adverse events such as delayed menstruation and delayed puberty. In addition, publications regarding other antipsychotics have suggested that long-term antipsychotic therapy and the resulting increase in blood prolactin level are unlikely to have clinically significant effects on sexual maturation. The package insert of blonanserin already includes cautionary statement regarding the development of "prolactin" adverse events. In view of this, as well as the above clinical study results, the available post-marketing safety information for blonanserin in Japan and in the published literature, and because no clinically significant effects of blonanserin have been identified in pediatric patients aged ≥12 to ≤18 years who receive blonanserin for schizophrenia, no further caution through the package insert will be needed.

PMDA's view:
In light of the mechanisms of action of blonanserin, an increase in blood prolactin level is expected, and the results of Studies D4907001 and D4907002, in fact, showed that a high proportion of patients had an abnormally high level of blood prolactin. However, these studies reported neither serious or severe "prolactin" adverse events, nor sexual maturation-related adverse events such as delayed menstruation and delayed puberty. In addition, the available post-marketing safety information for blonanserin in Japan has shown no tendency for patients ≤18 years to have a clearly higher incidence of "prolactin" adverse events than those aged <18 years. In view of these results, the increase in blood prolactin level is unlikely to become a clinical concern in pediatric patients aged ≥12 to ≤18 years with schizophrenia treated with blonanserin. The applicant's explanation that no further caution through the package insert is needed at present, is thus acceptable.

As a result of the discussions presented in Sections 7.R.2.1 to 7.R.2.7, no clear differences in the safety profile of blonanserin have been identified between children and adults, and no new safety risks associated with blonanserin therapy for pediatric patients with schizophrenia have been suggested. Therefore, PMDA has concluded that the safety of blonanserin in pediatric patients with schizophrenia is acceptable, based on the assumption that blonanserin is administered properly, while following cautions similar to those for adults.

The PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

7.R.3 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of blonanserin.

The applicant's explanation:

- The patient survey in Japan (Patient Survey by Ministry of Health, Labour and Welfare, 2017) estimates that 1,000 children at an age of 10 to 14 years, and 7,000 children at an age of 15 to 19 years are diagnosed with "schizophrenia, schizotypal, and delusional disorders." The development of schizophrenia gradually increases beyond the age of 15 years, and peaks between the age of 18 and 29 years. Patients who have schizophrenia before the age of 18 years suffer from severe symptoms later, and have more severe cognitive deficits than those with late-onset schizophrenia (*Br J Psychiatry*. 2009;195:286-93).

- In the US and the EU, several drugs, including risperidone, quetiapine, aripiprazole, and olanzapine, are approved for the treatment of schizophrenia in children. The basic approach for the treatment of schizophrenia in children recommended by the guidelines of the American Academy of Child and Adolescent Psychiatry (AACAP) committee is antipsychotic medications combined with psychosocial interventions (*J Am Acad Child Adolesc Psychiatry*. 2013;52:976-90). In addition, the National Institute for Health and Care Excellence (NICE) guideline "Psychosis in Children and Young People"[38] recommends antipsychotic medications in conjunction with psychosocial interventions.
- In Japan, no drugs have been approved for the treatment of schizophrenia in children, and no systematic treatment algorithm has been established for patients with schizophrenia aged <20 years. Accordingly, pediatric patients are treated based on the experience or discretion of individual physicians ("The Guidelines for Pharmacological Treatment of Mental Disorders in Childhood and Adolescence," Jiho Inc.: 2018. pp. 40-49). Even under such circumstances, treatments for pediatric patients with schizophrenia should include antipsychotic medications in combination with psychosocial interventions such as psychoeducation, supportive psychotherapy, and social and educational programs (*Japanese Journal of Clinical Medicine.* 2013;71:701-5), and pediatric patients with a first episode of schizophrenia should be treated primarily with psychosocial interventions, and start treatment with atypical antipsychotics as early as possible (*Jpn. J. Child Adolesc. Psychiatr*. 2019; 60: 92-6).
- The use of antipsychotics in pediatric patients is associated with increased risks of extrapyramidal symptoms, sedation, weight increased, and metabolic adverse drug reactions, compared with adult patients (*J Clin Psychiatry*. 2011;72:655-70). The AACAP guidelines recommend that the risks of obesity or metabolic adverse drug reactions should be considered in antipsychotic therapy for children and adolescents with schizophrenia spectrum disorder, and that the use of antipsychotics that are associated with a risk for weight gain as a first-line treatment for children and adolescents with schizophrenia should be limited (*J Am Acad Child Adolesc Psychiatry*. 2013;52:976-90).
- Blonanserin, an atypical antipsychotic that exerts its antagonistic effects against dopamine D_2 receptors, dopamine D_3 receptors, and serotonin 5-HT_{2A} receptors, has efficacy comparable to that of other antipsychotics and favorable tolerability, as demonstrated by a systematic review and the results of a meta-analysis (*J Psychiatr Res.* 2013;47:149-54). Among the antipsychotics approved in Japan, blonanserin has the lowest risk of weight change, and the second lowest risks of somnolence, drowsiness, and sedation (*Neuropsychiatr Dis Treat.* 2017;13:1281-302).
- The results of the primary endpoint, etc. in the Japanese phase III study (CTD 5.3.5.1.01, Study D4907001) demonstrated the efficacy of blonanserin in the treatment of schizophrenia in children [see Sections 7.1.1 and 7.R.1], and the results from Study D4907001 and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) demonstrated no trend that the safety profile of blonanserin in pediatric patients clearly differs from that in adult patients [see Section 7.R.2].
- Similarly, the published literature regarding the treatment of schizophrenia in children and the clinical study results have indicated that blonanserin will be the first-line pharmacotherapy for pediatric patients with schizophrenia.

