

Report on the Deliberation Results

February 24, 2016

Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Risperdal Tablets 1 mg Risperdal Tablets 2 mg Risperdal Fine Granules 1% Risperdal OD Tablets 0.5 mg Risperdal OD Tablets 1 mg Risperdal OD Tablets 2 mg Risperdal Oral Solution 1 mg/mL
[Non-proprietary name]	Risperidone (JAN*)
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	April 24, 2015

[Results of deliberation]

In its meeting held on February 5, 2016, the First Committee on New Drugs concluded that the products may be approved and that its result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 4 years.

[Conditions for approval]

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

**Japanese Accepted Name (modified INN)*

Review Report

January 15, 2016

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical products submitted for registration are as follows.

[Brand name]	(1) Risperdal Tablets 1 mg Risperdal Tablets 2 mg (2) Risperdal Fine Granules 1% (3) Risperdal OD Tablets 0.5 mg Risperdal OD Tablets 1 mg Risperdal OD Tablets 2 mg (4) Risperdal Oral Solution 1 mg/mL
[Non-proprietary name]	Risperidone
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	April 24, 2015
[Dosage form/Strength]	(1) Each 1 mg tablet contains 1 mg of Risperidone. Each 2 mg tablet contains 2 mg of Risperidone. (2) Each 1 g of fine granules contains 10 mg of Risperidone. (3) Each 0.5 mg oral dispersing tablet contains 0.5 mg of Risperidone. Each 1 mg oral dispersing tablet contains 1 mg of Risperidone. Each 2 mg oral dispersing tablet contains 2 mg of Risperidone. (4) Each 1 mL of oral solution contains 1 mg of Risperidone.
[Application classification]	Prescription Drug, (4) Drug with a new indication; (6) Drug with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug III

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

Review Results

January 15, 2016

[Brand name]	(1) Risperdal Tablets 1 mg Risperdal Tablets 2 mg (2) Risperdal Fine Granules 1% (3) Risperdal OD Tablets 0.5 mg Risperdal OD Tablets 1 mg Risperdal OD Tablets 2 mg (4) Risperdal Oral Solution 1 mg/mL
[Non-proprietary name]	Risperidone
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	April 24, 2015

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the products in the treatment of irritability associated with autism spectrum disorder in pediatric patients has been demonstrated and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the products may be approved for the indications and dosage and administration as shown below, with the following conditions.

[Indications]	Schizophrenia <u>Irritability associated with autism spectrum disorder in pediatric patients</u> (Underline denotes additions.)
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[Dosage and administration]

- (1) Risperdal Tablets 1 mg, Risperdal Tablets 2 mg;
- (2) Risperdal Fine Granules 1%;
- (3) Risperdal OD Tablets 0.5 mg, Risperdal OD Tablets 1 mg, and Risperdal OD Tablets 2 mg:

(a) Schizophrenia

The usual adult starting dose is 1 mg of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day, usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg.

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg of risperidone administered once daily.

From Day 4 onward, the daily dose should be increased to 0.5 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day at intervals of at least 1 week. The daily dose should not exceed 1 mg.

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day at intervals of at least 1 week. The daily dose should not exceed 2.5 mg in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg in patients weighing ≥ 45 kg.

(4) Risperdal Oral Solution 1 mg/mL:

(a) Schizophrenia

The usual adult starting dose is 1 mg (1 mL) of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day (2 to 6 mL/day), usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg (12 mL).

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg (0.25 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 0.5 mg (0.5 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day (0.25 mL/day) at intervals of at least 1 week. The daily dose should not exceed 1 mg (1 mL).

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg (0.5 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg (1 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day (0.5 mL/day) at intervals of at least 1 week. The daily dose should not exceed 2.5 mg (2.5 mL) in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg (3 mL) in patients weighing ≥ 45 kg.

(Underline denotes additions.)

[Conditions for approval] The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

November 18, 2015

I. Product Submitted for Registration

[Brand name]	(1) Risperdal Tablets 1 mg Risperdal Tablets 2 mg (2) Risperdal Fine Granules 1% (3) Risperdal OD Tablets 0.5 mg Risperdal OD Tablets 1 mg Risperdal OD Tablets 2 mg (4) Risperdal Oral Solution 1 mg/mL
[Non-proprietary name]	Risperidone
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	April 24, 2015
[Dosage form/Strength]	(1) Each 1 mg tablet contains 1 mg of Risperidone. Each 2 mg tablet contains 2 mg of Risperidone. (2) Each 1 g of fine granules contains 10 mg of Risperidone. (3) Each 0.5 mg oral dispersing tablet contains 0.5 mg of Risperidone. Each 1 mg oral dispersing tablet contains 1 mg of Risperidone. Each 2 mg oral dispersing tablet contains 2 mg of Risperidone. (4) Each 1 mL of oral solution contains 1 mg of Risperidone.
[Proposed indication]	Schizophrenia <u>Irritability associated with autistic disorder in pediatric patients</u> (Underline denotes additions.)
[Proposed dosage and administration]	(1) Risperdal Tablets 1 mg, Risperdal Tablets 2 mg; (2) Risperdal Fine Granules 1%; (3) Risperdal OD Tablets 0.5 mg, Risperdal OD Tablets 1 mg, and Risperdal OD Tablets 2 mg: (a) <u>Schizophrenia</u> The usual adult starting dose is 1 mg of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day, usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg. (b) <u>Irritability associated with autistic disorder in pediatric patients</u> <u>Patients weighing <20 kg:</u> <u>The usual starting dose is 0.25 mg of risperidone administered once daily for 3 days. From Day 4 onward, the daily dose should be increased to 0.5 mg, divided into 2 doses. The dose may be adjusted</u>

according to the patient's symptoms. The daily dose should not exceed 1 mg.

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg of risperidone administered once daily for 3 days. From Day 4 onward, the daily dose should be increased to 1 mg, divided into 2 doses. The dose may be adjusted according to the patient's symptoms. The daily dose should not exceed 2.5 mg in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg in patients weighing ≥ 45 kg.

(4) Risperdal Oral Solution 1 mg/mL:

(a) Schizophrenia

The usual adult starting dose is 1 mg (1 mL) of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day (2 to 6 mL/day), usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg (12 mL).

(b) Irritability associated with autistic disorder in pediatric patients

Patients weighing < 20 kg:

The usual starting dose is 0.25 mg (0.25 mL) of risperidone administered once daily for 3 days. From Day 4 onward, the daily dose should be increased to 0.5 mg (0.5 mL), divided into 2 doses. The dose may be adjusted according to the patient's symptoms. The daily dose should not exceed 1 mg (1 mL).

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg (0.5 mL) of risperidone administered once daily for 3 days. From Day 4 onward, the daily dose should be increased to 1 mg (1 mL), divided into 2 doses. The dose may be adjusted according to the patient's symptoms. The daily dose should not exceed 2.5 mg (2.5 mL) in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg (3 mL) in patients weighing ≥ 45 kg.

(Underline denotes additions.)