[38] https://www.nice.org.uk/guidance/cg155 (last accessed on December 17, 2020)

PMDA's view:

In view of the submitted clinical study results and other available findings, blonanserin will be a treatment option for pediatric patients with schizophrenia. The PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

7.R.4 Indication

7.R.4.1 Schizophrenia as the indication

PMDA's view:

The present application is intended for a new dosage for pediatric patients with schizophrenia. On the basis of the discussions presented in Sections 7.R.1 to 7.R.3, PMDA concluded that there is no particular problem with the indication of blonanserin being schizophrenia.

7.R.4.2 Age of the intended patient population of blonanserin

PMDA asked the applicant to explain the age of the intended patient population of blonanserin therapy.

The applicant's explanation:

- At the time the phase III study (CTD 5.3.5.1.01, Study D4907001) was being planned, the appropriate target study population was considered to be patients who are in junior high school or high school, and the study was to target patients aged ≥13 to ≤18 years, based on the following: (a) The Patient Survey in Japan (Patient Survey by Ministry of Health, Labour and Welfare, 2008) revealed that the onset of schizophrenia is usually at an age of ≥10 years, and (b) the Guidance on Clinical studies on Drugs in Pediatric Populations (PMSB/ELD Notification No. 1334, issued by Director of Evaluation and Licensing Division, Pharmaceuticals and Medical Safety Bureau, Ministry of Health and Welfare, dated December 15, 2000) defines adolescents as individuals aged from 12 to 16 or 18 years. Subsequently, the use-results survey for blonanserin revealed that blonanserin had been administered to patients aged ≥12 years, and despite a small number of patients, that patients aged 12 years had a duration and frequency of schizophrenia similar to those in patients aged ≥13 to ≤18 years, and had no unbalanced disease types. However, definite diagnoses are expected to be difficult in patients aged <12 years, as a result of poor information regarding the course of symptoms from the onset. Taken together, the lower age limit of the target patient population of Study D4907001 was changed from 13 years to 12 years of age.[5)]
- The primary endpoint results, etc. from Study D4907001, in pediatric patients with schizophrenia aged ≥12 to ≤18 years, successfully demonstrated the efficacy of blonanserin in the treatment of schizophrenia in children [see Sections 7.1.1 and 7.R.1], and the results from Study D4907001 and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) showed no evident tendency of blonanserin to have a safety profile in children different from that in adults [see Section 7.R.2].
- The basic approach for the treatment of schizophrenia in children recommended by the AACAP guidelines is antipsychotic medications combined with psychosocial interventions, just as in adults (*J Am Acad Child Adolesc Psychiatry* 2013; 52: 976-90). Childhood-onset schizophrenia is recommended to be treated with antipsychotic medications combined with non-medication interventions (*Child Adolesc Psychiatr Clin N*

Am 2020;29:71-90). In addition, the long-term prognosis of schizophrenia is improved by appropriate intervention provided early after the onset. Accordingly, earlier intervention is essential (*Jpn. J. Child Adolesc. Psychiatr.* 2017;58:64-9, *Jpn. J. Child Adolesc. Psychiatr.* 2019;60:92-6).

- As shown in Table 27, the post-marketing adverse reaction reports for blonanserin in Japan[24)] include 17 cases of adverse events in 16 patients with schizophrenia aged <12 years. Of these 17 cases, 1 case of iron deficiency anaemia was serious, while the remaining cases were non-serious. A total of 13 cases of adverse drug reactions were reported in 13 patients aged <12 years, all of which were known adverse events of blonanserin.

Table 27. Adverse events reported from patients aged <12 years in the post-marketing setting

Age (years)	Sex	Therapeutic indication	Daily dose	Adverse events	Causal relationship to blonanserin	Serious/non-serious
6	Male	Unknown	Unknown	Salivary hypersecretion	Related	Non-serious
7	Male	Tic disorder	6 mg	Somnolence	Related	Non-serious
8	Unknown	Tic	8 mg	Somnolence	Related	Non-serious
10	Male	Tic disorder	4 mg	Pruritus	Related	Non-serious
10	Male	Tic syndrome	10 mg	Dysphagia	Related	Non-serious
10	Female	Schizophrenia	16 mg	Akathisia	Related	Non-serious
10	Male	Unknown	Unknown	Rash	Related	Non-serious
10	Male	Tic symptoms	6 mg	Somnolence	Related	Non-serious
10	Male	Tic symptoms	8 mg	Somnolence	Related	Non-serious
10	Female	Schizophrenia	24 mg	Hallucination, auditory	Related	Non-serious
10	Female	Schizophrenia	16 mg[a)]	Limb discomfort	Related	Non-serious
10	Female	Schizophrenia	16 mg	Somnolence	Related	Non-serious
10	Male	Unknown	Unknown	Iron deficiency anaemia	Unrelated	Serious
10	Male	Unknown	6 mg[b)]	Dermatitis	Unrelated	Non-serious
11	Male	Unknown[c)]	Unknown	Vomiting/emetophobia	Unrelated	Non-serious
11	Male	Schizophrenia	4 mg	Headache	Related	Non-serious

a) The patient also received blonanserin, at a dose of 8 mg/day.
b) The patient also received blonanserin, at a dose of 4 or 8 mg/day.
c) The patient had autism spectrum disorder and obsessive-compulsive disorder as complications

- As above, Studies D4907001 and D4907002 enrolled pediatric patients with schizophrenia aged ≥12 years, and neither the efficacy nor safety of blonanserin was evaluated in patients aged <12 years in these studies. However, early interventions, including antipsychotic medications are recommended for pediatric patients with schizophrenia, regardless of age of onset. Antipsychotic therapy should therefore be considered, even for children aged <12 years, if they have been definitively diagnosed with schizophrenia. Further, despite a small number of patients, the available post-marketing safety information for blonanserin in Japan has revealed no substantial safety differences between patients aged 10 or 11 years and those aged ≥12 years. Taken together, the "PRECAUTIONS CONCERNING INDICATIONS" section of the package insert should include a cautionary statement that blonanserin should be used, in principle, in patients with an age of ≥12 years.

PMDA's view:

- Regarding the age of the target patient population of Study D4907001, which was set at ≥12 to ≤18 years, the applicant's explanation that a definitive diagnosis of schizophrenia may be difficult in patients aged <12 years is understandable. Therefore, there are no particular problems with the lower age limit of the target patient population of Study D4907001, set at 12 years old.

- Similarly, Studies D4907001 and D4907002 enrolled pediatric patients with schizophrenia aged ≥12 years, because a definitive diagnosis of the disease is difficult in children aged <12 years and for other reasons, and the studies demonstrated the efficacy and safety of blonanserin in patients aged ≥12 years. In view of this, blonanserin should be intended for patients with schizophrenia aged ≥12 years, in principle.
- Meanwhile, PMDA understands the applicant's explanation that antipsychotic therapy should be considered even for children aged <12 years, if they have been definitively diagnosed with schizophrenia because antipsychotic medications and non-medication treatments are recommended regardless of age of onset, and early intervention is essential for pediatric patients with schizophrenia.
- In view of the above, the applicant's explanation that a cautionary statement regarding the age of the intended patient population will be included in the "PRECAUTIONS CONCERNING INDICATIONS" section of the package insert is acceptable.
- The PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Starting dose and dosage adjustment

PMDA asked the applicant to explain the rationale for the starting dose and dosage adjustment to achieve the maintenance dose in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) in pediatric patients with schizophrenia, and then to explain the appropriateness of the proposed starting dose and dosage adjustment of blonanserin in children.