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

As the present application is for a new indication and new dosage, no data relating to quality were submitted. No pharmacodynamic data were submitted because no primary pharmacodynamics studies were conducted for the present application (for the proposed indication) for the following reasons: (1) Dopamine receptor antagonists are effective in the treatment of symptoms related to autistic disorder in humans, such as self-injurious behavior, aggression, stereotypic behavior, and hyperactivity; excessive activation of dopamine receptors contributes to these behavioral disorders (Kristen SL et al. *Res Dev Disabil.* 2006;27:254-89). (2) During the initial approval process for Risperdal Tablets 1 mg, Tablets 2 mg, and Fine Granules 1%, the following data were reviewed: *in vitro* and *in vivo* dopamine receptor antagonism by risperidone (Initial New Drug Application Data, Attachment E-1 [only in Japanese]) and inhibitory effects of dopamine agonists or psychostimulants on excitement/stereotypic behavior, hyperactivity, or increased ambulation (Initial New Drug Application Data, Attachment E-3, E-4 [only in Japanese]). (3) Risperidone has been reported to reduce self-injurious and aggressive behavior in animal models.¹⁾

1. Origin or history of discovery, use in foreign countries, and other information

Risperidone is the active ingredient of Risperdal Tablets, Fine Granules, OD Tablets, and Oral Solution. It is an atypical antipsychotic developed by Janssen Pharmaceutica NV in Belgium. In Japan, Risperdal has been approved for the treatment of schizophrenia: 1 mg Tablets, 2 mg Tablets, and Fine Granules were approved in April 1996; Oral Solution in March 2002; 3 mg Tablets in December 2002; OD Tablets 1 mg and OD Tablets 2 mg in March 2007; OD Tablets 0.5 mg in July 2009; Long-Acting Intramuscular Injection in April 2009.

Outside Japan, as of October 2015, risperidone is approved in at least 100 countries and regions for the treatment of schizophrenia and other psychotic disorders, and in 16 countries and regions, including the United States, for the treatment of autistic disorder or irritability associated with autistic disorder. In Japan, pimozide is approved for the treatment of symptoms associated with autistic disorder in pediatric patients.

In 2010, the Review Committee on Unapproved New Drugs and New Indications with High Medical Needs concluded that a high medical need existed for risperidone for the treatment of "autism and disruptive behavior disorders in pediatric patients." In December 2010, the Ministry of Health, Labour and Welfare requested that the applicant develop the drug for this indication (HPB/RDD Notification No. 1213-1 dated December 13, 2010, by the Research and Development Division, Health Policy Bureau; PFSB/ELD Notification No. 1213-1 dated December 13, 2010, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau). In response to the request, the applicant initiated a clinical study in August 2012, and submitted a partial change approval application based on the study

1) Skrebuhhova-Malmros T et al. *Pharmacol Biochem Behav.* 2000;67:339-43; Ricci LA et al. *Biol Psychiatry.* 2007;62:218-25; Wagner GC et al. *Neuropharmacology.* 2004;46:700-8.

results confirming the efficacy and safety of risperidone in the treatment of irritability associated with autistic disorder in pediatric patients.

2. Non-clinical data

2.(1) Summary of toxicology studies

2.(1).A Summary of the submitted data

Data on the toxicity studies of risperidone were reviewed during the initial approval process. However, as the present application is for use in pediatric patients, additional repeated oral toxicity studies in juvenile animals were submitted as a supplement to the assessment of safety of risperidone in children and adolescents.

2.(1).A.(1) Repeated toxicity studies

Repeated oral toxicity studies were conducted in juvenile rats (a 39-day study) and juvenile dogs (a 40-week study). The main toxicological findings were hyperplasia of mammary gland, mammary secretory activation, and slow bone growth. In juvenile rats (the 39-day study), the AUC_{0-24h} of the active moiety (risperidone and its active metabolite 9-OH-risperidone) at the no-observed-adverse-effect level (NOAEL) (0.63 mg/kg/day) was 751 to 888 ng·h/mL. In juvenile dogs (the 40-week study), the AUC_{0-24h} of the active moiety at the NOAEL (1.25 mg/kg/day) was 5351 to 6333 ng·h/mL. The AUC_{0-24h} in the rats (751 to 888 ng·h/mL) and the dogs (5351 to 6333 ng·h/mL) was approximately 1-fold and approximately 7-fold, respectively, of the estimated AUC_{0-24h} at the highest pediatric clinical dose of 3 mg/day (762 to 948 ng·h/mL).²⁾

2.(1).A.(1).1 A 39-day low-dose repeated oral toxicity study in juvenile rats (4.2.3.2.2)

Juvenile Sprague-Dawley rats aged 12 days (36/sex/group) were given oral risperidone at 0 (vehicle³⁾), 0.04, 0.16, or 0.63 mg/kg once daily for 39 days until 50 days of age. Then, some animals (11-12/sex/group) were tested for fertility after a recovery period of 14 days.⁴⁾ No deaths were caused by administration of risperidone. Clinical observations showed partial eye closure and decreased activity in the ≥ 0.16 mg/kg/day groups. Hematology revealed increased prolactin levels in the ≥ 0.04 mg/kg/day groups. Necropsy revealed decreased spleen weight in the ≥ 0.04 mg/kg/day groups, and decreased ovary weight in the 0.63 mg/kg/day group. Histopathological examination revealed increased formation of corpora lutea, hyperplasia of mammary gland, mammary secretory activation, endometrial cells in the diestrus phase, reduced granulocyte infiltration in the endometrium, and mucification of vaginal epithelium in the ≥ 0.04 mg/kg/day groups; these findings are all prolactin-mediated changes. The

2) AUC_{0-24h} in Japanese children and adolescents with autistic disorder receiving risperidone at the maximum clinical dose of 3 mg/day was estimated on the basis of the AUC_{τ, SS} of the active moiety in non-Japanese children (5 to 11 years) and adolescents (12 to 16 years) with mental disorder (pervasive developmental disorders, attention-deficit and disruptive behavior disorders, and schizophrenia) following administration of risperidone at a dose ranging from 0.01 to 0.08 mg/kg/day (4 mg/day at maximum) twice daily for 8 to 31 days (Study RIS-USA 160). The AUC_{τ, SS} was corrected to 1 mg twice daily: 316 ng·h/L in children and 254 ng·h/L in adolescents.

3) Aqueous tartaric acid solution (pH 5.0)

4) Males and females in the same dose group were mated. Females were necropsied at Day 13 of gestation, and males at approximately 97 days of age.

applicant concluded that risperidone induced pseudopregnancy. The fertility test revealed increased corpora lutea counts and an increased number of implantations in the 0.63 mg/kg/day group. After the 14-day recovery period, all findings noted during the treatment period were reversible. On the basis of the above findings, the applicant concluded that the NOAEL was 0.63 mg/kg/day.