The applicant's explanation:

- Since pediatric patients with schizophrenia have been reported to be vulnerable to major adverse events associated with antipsychotic therapy, such as weight gain and metabolic problems, compared with adult patients (*Schizophr Bull.* 2008;34:60-71), the starting dose was set to 4 mg/day twice daily, which is half of the minimum adult maintenance dose in both Studies D4907001 and D4907002, taking into account the safety of the patients.
- In Study D4907001, the dose of blonanserin was to be started at 4 mg/day, and then increased to 8 mg/day after 1 week, which was further increased to 16 mg/day after another 1 week in the 16 mg/day group, for the following reasons: (a) A dose escalation within a short time might lead to the development of adverse events or drug discontinuation, and (b) in a phase III study in patients with schizophrenia conducted as part of the clinical development program in adult patients (CTD 5.3.5.1-2 for the initial approval, Study AD5423-308-17), the dose was adjusted at each assessment timepoint (at Weeks 1, 2, 3, 4, and 6) as a general rule. In Study D4907002, the dose was adjusted in increments or decrements of ≤8 mg/day, and the dose was maintained for ≥1 week after each dose increase or decrease, while taking into account the safety of the patients.
- Table 28 shows the incidences of adverse events by the timing of first onset in Study D4907001. The incidence of akathisia tended to increase when the dose was increased, and more patients experienced somnolence on Days 1 to 7 or Days 15 to 28 in the 8 mg/day group, and on Days 1 to 7 or Days 8 to 14 in the 16 mg/day group. However, serious adverse events or adverse events leading to drug discontinuation

did not tend to occur at particular times in the study treatment period, indicating that no safety concerns characteristic to dose escalation period were observed.

Table 28. Incidences of adverse events by the timing of first onset (Study D4907001, safety analysis set)

	Placebo				Blonanserin 8 mg/day				Blonanserin 16 mg/day			
Timing of first onset	Days 1 to 7	Days 8 to 14	Days 15 to 28	Days 29 to 42	Days 1 to 7	Days 8 to 14	Days 15 to 28	Days 29 to 42	Days 1 to 7	Days 8 to 14	Days 15 to 28	Days 29 to 42
N	47	46	45	41	51	49	46	39	53	50	47	39
All adverse events	10 (21.3)	6 (13.0)	5 (11.1)	3 (7.3)	13 (25.5)	16 (32.7)	4 (8.7)	2 (5.1)	13 (24.5)	15 (30.0)	16 (34.0)	3 (7.7)
Serious adverse events	0	1 (2.2)	0	0	1 (2.0)	0	0	0	0	0	0	0
Adverse events leading to drug discontinuation	0	1 (2.2)	1 (2.2)	1 (2.4)	1 (2.0)	2 (4.1)	2 (4.3)	0	2 (3.8)	2 (4.0)	2 (4.3)	0
Major adverse events												
Akathisia	1 (2.1)	1 (2.2)	0	0	2 (3.9)	3 (6.1)	2 (4.3)	0	1 (1.9)	4 (8.0)	11 (23.4)	1 (2.6)
Nausea	0	2 (4.3)	1 (2.2)	1 (2.4)	0	2 (4.1)	2 (4.3)	0	0	0	4 (8.5)	0
Dystonia	0	0	0	0	0	1 (2.0)	0	0	1 (1.9)	1 (2.0)	4 (8.5)	1 (2.6)
Hyperprolactinaemia	1 (2.1)	0	0	0	0	5 (10.2)	0	0	1 (1.9)	7 (14.0)	1 (2.1)	0
Blood prolactin increased	0	0	0	1 (2.4)	0	3 (6.1)	0	0	0	4 (8.0)	3 (6.4)	0
Somnolence	1 (2.1)	0	0	0	5 (9.8)	0	2 (4.3)	0	3 (5.7)	6 (12.0)	0	0
Salivary hypersecretion	0	0	0	0	0	0	0	0	0	1 (2.0)	3 (6.4)	0
Tremor	0	0	0	0	2 (3.9)	1 (2.0)	2 (4.3)	0	0	1 (2.0)	3 (6.4)	1 (2.6)

n (%)

- In Study D4907001, 1 patient in the 16 mg/day group underwent a dose increase at an interval of <1 week. Among patients who were assigned to placebo in Study D4907001 and entered in Study D4907002, only 3 patients underwent a dose increase to 8 mg/day or 16 mg/day at an interval of <1 week, and other patients underwent dose increases at intervals of ≥1 week.
- The above findings indicated that it is appropriate to start blonanserin therapy for pediatric patients with schizophrenia at a dose of 4 mg/day. In Studies D4907001 and D4907002, few patients underwent dose increases to the maintenance dose at intervals of <1 week. Therefore, the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the package insert will include a cautionary statement that the dose of blonanserin should be increased at intervals of ≥1 week, in principle. In Study D4907002, the dose increment was set to be ≤8 mg/day, considering the efficacy and patient safety. Consequently, no major safety problems with continuation of the study treatment arose throughout the study. In view of this, the dose of blonanserin for children, as well as adults, should be increased in increments based on the clinical judgment of physicians, with no specific dose increment recommended in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section.