2.(1).A.(1).2) A 39-day high-dose repeated oral toxicity study in juvenile rats (4.2.3.2.3)

Juvenile Sprague-Dawley rats aged 12 days (45/sex/group) were given oral risperidone at doses of 0 (vehicle),³⁾ 1.25, or 2.5/1.25⁵⁾ mg/kg/day once daily for 39 days until 50 days of age. Then, some animals (15/sex/group) were tested for fertility after a 14-day recovery period.⁶⁾ Two males in the 1.25 mg/kg/day group and 7 males and 3 females in the 2.5/1.25 mg/kg/day group died or were sacrificed moribund.⁷⁾ In clinical observations, animals receiving risperidone showed partial eye closure, decreased activity, shallow and rapid breathing, muscle cramp, scrotal swelling, body weight losses and decreases in body weight gain, and delayed eyelid opening, but showed no impact on sexual maturity (balanopreputial separation and vaginal opening). In the Morris water maze, the time to achieve the platform was prolonged in animals receiving risperidone, but this finding did not persist throughout the test period. Hematology revealed elevated prolactin levels in animals receiving risperidone. Necropsy revealed an increase in liver and ovary weights in females receiving risperidone, and a decrease in adrenal weight in males and females receiving risperidone. Histopathological examination revealed mucification of vaginal epithelium (evidence of cyclic changes), hyperplasia of mammary gland, mammary secretory activation, and uterine atrophy in animals receiving risperidone. After the 14-day recovery period, all findings were reversible, except those in the mammary gland (hyperplasia of mammary gland and secretory activation). On the basis of these results and the results of the low-dose repeated oral toxicity study in juvenile rats (4.2.3.2.2), the applicant concluded that the NOAEL was 0.63 mg/kg/day.

2.(1).A.(1).3) A 40-week repeated oral toxicity study in juvenile dogs (4.2.3.2.4)

Juvenile beagle dogs aged 10 weeks (8/sex/group) were given oral risperidone at 0 (vehicle³⁾), 0.31, 1.25, or 5 mg/kg/day once daily for 40 weeks until 50 weeks of age. No deaths were caused by administration of risperidone. In clinical observations, animals given ≥ 0.31 mg/kg/day showed decreased activity, miosis, scleral redness, tremor, and loss of estrus. Electrocardiogram revealed increased heart rate in animals given ≥ 1.25 mg/kg/day. Hematology revealed increased prolactin levels and decreased progesterone and testosterone levels in animals given ≥ 0.31 mg/kg/day. Necropsy of animals given ≥ 0.31 mg/kg/day revealed a decrease in ovary and prostate weights. Necropsy of animals given ≥ 1.25 mg/kg/day revealed decreased femoral bone mineral density (only in females) and a decrease in testis and ovary weights. Necropsy of animals given 5 mg/kg/day revealed suppressed growth of the right femur (only in females) and suppressed growth in shoulder height. Histopathology revealed a

5) In the 2.5 mg/kg/day group, some animals were sacrificed moribund due to body weight losses or poor clinical signs. The dose in the group was therefore reduced to 1.25 mg/kg/day from 14 or 15 days of age. After weaning (21 days of age), the animals in the group were included in the 1.25 mg/kg group.

6) Males and females in the same dose group were mated. Females were necropsied at Day 13 of gestation, and males at 97 to 98 days of age.

7) All animals that died or were sacrificed moribund in the 2.5/1.25 mg/kg/day group had received risperidone 2.5 mg/kg/day for 2 or 3 days.

decrease/atrophy of colloids in the prostate in males in the ≥ 1.25 mg/kg/day groups. Histopathological examination in the vehicle control group showed mammary gland development, distinct corpora lutea, and endometrial gland hyperplasia; none of these findings were observed in the risperidone groups. After the 12-week recovery period, all findings were reversible, except estrus suppression in animals given 5 mg/kg/day. On the basis of the above findings, the applicant concluded that the NOAEL was 1.25 mg/kg/day.

2.(1).B *Outline of the review by PMDA*

2.(1).B.(1) Effect on the growth and development of pediatric patients

Risperidone had effects on sex hormone levels (prolactin, progesterone, and testosterone) and bone growth in juvenile animals. PMDA therefore asked the applicant to explain the safety of risperidone in terms of growth and development (physical growth, sexual maturity, and bone growth) of pediatric patients.

The applicant's explanation:

In the 40-week repeated oral toxicity study in juvenile dogs (4.2.3.2.4), the vehicle control group showed impact on sexual maturity (i.e., mammary gland development, distinct corpora lutea, and endometrial hyperplasia), but these findings were not observed in the risperidone groups. The risperidone groups showed a decrease/atrophy of colloids in the prostate and effects on bones (i.e., decreased femoral bone mineral density). These findings are considered to be attributable to increased prolactin levels, a pharmacological effect of risperidone. However, the findings were mild and observed at approximately ≥ 6.7 -fold the exposure at the maximum clinical dose, and were clearly reversible after a recovery period. Therefore, the toxicological significance of the findings is minor.

PMDA's view:

There are no particular concerns about the applicant's discussion on the findings in toxicological studies. The possible effect of risperidone on the growth and development of pediatric patients is further discussed in the clinical data section (see "3.(ii).B.(2).2) Effects on growth and body weight gain").

3. Clinical data

3.(i) Summary of clinical pharmacology studies

3.(i).A *Summary of the submitted data*

The applicant submitted evaluation data: the results of a Japanese phase III study in Japanese children and adolescents with autistic disorder (5.3.5.1.1: Study RIS-AUT-JPN-01). The applicant also submitted reference data: the results of a foreign phase I study in Japanese and non-Japanese healthy adults (Reference 5.3.3.1.1: Study RIS-P01-101), a foreign phase I study in non-Japanese children and

adolescents with mental disorders⁸⁾ (Reference 5.3.3.2.1: Study RIS-USA-160), foreign phase II studies in non-Japanese children with autistic disorder (Reference 5.3.3.2.2, Study RIS-BEL-21; Reference 5.3.5.2.1, Study RIS-BEL-22), a foreign phase III study in non-Japanese children and adolescents with autistic disorder (Reference 5.3.3.2.3: Study RIS-USA-150), a foreign phase III study in non-Japanese children and adolescents with behavioral disorder or other disruptive behavior disorders (Reference 5.3.5.4.1: Study RIS-INT-41), and a foreign phase IV study in non-Japanese children and adolescents with autistic disorder (Reference 5.3.5.1.5: Study RIS-AUT-4002). Concentrations of unchanged risperidone and its active metabolite, 9-OH-risperidone (9-OH-RIS), in human biological samples (plasma and urine) were quantified using a radioimmunoassay (lower limit of quantification, 0.2 ng/mL in plasma for both compounds) or a high-performance liquid chromatography tandem mass spectrometry (lower limit of quantification, 0.1 ng/mL in plasma and 2.0 ng/mL in urine for both compounds). Unless otherwise specified, t_{max} is expressed as median, and other pharmacokinetic parameters are expressed as mean \pm standard deviation. The values for the active moiety represent the sum of the values for unchanged risperidone and 9-OH-RIS.

3.(i).A.(1) Studies in healthy adults

Japanese and non-Japanese healthy adults (24 Japanese and 24 non-Japanese subjects included in the pharmacokinetic analysis) received single oral administration of risperidone (1 mg tablet) in a fasting state on Day 1. After a 3-day washout period, the subjects received oral risperidone (1 mg tablet) once daily for 7 days from Day 5 to Day 11. Tables 1 and 2 summarize the plasma pharmacokinetic parameters of the active moiety, unchanged risperidone, and 9-OH-RIS in Japanese and non-Japanese subjects on Days 1 and 11. Urinary secretion of the active moiety after repeated doses was $34\% \pm 8\%$ in Japanese subjects and $29\% \pm 8\%$ in non-Japanese subjects. There were no substantial differences between Japanese and non-Japanese subjects in pharmacokinetics of the active moiety, unchanged risperidone, and 9-OH-RIS (Reference 5.3.3.1.1: Study RIS-P01-101).

Table 1. Pharmacokinetic parameters in Japanese and non-Japanese healthy adults following a single oral dose of risperidone 1 mg tablet

Compounds	Subjects	C_{max} (ng/mL)	t_{max} (h) ^{a)}	$t_{1/2}$ (h)	AUC _{0-∞} (ng·h/mL)	CL/F (mL/min)
Active moiety	Japanese	11.4 \pm 2.9	1.0 (1.0, 3.0)	20.4 \pm 3.0	167 \pm 35	105 \pm 27
	Non-Japanese	11.5 \pm 5.4	1.5 (0.5, 6.0)	21.7 \pm 4.1	200 \pm 93	96.9 \pm 35
Unchanged risperidone	Japanese	6.33 \pm 2.37	1.0 (0.5, 2.0)	3.1 \pm 1.8	28.6 \pm 20.9	873 \pm 740
	Non-Japanese	7.46 \pm 5.25	1.0 (0.5, 4.0)	3.6 \pm 3.3	42.5 \pm 43.5	794 \pm 774
9-OH-RIS	Japanese	5.89 \pm 1.80	3.5 (1.0, 8.0)	20.6 \pm 2.9	138 \pm 30	127 \pm 31
	Non-Japanese	5.65 \pm 2.53	5.0 (1.5, 24.2)	22.4 \pm 5.3	158 \pm 68	120 \pm 40

Mean \pm standard deviation; N = 24 Japanese + 24 non-Japanese

a) Median (min, max)

8) Patients diagnosed with pervasive developmental disorder, attention-deficit and disruptive behavior disorders, schizophrenia, or other psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition.

Table 2. Pharmacokinetic parameters in Japanese and non-Japanese healthy adults following repeated oral doses of risperidone 1 mg tablet

Compounds	Subjects	C _{trough} (ng/mL)	C _{max} (ng/mL)	t _{max} (h) ^{a)}	t _{1/2} (h)	AUC _τ (ng·h/mL)	CL/F (mL/min)
Active moiety	Japanese	3.29 ± 0.95	15.0 ± 5.0	1.0 (0.5, 2.0)	24.4 ± 4.3	176 ± 51	103 ± 32
	Non-Japanese	4.18 ± 2.04	16.0 ± 6.7	1.0 (0.5, 6.0)	26.3 ± 3.8	194 ± 70	95.6 ± 30.8
Unchanged risperidone	Japanese	BQL	6.94 ± 3.79	1.0 (0.5, 2.0)	4.7 ± 6.0	30.2 ± 21.5	899 ± 844
	Non-Japanese	BQL	7.89 ± 4.96	1.0 (0.5, 4.0)	4.7 ± 4.5	38.8 ± 29.8	671 ± 427
9-OH-RIS	Japanese	3.15 ± 0.89	9.23 ± 2.86	3.5 (1.0, 8.0)	25.1 ± 5.1	145 ± 45	124 ± 36
	Non-Japanese	3.96 ± 1.93	9.31 ± 3.17	4.0 (1.0, 8.3)	30.3 ± 9.1	155 ± 57	120 ± 39

Mean ± standard deviation; N = 24 Japanese + 24 non-Japanese; BQL = below quantifiable limit

a) Median (min, max)

3.(i).A.(2) Studies in patients

3.(i).A.(2).1 Results in Japanese patients

Japanese children and adolescents with autistic disorder (5 to 17 years of age; 35 patients included in the pharmacokinetic analysis) received repeated oral doses of risperidone (oral solution or OD tablets) according to the dosage regimen in Table 8. Table 3 shows plasma concentrations of the active moiety, unchanged risperidone, and 9-OH-RIS at Weeks 8, 32, and 56 of treatment (i.e., Day 1, Weeks 24, and Week 48, respectively, in the long-term extension phase), corrected to the dose administered immediately before blood sampling (2 mg/day twice daily) or dose by body weight (0.04 mg/kg/day twice daily). No substantial difference was observed either in post-dose concentrations or trough concentrations at any of the time points (5.3.5.1.1: Study RIS-AUT-JPN-01).

Table 3. Plasma concentrations (ng/mL) of risperidone and its active metabolite in Japanese children and adolescents following repeated oral doses of risperidone (oral solution or OD tablets)

Corrected to	Time point	Active moiety		Unchanged risperidone		9-OH-RIS	
		Post-dose ^{a)}	Trough ^{b)}	Post-dose ^{a)}	Trough ^{b)}	Post-dose ^{a)}	Trough ^{b)}
2 mg/day twice daily	Week 8	21.7 ± 10.2	19.8 ± 9.76	4.31 ± 3.34	1.87 ± 1.70	17.4 ± 7.86	17.9 ± 9.46
	Week 32	27.4 ± 16.7	11.0 ± 5.29	6.83 ± 7.25	0.83 ± 1.11	20.6 ± 11.7	10.1 ± 4.62
	Week 56	26.4 ± 17.5	15.3 ± 6.39	5.87 ± 8.06	1.23 ± 1.72	20.6 ± 10.8	14.1 ± 5.40
0.04 mg/kg/day twice daily	Week 8	14.6 ± 7.05	10.8 ± 5.44	3.17 ± 2.78	1.02 ± 0.94	11.4 ± 4.79	9.83 ± 5.24
	Week 32	18.4 ± 11.3	7.45 ± 3.70	4.37 ± 4.83	0.55 ± 0.58	14.0 ± 8.43	6.90 ± 3.45
	Week 56	17.9 ± 10.5	9.54 ± 4.42	3.60 ± 4.24	0.66 ± 0.84	14.3 ± 7.52	8.88 ± 4.21

Mean ± standard deviation

a) Plasma concentrations in blood samples taken between ≥0 and ≤8 hours post-dose.

No. of subjects: 11 at Week 8, 21 at Week 32, and 15 at Week 56.

b) Trough plasma concentrations in blood samples taken between >8 and ≤30 hours post-dose.

No. of subjects: 7 at Week 8, 10 at Week 32, and 11 at Week 56.

3.(i).A.(2).2 Results in non-Japanese patients

Table 4 summarizes the pharmacokinetic parameters of the active moiety, unchanged risperidone, and 9-OH-RIS in non-Japanese children with autistic disorder (4 to 8 years of age; 6 patients included in the pharmacokinetic analysis) following a single oral dose of risperidone oral solution at 0.015 or 0.03 mg/kg (Reference 5.3.3.2.2: Study RIS-BEL-21).