7.R.5.2 Maintenance dose of blonanserin

PMDA asked the applicant to explain the rationale for the maintenance dose of blonanserin in the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) in pediatric patients with schizophrenia, and then to explain the appropriateness of setting the proposed maintenance dose for children at 8 to 16 mg/day.

The applicant's explanation:

- In Study D4907001, the maintenance doses of blonanserin were set at 8 mg/day and 16 mg/day, with reference to the lower (8 mg/day) and upper (16 mg/day) limits of the approved maintenance dose for adults. In Study D4907002, the dose was adjusted within the range of 4 to 24 mg/day to also obtain safety information from pediatric patients treated with blonanserin at a dose of 24 mg/day, the highest maintenance dose for adults.
- The results of Study D4907001 demonstrated the superiority of blonanserin 16 mg/day over placebo in the change from baseline in PANSS total score to Week 6, which was the primary endpoint [see Section 7.1.1]. In contrast, the superiority of blonanserin 8 mg/day over placebo failed to be demonstrated. This might be attributed to the results from patients with schizophrenia with first onset at an age of <13 years, which is prone to be intractable. However, the efficacy of blonanserin 8 mg/day was suggested in patients with schizophrenia with first onset at an age of ≥13 years. The percentages of PANSS responders and the percent improvement in CGI-I, which were secondary endpoints, tended to be consistently higher in the 8 mg/day group than in the placebo group. In addition, the most common modal dose of blonanserin in Study D4907002 was 4 to 8 mg, regardless of the treatment assigned in Study D4907001. Taken together, the efficacy of blonanserin administered as a maintenance dose of 8 mg/day can be expected, as well [see Section 7.R.1.2].
- In the blonanserin groups of Study D4907001, the incidences of some adverse events, including "extrapyramidal syndrome" and "prolactin" adverse events, tended to increase in a dose-dependent manner. However, the results from Studies D4907001 and D4907002 demonstrated no trend that the safety profile of blonanserin in children clearly differs from that in adults [see Section 7.R.2].
- Although Study D4907002 allowed an increase in the dose of blonanserin up to 24 mg/day, only 4.7% (5 of 106) of patients received blonanserin at a dose of 24 mg/day, and only 2.8% (3 of 106) of patients had a modal dose of 24 mg/day, precluding a precise evaluation of the safety of blonanserin administered at a dose of 24 mg/day based on the results of Study D4907002.
- Table 29 shows the percentages of patients who increased the dose of blonanserin due to inadequate response in Study D4907002 and achieved a 30%, 40%, or 50% improvement in PANSS total score, as compared with baseline, in Study D4907001 or D4907002 at least once after dose increases (i.e., 30%, 40%, or 50% PANSS responders). High percentages of responders were yielded in Study D4907002, regardless of the treatment assigned in Study D4907001.

Table 29. Percentages of responders after dose increases in Study D4907002

		Treatment assigned in Study D4907001			
		Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day	Overall study population
N[a)]		30	27	30	87
Change from baseline in Study D4907001	30% Responders	23 (76.7)	20 (74.1)	26 (86.7)	69 (79.3)
	40% Responders	22 (73.3)	19 (70.4)	21 (70.0)	62 (71.3)
	50% Responders	20 (66.7)	17 (63.0)	15 (50.0)	52 (59.8)
Change from baseline in Study D4907002	30% Responders	20 (69.0)	17 (63.0)	13 (43.3)	50 (58.1)
	40% Responders	15 (51.7)	12 (44.4)	9 (30.0)	36 (41.9)
	50% Responders	14 (48.3)	9 (33.3)	7 (23.3)	30 (34.9)

n (%)
a) Number of patients who increased the dose of blonanserin due to inadequate response in Study D4907002

- The above findings indicated that the maintenance dose of blonanserin for pediatric patients with schizophrenia should be 8 to 16 mg/day. The percentages of responders after dose increases due to inadequate response were high. Dose escalation to 16 mg/day, depending on the patient's condition is thus meaningful.