Table 4. Pharmacokinetic parameters in non-Japanese children with autistic disorder following a single dose of risperidone (oral solution)

Compounds	Dose	C _{max} (ng/mL)	t _{max} (h) ^{a)}	t _{1/2} (h)	AUC _{0-∞} (ng·h/L)
Active moiety	0.015 mg/kg	16.8 ± 5.8	1.02 (0.98, 1.03)	11.1 ± 2.5	141 ± 50
	0.03 mg/kg	23.6 ± 9.6	1.03 (0.88, 1.05)	15.5 ± 4.8	279 ± 89
Unchanged risperidone	0.015 mg/kg	10.2 ± 2.2	1.02 (0.98, 1.03)	2.1 ± 0.3	34 ± 9.1
	0.03 mg/kg	15.1 ± 3.9	1.03 (0.88, 1.05)	1.9 ± 0.2	49 ± 12
9-OH-RIS	0.015 mg/kg	8.2 ± 2.3	2.00 (1.02, 2.00)	11.8 ± 2.7	108 ± 41
	0.03 mg/kg	11.7 ± 3.5	2.02 (1.97, 4.03)	14.7 ± 2.5	228 ± 78

Mean ± standard deviation; N = 3 subjects receiving 0.015 mg/kg + 3 subjects receiving 0.03 mg/kg

a) Median (min, max)

Non-Japanese children with autistic disorder (3 to 9 years of age; 4 patients included in the pharmacokinetic analysis) received repeated doses of risperidone oral solution at 0.06 mg/kg twice daily for 28 days. (The starting dose was 0.005 mg/kg, with subsequent increases to 0.01 mg/kg on Day 3, 0.02 mg/kg on Day 5, 0.04 mg/kg on Day 7, and 0.06 mg/kg from Day 9 onward; dose reduction was allowed in case of adverse events.) Trough plasma concentration of the active moiety on Day 28 ranged between 2.32 and 4.57 ng/mL (Reference 5.3.5.2.1: Study RIS-BEL-22).

Non-Japanese children (6 to 11 years of age) and adolescents (12 to 16 years of age) with mental disorders (12 children and 12 adolescents included in the pharmacokinetic analysis) received risperidone tablets 0.01 to 0.08 mg/kg/day (4 mg/day at maximum) twice daily for ≥7 days. Table 5 summarizes the steady-state plasma pharmacokinetic parameters of the active moiety, unchanged risperidone, and 9-OH-RIS, corrected to the dose administered immediately before blood sampling (2 mg/day) or dose by body weight (0.04 mg/kg/day) (Reference 5.3.3.2.1: Study RIS-USA-160).

Table 5. Pharmacokinetic parameters at steady state in non-Japanese children and adolescents with mental disorders following repeated oral doses of risperidone (tablets)

Compounds	Corrected to	Subjects	C _{trough} (ng/mL)	C _{max} (ng/mL)	AUC _τ (ng·h/L)	CL _{tot} (mL/min/kg)	Plasma protein binding (%)
Active moiety	2 mg/day	Children	16.2 ± 6.1	40.3 ± 14.6	316 ± 106		
		Adolescents	15.2 ± 8.7	28.4 ± 12.5	254 ± 131		
	0.04 mg/kg/day	Children	11.4 ± 5.0	28.2 ± 12.4	221 ± 87	1.75 ± 0.71	-
		Adolescents	20.7 ± 16.3	38.5 ± 26.6	347 ± 263	1.56 ± 1.04	-
Unchanged risperidone	2 mg/day	Children	2.63 ± 3.18	17.1 ± 10.1	114 ± 72 ^{a)}		
		Adolescents	5.63 ± 7.90	15.5 ± 13.6	127 ± 137 ^{b)}		
	0.04 mg/kg/day	Children	2.06 ± 2.68	12.4 ± 9.0	87.5 ± 61.5 ^{a)}	6.11 ± 4.15 ^{a)}	11.7
		Adolescents	8.61 ± 13.10	22.5 ± 23.9	190 ± 235 ^{b)}	6.51 ± 6.72 ^{b)}	14.7
9-OH-RIS	2 mg/day	Children	13.0 ± 5.3	24.5 ± 10.7	222 ± 98		
		Adolescents	9.20 ± 3.89	13.4 ± 4.3	136 ± 48		
	0.04 mg/kg/day	Children	8.98 ± 3.58	16.7 ± 6.8	152 ± 58	2.52 ± 1.00	25.0
		Adolescents	11.7 ± 6.9	16.8 ± 8.8	172 ± 94	2.37 ± 1.01	29.1

Mean ± standard deviation; N = 12 children + 12 adolescents

a) N = 9; b) N = 11

3.(i).A.(3) Population pharmacokinetic analysis

A population pharmacokinetic analysis was performed using data on plasma concentrations of the active moiety and the unchanged risperidone obtained in foreign clinical studies in non-Japanese children and adolescents with autistic disorder⁹⁾ and in non-Japanese children and adolescents with mental disorders¹⁰⁾ (2165 concentrations from 1080 patients). The effects of the following variables on plasma concentrations of the active moiety and unchanged risperidone were assessed: gender, race, age, body weight, height, serum creatinine level, creatinine clearance, lean body mass, body mass index (BMI), body surface area, and study. As a result, the pharmacokinetics of risperidone was described with a 2-compartment model with absorption. Creatinine clearance, age, and study (Study RIS-BEL-21) were significant covariates for apparent systemic clearance of the active moiety in plasma (Reference 5.3.3.5.1).

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Difference in pharmacokinetics of risperidone between children/adolescents and adults

PMDA asked the applicant to compare the pharmacokinetics of risperidone in children/adolescents and adults.

The applicant's explanation:

Table 6 shows plasma concentrations of the active moiety in children, adolescents, and healthy adults following repeated oral doses of risperidone. Although the differences in frequency of administration and sampling points among studies should be considered, the post-dose and trough plasma concentrations of the active moiety did not differ substantially between children/adolescents and adults when the values are corrected to dose by body weight.

9) Study RIS-BEL-21 (Reference 5.3.5.2.2) and Study RIS-USA-150 (Reference 5.3.3.2.3)

10) Study RIS-USA-160 (Reference 5.3.3.2.1), Study RIS-USA-93, Study RIS-CAN-19, Study RIS-INT-41 (Reference 5.3.5.4.1)

Table 6. Post-dose and trough plasma concentrations of the active moiety following repeated oral doses of risperidone corrected to dose by body weight (ng/mL)

Study	Age (Subjects)	Frequency	Corrected to	Time point	Plasma active moiety concentration			
					N	Post-dose	N	Trough
RIS-AUT-JPN-01	5 to 17 years (Japanese)	Twice daily	0.04 mg/kg/day twice daily	Week 8	11	14.6 ± 7.1 (6.32, 27.4) ^{a)}	7	10.8 ± 5.44 (2.91, 19.4) ^{c)}
				Week 32	21	18.4 ± 11.3 (BQL, 40.7) ^{a)}	10	7.45 ± 3.70 (3.66, 16.1) ^{c)}
				Week 56	15	17.9 ± 10.5 (BQL, 40.0) ^{a)}	11	9.54 ± 4.42 (2.92, 18.1) ^{c)}
RIS-P01-101	21 to 50 years (Japanese)	Once daily	0.04 mg/kg/day once daily	Day 7	24	26.4 ± 7.7 (12.9, 45.9) ^{b)}	24	8.29 ± 2.95 (4.32, 18.5) ^{d)}
	20 to 49 years (Non-Japanese)			Day 7	24	31.8 ± 10.5 (18.2, 68.7) ^{b)}	24	10.7 ± 3.64 (3.87, 18.4) ^{d)}
RIS-USA-150	5 to 16 years (Non-Japanese)	Twice daily	0.04 mg/kg/day twice daily	Week 8	15	22.9 ± 11.6 (5.57, 41.7) ^{a)}	30	9.64 ± 6.52 (1.40, 33.1) ^{c)}
				Week 24	12	26.5 ± 20.2 (8.32, 67.6) ^{a)}	21	13.7 ± 11.5 (6.02, 60.2) ^{c)}
RIS-USA-160	6 to 11 years (Non-Japanese)	Twice daily	0.04 mg/kg/day once daily	Day 7	12	21.0 ± 10.1 (11.1, 45.6) ^{b)}	12	11.7 ± 5.27 (5.25, 20.0) ^{e)}
	12 to 16 years (Non-Japanese)		0.04 mg/kg/day once daily	Day 7	12	34.0 ± 26.4 (9.68, 97.3) ^{b)}	12	20.8 ± 16.4 (5.32, 56.3) ^{e)}
RIS-INT-41	4 to 14 years (Non-Japanese)	Once daily	0.04 mg/kg/day once daily	Week 4	32	20.7 ± 13.1 (BQL, 51.0) ^{a)}	367	11.4 ± 9.87 (BQL, 68.1) ^{c)}
				Week 24	30	23.6 ± 16.4 (0.83, 70.3) ^{a)}	318	12.3 ± 11.0 (BQL, 111) ^{c)}
				Week 52	39	22.7 ± 26.2 (0.34, 158) ^{a)}	273	11.6 ± 9.46 (BQL, 57.5) ^{c)}