PMDA's view regarding the dosage and administration of blonanserin for pediatric patients with schizophrenia, based on the discussions presented in Sections 7.R.5.1 to 7.R.5.2:

- The starting dose of 4 mg/day is appropriate.
- Dosage adjustments of blonanserin to achieve the maintenance dose should be made at intervals of ≥1 week, based on the procedure in the clinical studies, and this should be stated in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the package insert, in view of the following facts: (a) A small number of pediatric patients with schizophrenia have undergone dose increases at intervals of <1 weeks; (b) an analysis using the results from Studies D4907001 and D4907002 showed no clear differences in the safety profile of blonanserin between children and adults; however, pediatric patients with schizophrenia, as compared with adult patients, have been reported to be vulnerable to adverse events associated with antipsychotic therapy; and (c) the half-life of blonanserin is approximately 68 hours. In addition, the applicant's explanation that the caution on a specific dose increment for children in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section will be unnecessary, as for adults, is acceptable.
- The primary endpoint results from Study D4907001 demonstrated the superiority of blonanserin administered as a maintenance dose of 16 mg/day over placebo. Blonanserin administered as a maintenance dose of 8 mg/day was not superior over placebo in the primary endpoint. However, the efficacy of blonanserin in the treatment of schizophrenia in children can be expected over the dose range from 8 mg to 16 mg, in view of the following findings: (a) The change from baseline in PANSS total score to Week 6 in the 8 mg/day group tended to improve compared with the placebo group, and the percentages of PANSS responders and the percent improvement in CGI-I in the 8 mg/day group tended to be consistently higher than those in the placebo group; and, (b) the most common modal dose of blonanserin in Study D4907002 was 4 to 8 mg, regardless of the treatment assigned in Study D4907001, suggesting that the treatment effect of blonanserin could be maintained with a dose of 4 to 8 mg/day in most patients [see Section 7.R.1.2]. Safety analyses based on the results from Studies D4907001 and D4907002 showed that the incidences of some adverse events in children tended to increase in a dose-dependent manner. However, the safety profile

of blonanserin in these studies did not clearly differ from that observed in clinical studies conducted as part of the clinical development program in adult patients [see Section 7.R.2]. These study results indicated that the applicant's explanation that the maintenance dose of blonanserin for children should be 8 to 16 mg/day, and that the dose should be adjusted depending on the patient's condition is acceptable.

- The appropriateness of the PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

7.R.6 Post-marketing investigations

PMDA asked the applicant to explain the post-marketing investigations regarding the use of blonanserin in children.

The applicant's explanation:

- Blonanserin has been used extensively in Japan since its approval in January 2008 for the indication of schizophrenia and for the dosage and administration for adults.
- Although the use of antipsychotics in children has been reported to be associated with increased risks of extrapyramidal symptoms, sedation, weight increased, and metabolic adverse drug reactions compared with adult patients (*J Clin Psychiatry.* 2011;72:655-70), the results from the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) showed that the safety profile, including "extrapyramidal syndrome," "sedation," "weight increased," "glucose tolerance abnormal," and "lipid metabolism disorder" adverse events, of blonanserin in children does not clearly differ from that in adults, and the available post-marketing safety information has not shown that the safety of blonanserin clearly differs between patients aged ≤18 years and those aged >18 years [see Section 7.R.2].
- No particular differences in plasma blonanserin concentration were noted between children aged ≥12 years and adults [see Section 6.R.1], and the dosage regimen for pediatric patients with schizophrenia are within the range of the approved dosage and administration [see Section 7.R.5].
- The above findings indicated that the safety risks associated with the use of blonanserin in pediatric patients with schizophrenia are expected to be clinically similar to those in adult patients, with no pediatric-specific safety concerns identified. Therefore, the applicant will collect information regarding the safety of blonanserin, including the safety specifications,[39)] through routine pharmacovigilance practice, without conducting additional pharmacovigilance activities.

PMDA's view:

On the basis of the discussion presented in Section 7.R.2 and the above explanation of the applicant, PMDA has concluded that there are no major problems at present with detecting safety signals through routine pharmacovigilance practice, followed by a consideration of the conduct of additional pharmacovigilance activities, as necessary, without conducting additional pharmacovigilance activities immediately after the market launch. The PMDA's conclusion will be finalized, based on comments from the Expert Discussion.

[39)] Important identified risks; neuroleptic malignant syndrome, extrapyramidal symptoms/tardive dyskinesia, ileus paralytic, syndrome inappropriate ADH (SIADH), rhabdomyolysis, agranulocytosis, pulmonary embolism/deep vein thrombosis, hepatic function disorder, hyperglycaemia/diabetic ketoacidosis/diabetic coma: Important potential risks; suicide/suicidal ideation, QT prolonged

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.01, CTD 5.3.5.2.01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that blonanserin has efficacy in the treatment of schizophrenia in children, and that blonanserin has acceptable safety in view of its benefits. Blonanserin is clinically meaningful because it offers a treatment option for pediatric patients with schizophrenia. At the same time, the efficacy, safety, clinical positioning, indication, and dosage and administration of blonanserin, as well as the appropriateness of post-marketing investigations, etc. should be discussed further at the Expert Discussion.

PMDA has concluded that blonanserin may be approved if blonanserin is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 3, 2021

Products Submitted for Approval

Brand Name	(a) Lonasen Tablets 2 mg, (b) Lonasen Tablets 4 mg, (c) Lonasen Tablets 8 mg, (d) Lonasen Powder 2%
Non-proprietary Name	Blonanserin
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	May 28, 2020

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

In a phase III study (CTD 5.3.5.1.01, Study D4907001), a statistically significant difference in the change from baseline in PANSS total score to Week 6, the primary endpoint, was demonstrated between the blonanserin 16 mg group and the placebo group, but not between the 8 mg/day group and the placebo group. However, in view of the following findings, PMDA has concluded that the efficacy of blonanserin in the treatment of schizophrenia in children can also be expected at a dose of 8 mg/day [see Section 7.R.1 of the Review Report (1)].

- In Study D4907001, the change from baseline in PANSS total score to Week 6 tended to improve in the 8 mg/day group compared with the placebo group, and the percentages of PANSS responders and the percent improvement in CGI-I, which were secondary endpoints, tended to be consistently higher in the 8 mg/day group than in the placebo group.
- In a long-term treatment study (CTD 5.3.5.2.01, Study D4907002), the most common modal dose of blonanserin was 4 to 8 mg/day, regardless of the treatment assigned in Study D4907001, indicating that the efficacy of blonanserin could be maintained at a dose of 4 to 8 mg/day in most patients.

The PMDA's conclusion was supported by the expert advisors.

At the same time, the expert advisors commented that the percentages of PANSS responders, a secondary endpoint in Study D4907001, require an analysis that defines drop-outs as non-responders, in addition to the

analysis whereby drop-outs were imputed using the LOCF approach [see Table 9 of the Review Report (1)]. In response to the comment from the expert advisors, PMDA instructed the applicant to perform the additional analysis.

The applicant's response:
Table 30 shows the percentages of PANSS responders when drop-outs before Week 6 in Study D4907001 are defined as non-responders. The results tend to be similar to the LOCF-imputed outcomes. Thus, the efficacy of blonanserin administered at a dose of 8 to 16 mg/day has also been demonstrated when drop-outs are handled as non-responders.

Table 30. Percentages of PANSS responders, when drop-outs before Week 6 are defined as non-responders (Study D4907001, FAS)

	Placebo	Blonanserin 8 mg/day	Blonanserin 16 mg/day
N	47	51	52
30% Responders	15 (31.9)	20 (39.2)	28 (53.8)
40% Responders	9 (19.1)	13 (25.5)	22 (42.3)
50% Responders	6 (12.8)	11 (21.6)	13 (25.0)

n (%)

On the basis of the above, including the results of the additional analysis, PMDA has concluded that there are no particular problems with the efficacy of blonanserin in the treatment of schizophrenia in children. The PMDA's conclusion was supported by the expert advisors.

1.2 Safety

An assessment of the results from the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) revealed no new safety risks associated with the use of blonanserin in pediatric patients with schizophrenia. On the basis of this result, PMDA has concluded that the safety of blonanserin in the treatment of schizophrenia in children is acceptable, as long as blonanserin is used properly, following cautions similar to those for adults [see Section 7.R.2 of the Review Report (1)]. The PMDA's conclusion was supported by the expert advisors. At the same time, the expert advisors commented that attention should be paid to the fact that completed suicide, even though a causal relationship to blonanserin was denied, occurred in 2 patients in Study D4907002, from which patients with strong suicidal ideation and those with a history of suicide attempt were excluded, and in which patients were periodically monitored for suicidal ideation using the CGI-SS [see Table 18 of the Review Report (1)]. On that basis, the expert advisors supported the PMDA's conclusion that the development of "suicide" adverse events should be carefully monitored in pediatric patients treated with blonanserin for schizophrenia as well as adult patients, and that the applicant should continue to closely monitor the incidence of "suicide" adverse events in the post-marketing setting [see Section 7.R.2.4 of the Review Report (1)].

On the basis of the above, PMDA instructed the applicant to carefully monitor the incidence of "suicide" adverse events in patients treated with blonanserin in the post-marketing setting, and to adequately collect information regarding the risk of "suicide" adverse events from children treated with blonanserin or similar drugs for schizophrenia and take appropriate safety measures, as necessary. The applicant agreed.