Mean ± standard deviation (min, max); BQL = below lower limit of quantification

a) Concentrations in blood samples taken between ≥0 and ≤8 hours post-dose.

b) Concentrations in blood samples taken at 4 hours post-dose.

c) Concentrations in blood samples taken between >8 and ≤30 hours post-dose.

d) Concentrations in blood samples taken at 24 hours post-dose.

e) Concentrations in blood samples taken at 12 hours post-dose.

PMDA accepted the above explanation, and considers that the pharmacokinetics of risperidone does not differ substantially between children/adolescents and adults.

3.(ii) Summary of clinical efficacy and safety

3.(ii).A Summary of the submitted data

The applicant submitted the following data:

- (1) Evaluation data for efficacy and safety review: the results of a Japanese phase III study in children and adolescents with autistic disorder and irritability (5.3.5.1.1, Study RIS-AUT-JPN-01).
- (2) Reference data for efficacy and safety review: the results of a foreign phase II study in non-Japanese children with autistic disorder (Reference 5.3.5.2.1, Study RIS-BEL-22); foreign phase III studies in non-Japanese children and adolescents with autistic disorder, and in non-Japanese children with autistic disorder or other pervasive developmental disorder (Reference 5.3.5.1.2, Study RIS-USA-150 Part 1; Reference 5.3.5.1.3, Study RIS-USA-150 Part 2/3; and Reference 5.3.5.1.4, Study RIS-CAN-23); and a foreign phase IV study in non-Japanese children and adolescents with autistic disorder (Reference 5.3.5.1.5, Study RIS-AUT-4002).
- (3) Reference data for safety review: the results of a foreign phase II study in non-Japanese children with autistic disorder (Reference 5.3.3.2.2, Study RIS-BEL-21), and foreign phase III studies in non-Japanese children and adolescents with behavioral disorder or other disruptive behavior

disorders (Reference 5.3.5.4.1, Study RIS-INT-41; and Reference 5.3.5.4.2, Study RIS-INT-84).

3.(ii).A.(1) Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01; August 2012 to October 2014)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of risperidone in patients ≥ 5 to <18 years of age who had irritability with autistic disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (Table 7). Target sample size was 38 patients (19 per group). This study is referred to as the "double-blind phase." Patients allowed to continue treatment after the double-blind phase (Table 7) were rolled over to an open-label, uncontrolled long-term extension study. This study is referred to as the "long-term extension phase" (for pharmacokinetic results, see "3.(i) Summary of clinical pharmacology studies.")

Table 7. Main inclusion criteria for the Japanese phase III study

Double-blind phase	<ul style="list-style-type: none"> - CGI-S score of ≥ 4 at screening - ABC-J Irritability (Agitation) subscale score of ≥ 18 at screening - Mental or developmental age of >18 months as measured by an appropriate scale (e.g., the Tanaka-Binet Intelligence Scale, the Kyoto Scale of Psychological Development) within 1 year before screening; or - A full scale intelligence quotient (IQ) of ≥ 35 according to the Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children-III or -IV, etc. within 1 year before screening.
Long-term extension phase	<ul style="list-style-type: none"> - Patients who completed the double-blind phase; or - Patients deemed by the investigator or subinvestigator to be unable to continue the study after Week 4 of the double-blind phase because of inadequate response (i.e., 2 consecutive CGI-C ratings of "moderate or marked worsening" at scheduled visits after Week 3.) - Patients who completed the ABC-J at the last assessment in the double-blind phase (at Week 8 or the time of discontinuation)

Abbreviations: ABC-J, Aberrant Behavior Checklist-Japanese Version; CGI-C, Clinical Global Impression-Change; CGI-S, Clinical Global Impression-Severity

Study RIS-AUT-JPN-01 consisted of a screening phase, an 8-week double-blind phase, a 48-week long-term extension phase, and a 1-week follow-up phase. Table 8 summarizes the dosage regimen of risperidone oral solution in the double-blind phase.

Table 8. Dosage regimen in the double-blind phase of the Japanese phase III study

<ul style="list-style-type: none"> • Subjects weighing <20 kg: Starting dose is risperidone 0.25 mg/day or placebo once daily in the evening. On Day 4, the dose is increased to 0.5 mg/day twice daily. Subsequently, the dose is increased in increments of 0.25 mg/day at each scheduled visit, up to 1.0 mg/day twice daily. A daily dose of 0.75 mg/day is divided into 0.25 mg in the morning and 0.5 mg in the evening. • Subjects weighing ≥ 20 kg: Starting dose is risperidone 0.5 mg/day or placebo once daily in the evening. On Day 4, the dose is increased to 1.0 mg/day twice daily. Subsequently, the dose is increased in increments of 0.5 mg/day at each scheduled visit, up to 2.5 mg/day (3.0 mg/day in subjects weighing ≥ 45 kg) twice daily. • In both body weight categories, subjects are allowed to stop dose escalation if they have "moderate or marked improvement" as assessed by CGI-C, or if they appear intolerant of higher doses due to occurrence of AEs. The dose must not be changed after Week 6. The dose may be reduced to 0.25 mg/kg if deemed necessary due to occurrence of AEs.

In the long-term extension phase, the starting dose of risperidone (oral solution or OD tablet) was 0.25 or 0.5 mg/day administered in the same manner as in the double-blind phase. However, doses were

adjusted at the discretion of the investigator or subinvestigator, to ensure the efficacy, safety, and tolerability.

In the double-blind phase, all of the 39 randomized subjects (18 in the placebo group, 21 in the risperidone group) were included in the full analysis set (FAS) for safety and efficacy analysis. Ten subjects (7 in the placebo group, 3 in the risperidone group) discontinued study treatment: 8 subjects due to inadequate response (7 in the placebo group, 1 in the risperidone group) and 2 subjects due to consent withdrawal (both in the risperidone group). In the long-term extension phase, all of the 35 subjects who received treatment (17 placebo rollover subjects and 18 risperidone rollover subjects) were included in the FAS for safety and efficacy analysis. Nine subjects (3 placebo rollover subjects and 6 risperidone rollover subjects) discontinued study treatment; common reasons for discontinuation were treatment interruption for ≥ 7 consecutive days in 3 subjects (1 placebo rollover subject and 2 risperidone rollover subjects) and inadequate response in 3 subjects (1 placebo rollover subject and 2 risperidone rollover subjects).

The modal dose (mean \pm standard deviation) of risperidone in the FAS was 1.87 ± 0.70 mg/day in the double-blind phase, and 1.61 ± 0.73 mg/day in the long-term extension phase.

The primary endpoint was change in the Aberrant Behavior Checklist-Japanese Version (ABC-J)¹¹⁾ irritability (agitation) subscale score from baseline to the last assessment in the double-blind phase (at Week 8 or discontinuation) in the FAS (for results, see Table 9). A statistically significant difference was observed between the placebo and risperidone groups ($P = 0.0030$, an analysis of covariance using treatment groups as factors, and baseline values as covariates).

Table 9. Change in ABC-J irritability (agitation) subscale score in the double-blind phase of the Japanese phase III clinical study (FAS, LOCF)

Treatment group	No. of subjects assessed	Subscale score		Change from baseline	Comparison with placebo ^{a)}	
		Baseline	Last assessment		Between-group difference [95% CI]	P value
Placebo	18	27.5 \pm 5.26	24.7 \pm 9.47	-2.8 \pm 6.62	-7.1 [-11.6, -2.6]	0.0030
Risperidone	21	28.2 \pm 6.36	18.5 \pm 10.57	-9.7 \pm 7.29		

Mean \pm standard deviation; LOCF = last observation carried forward; CI = confidence interval

a) Based on an analysis-of-covariance model using treatment groups as factors and baseline values as covariates.

A secondary endpoint was change in the ABC-J irritability (agitation) subscale score from baseline to the last assessment in the long-term extension phase (at Week 48 or discontinuation) in the FAS (for results, see Table 10).

11) The Aberrant Behavior Checklist-Japanese Version (ABC-J) is a rating scale designed to assess the effects of pharmacotherapy on problem behaviors in people with intellectual disabilities. The scale consists of 58 items classified into 5 subscales: Irritability (Agitation) (15 items); Lethargy/social withdrawal (16 items); Stereotypic behavior (7 items); Hyperactivity/noncompliance (16 items); and Inappropriate speech (4 items). Each item is rated on a 4-point scale (0 = no problem, 1 = slight problem, 2 = moderate problem, 3 = severe problem). Rating was made by the investigator, subinvestigator etc., on the basis of information provided by appropriate caregivers (e.g., a parent) with ability to provide information on the patient.

Table 10. Change in ABC-J irritability (agitation) subscale score from baseline in the long-term extension phase of the Japanese phase III study (FAS, OC)

	Placebo rollover subjects		Risperidone rollover subjects	
	Subscale score	Change	Subscale score	Change
Baseline ^{a)}	24.5 ± 9.73 (17)		19.8 ± 10.65 (18)	
Week 8	12.9 ± 9.90 (16)	-10.8 ± 10.47 (16)	13.7 ± 10.46 (16)	-5.8 ± 8.75 (16)
Week 24	12.8 ± 9.90 (16)	-10.9 ± 10.76 (16)	13.1 ± 9.67 (14)	-6.8 ± 9.65 (14)
Week 48	11.6 ± 8.18 (14)	-12.5 ± 10.32 (14)	12.6 ± 9.84 (12)	-7.9 ± 9.18 (12)
Last assessment ^{b)}	13.1 ± 8.31 (17)	-11.4 ± 10.70 (17)	13.0 ± 10.28 (18)	-6.8 ± 9.70 (18)

Mean ± standard deviation (No. of subjects assessed); OC = observed cases

a) At the start of treatment in the long-term extension phase

b) LOCF

In the double-blind phase, adverse events (AEs) including abnormal laboratory values were observed in 88.9% (16 of 18 subjects) in the placebo group and 90.5% (19 of 21 subjects) in the risperidone group. No deaths were reported. A serious AE (SAE) was reported in 1 subject in the placebo group (dehydration), but a causal relationship of the event to the study drug was ruled out. In the long-term extension phase, AEs including abnormal laboratory values were observed in 97.1% (34 of 35 subjects), but no deaths were reported. Other SAEs were reported in 2 subjects (tracheobronchitis mycoplasmal and asthma in 1 subject and inguinal hernia in 1 subject), but a causal relationship of the events to the study drug was ruled out.

In the double-blind phase, AEs (including abnormal laboratory values) for which a causal relationship to the study drug could not be ruled out were observed in 27.8% (5 of 18 subjects) in the placebo group and 66.7% (14 of 21 subjects) in the risperidone group; commonly observed AEs included somnolence (2 subjects in the placebo group and 11 subjects in the risperidone group), increased appetite (none in the placebo group and 5 subjects in the risperidone group), and weight increased (none in the placebo group and 4 subjects in the risperidone group). In the long-term extension phase, AEs (including abnormal laboratory values) for which a causal relationship to the study drug could not be ruled out were observed in 80.0% (28 of 35) of subjects; commonly observed AEs included somnolence in 17 subjects, weight increased in 12 subjects, increased appetite in 9 subjects, and hyperprolactinaemia in 4 subjects.

No clinically significant changes were observed in vital signs (blood pressure or pulse rate). Abnormal electrocardiogram findings (prolonged QT interval) were observed in 1 subject receiving placebo and 1 subject receiving risperidone in the double-blind phase.

The applicant's conclusion based on the above results:

Risperidone at doses between 0.25 and 3.0 mg/day has been shown to be effective in patients with autistic disorder and irritability aged ≥5 to <18 years. The efficacy was maintained for a long period with no major safety concerns.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Efficacy of risperidone

3.(ii).B.(1).1 Protocol for the Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01)

(a) Primary endpoint

PMDA asked the applicant to rationalize the choice of the ABC-J irritability (agitation) subscale score as the primary endpoint in the Japanese phase III clinical study.

The applicant's explanation:

The ABC is a rating scale designed to assess treatment effects in patients of all generations, including children, who have developmental disabilities with physical or intellectual disabilities (Aman MG et al. *Am J Ment Defic.* 1985;89:485-91; Aman MG et al. *Am J Ment Defic.* 1985;89:492-502). A comparison of the standard diagnostic criteria for autistic disorder and the items of ABC has shown that the ABC covers the main symptoms of autistic disorders. The Japanese version of the ABC (ABC-J) was considered the most appropriate rating scale for the Japanese phase III study, for the following reasons: (1) The ABC-J has been shown to be reliable and appropriate for assessing patients with mental retardation (Ono Y. *Res Dev Disabil.* 1996;17:303-9). (2) The ABC-J showed good test-retest reliability in patients with autism spectrum disorder who displayed abnormal behavior (Enokizono T et al. *Rinsho Iyaku.* 2014;30:271-7). (3) The ABC-J has been used in clinical research of patients with autistic disorder (Kato K et al. *Clinical Neuropharmacology and Therapeutics.* 2011;2:9-11; Kato K et al. *Japanese Journal of Clinical Psychopharmacology.* 2011;14:1845-50). In addition, a foreign phase III study (5.3.5.1.2: Study RIS-USA-150 Part 1) used the ABC irritability (agitation) subscale score as the primary endpoint, and demonstrated the efficacy of risperidone in patients with autistic disorder and irritability. This is another reason the ABC-J irritability (agitation) subscale score was used as the primary endpoint in the Japanese phase III study.