1.3 Clinical positioning and indication

On the basis of the submitted clinical study results and other findings, PMDA has concluded that blonanserin can be a treatment option for pediatric patients with schizophrenia [see Section 7.R.3 of the Review Report (1)]. PMDA has also made the following conclusion regarding the age of the intended patient population [see Section 7.R.4.2 of the Review Report (1)]:

- The phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002) enrolled pediatric patients with schizophrenia aged ≥12 years, and the results of the study successfully demonstrated the efficacy and safety of blonanserin. Therefore, blonanserin should be used in patients aged ≥12 years, in principle.
- On the other hand, the importance of early interventions has been reported, and antipsychotic medications and non-medication treatments are recommended for pediatric patients with schizophrenia, regardless of age of onset. Antipsychotic therapy should be considered even for children aged <12 years, if they have been definitively diagnosed as schizophrenia. In view of these points, the "PRECAUTIONS CONCERNING INDICATIONS" section of the package insert should include cautionary statement regarding the age of the intended patient population of blonanserin.

The above PMDA conclusion was supported by the expert advisors.

1.4 Dosage and administration

PMDA has made the following conclusion regarding the dosage and administration of blonanserin in pediatric patients with schizophrenia [see Section 7.R.5 of the Review Report (1)].

- There are no particular problems with setting the starting dose at 4 mg/day and the maintenance dose at 8 to 16 mg/day.
- Dose escalation of blonanserin to achieve the maintenance dose should be conducted at intervals of ≥1 week, and this should be stated in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the package insert, because no clear differences in the safety profile of blonanserin between children and adults were demonstrated by assessing the results of the phase III study (CTD 5.3.5.1.01, Study D4907001) and the long-term treatment study (CTD 5.3.5.2.01, Study D4907002), in which the dose was defined to be increased at intervals of ≥1 week, and a limited number of pediatric patients with schizophrenia underwent dose increases at intervals of <1 weeks.

The expert advisors supported the PMDA's conclusion.

On the basis of the above, PMDA instructed the applicant to include the following cautionary statement in the "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" section of the package insert. The applicant responded appropriately.

Precautions Concerning Dosage and Administration

Dose increases in children should occur at intervals of ≥1 week. The safety of dose increases at intervals of <1 week has not been established (insufficient clinical data).

1.5 Risk management plan (draft)

In view of the discussion presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1) and the comments made by the expert advisors at the Expert Discussion [see Section 1.2], PMDA has concluded that the risk management plan (draft) for blonanserin should include the safety specifications presented in Table 31, and that the applicant should detect safety signals through routine pharmacovigilance practice, and then consider the conduct of additional pharmacovigilance activities, as necessary, without conducting additional pharmacovigilance activities or risk minimization activities immediately after the market launch.

Table 31. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
・ Neuroleptic malignant syndrome ・ Extrapyramidal symptoms/tardive dyskinesia ・ Ileus paralytic ・ Syndrome inappropriate ADH (SIADH) ・ Rhabdomyolysis ・ Agranulocytosis ・ Pulmonary embolism/deep vein thrombosis ・ Hepatic function disorder ・ Hyperglycaemia/diabetic ketoacidosis/diabetic coma	・ Suicide/suicidal ideation ・ QT prolonged	None
Efficacy specification		
None		

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below. Since the present application is intended for a new dosage, the re-examination period for the proposed indication and dosage and administration is 4 years.

Indication

Schizophrenia

(No change)

Dosage and administration

The usual adult starting dose is 4 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual adult maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 24 mg.

The usual pediatric starting dose is 2 mg of blonanserin administered orally twice daily after meals, and the dose should be increased gradually. The usual pediatric maintenance dose is 8 to 16 mg/day of blonanserin administered orally, divided into 2 doses after meals. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 16 mg.

(Underline denotes additions.)

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

blonanserin	blonanserin
blonanserin tape preparation	Lonasen Tape 20 mg, Lonasen Tape 30 mg, Lonasen Tape 40 mg
BMI	Body Mass Index
CGI-I	Clinical Global Impression of Global Improvement
CGI-S	Clinical Global Impression of Severity
CGI-SS	Clinical Global Impression of Suicide Severity
CI	Confidence interval
CTD	Common Technical Document
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text revision
FAS	Full Analysis Set
HLGT	High Level Group Terms
5-HT	5-Hydroxytryptamine
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model Repeated Measures
NICE	National Institute for Health and Care Excellence
PANSS	Positive And Negative Syndrome Scale
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population Pharmacokinetics
PT	Preferred Term
QTcB	Bazett-corrected QT Interval
QTcF	Fridericia-corrected QT Interval
SMQ	Standardized MedDRA Query
the product	Lonasen Tablets 2 mg, Lonasen Tablets 4 mg, Lonasen Tablets 8 mg, Lonasen Powder 2%