PMDA asked the applicant to explain the measures taken to assure the inter-rater reliability in the efficacy assessment in the Japanese phase III study.

The applicant's explanation:

In order to ensure consistency between raters in ABC-J ratings, investigators and subinvestigators were obliged to take a training course for raters (by participating in a face-to-face seminar or by watching the DVD recording of the seminar). They were also provided with a guidance book on ABC-J to maintain inter-rater consistency in assessment. As a measure to maintain uniformity of assessment, the same caregiver of each subject was interviewed by the same rater using the same criteria throughout the study. In addition, the inclusion criteria for the study¹²⁾ required subjects to have an appropriate caregiver so that the uniformity of assessment was assured. In summary, the efficacy of risperidone was properly

12) The inclusion criteria specify that all subjects require an adequate caregiver (e.g., a parent, a facility staff member) deemed by the investigator or subinvestigator to be capable of monitoring the subject's condition, providing information about the subject's condition, and assessing the subject's response to treatment appropriately.

assessed using ABC-J in the Japanese phase III study.

(b) Study patients

PMDA asked the applicant to provide the rationale for the following inclusion criterion in the Japanese phase III study: "Subjects with a Clinical Global Impression-Severity (CGI-S) score of ≥ 4 and an ABC-J irritability (agitation) subscale score of ≥ 18 at screening."

The applicant's explanation:

Risperidone is expected to be administered to patients with autistic disorder with moderate to severe irritability. A CGI-S score of ≥ 4 was included in the criterion, because it corresponds to moderate to severe autistic disorder. An ABC-J irritability (agitation) subscale score of 18 is 1.3- to 1.5 standard deviation above the population mean in several clinical studies in patients with developmental disorder (McCracken JT et al. *N Engl J Med.* 2002;347:314-21) and corresponds to the 85th percentile in the score distribution in children and students in special needs classes based on teachers' assessment (Aman MG, Singh NN. Clinical assessment of developmental disorder using the Aberrant Behavior Checklist-Japanese Version (ABC-J). Jiho, 2006). Accordingly, patients with autistic disorder with relatively severe irritability can be identified by the criterion "an ABC-J irritability (agitation) subscale score of ≥ 18 ."

PMDA accepted the above explanation, and considers that there should be no problem with reviewing the efficacy of risperidone on the basis of the results of the Japanese phase III study.

3.(ii).B.(1).2) Factors that may affect the efficacy of risperidone

PMDA asked the applicant to explain the factors that may affect the efficacy of risperidone.

The applicant's explanation:

Table 11 shows the change in the ABC-J irritability (agitation) subscale score from baseline to the last assessment in the double-blind phase of the Japanese phase III clinical study (listed by patient characteristics). The difference between risperidone and placebo tended to be small in the subgroups of subjects ≥ 9 years of age and subjects with an IQ score of ≤ 79 . However, such trend was not observed in foreign clinical studies (Reference 5.3.5.1.2, Study RIS-USA-150; and Reference 5.3.5.1.4, Study RIS-CAN-23); thus the impact of age or IQ score on the efficacy of risperidone is unclear. The impact of body weight on the efficacy of risperidone could not be assessed due to the limited number of subjects in the subgroups weighing < 20 kg or ≥ 45 kg. In addition, no subjects received central nervous system depressants, CYP2D6 inhibitors, or itraconazole¹³⁾ in combination with risperidone, and only 1 subject received concomitant non-pharmacotherapy (play therapy). Therefore, the impact of these concomitant medications or non-pharmacotherapy on the efficacy of risperidone could not be assessed.

13) These drugs are listed in the "Precautions for Concomitant Use" section in the package insert of risperidone, because the combination of risperidone and any of the drugs may enhance the effects of risperidone and the drug, or may increase blood concentrations of risperidone and its active moiety.

Table 11. Change in ABC-J irritability (agitation) subscale score from baseline to the last assessment in the double-blind phase of the Japanese phase III clinical study by patient characteristics (FAS, LOCF)

	Treatment group	No. of subjects assessed	Subscale score		Change from baseline	Between-group difference [95% CI] ^{a)}	
			Baseline	Last assessment			
Age	5 to 8 years	Placebo	10	29.0 ± 5.21	28.5 ± 7.26	-0.5 ± 4.03	-10.3 [-16.2, -4.4]
		Risperidone	11	28.3 ± 5.06	17.4 ± 9.52	-10.9 ± 7.78	
	9 to 12 years	Placebo	4	27.5 ± 4.51	24.3 ± 8.69	-3.3 ± 10.14	-3.1 [-16.3, 10.1]
		Risperidone	6	29.2 ± 9.47	23.0 ± 13.56	-6.2 ± 6.52	
	≥13 years	Placebo	4	23.8 ± 5.38	15.5 ± 10.66	-8.3 ± 6.24	-4.6 [-17.6, 8.3]
		Risperidone	4	26.8 ± 5.44	15.0 ± 8.60	-11.8 ± 6.80	
Gender	Male	Placebo	14	28.3 ± 5.40	26.3 ± 9.51	-2.0 ± 6.60	-7.4 [-12.6, -2.1]
		Risperidone	16	28.6 ± 6.87	19.3 ± 11.13	-9.3 ± 7.41	
	Female	Placebo	4	24.8 ± 4.19	19.0 ± 7.87	-5.8 ± 6.70	-5.4 [-18.8, 8.0]
		Risperidone	5	27.2 ± 4.82	16.2 ± 9.23	-11.0 ± 7.58	
Body weight	<20 kg	Placebo	2	28.5 ± 3.54	22.5 ± 4.95	-6.0 ± 1.41	-1.2 [-29.5, 27.0]
		Risperidone	3	32.7 ± 5.51	27.0 ± 9.85	-5.7 ± 6.66	
	≥20 kg to <45 kg	Placebo	15	27.1 ± 5.62	24.7 ± 10.26	-2.5 ± 7.17	-8.4 [-14.0, -2.8]
		Risperidone	14	28.0 ± 6.77	17.4 ± 10.75	-10.6 ± 7.44	
	≥45 kg	Placebo	1	31.0	29.0	-2.0	-6.8 [-61.3, 47.8]
		Risperidone	4	25.8 ± 4.72	16.3 ± 9.67	-9.5 ± 8.06	
IQ score ^{b)}	≤79	Placebo	8	26.3 ± 4.37	21.5 ± 9.55	-4.8 ± 6.50	-2.2 [-8.9, 4.5]
		Risperidone	12	28.9 ± 6.16	22.5 ± 9.22	-6.4 ± 6.78	
	>79	Placebo	10	28.5 ± 5.91	27.2 ± 9.09	-1.3 ± 6.63	-12.6 [-18.7, -6.5]
		Risperidone	9	27.3 ± 6.87	13.2 ± 10.34	-14.1 ± 5.64	
ABC-J irritability (agitation) subscale score at baseline ^{b)}	≤28	Placebo	12	24.8 ± 3.17	21.9 ± 9.47	-2.8 ± 7.69	-5.6 [-12.5, 1.4]
		Risperidone	10	23.2 ± 3.71	13.7 ± 9.24	-9.5 ± 7.75	
	>28	Placebo	6	33.0 ± 4.20	30.2 ± 7.31	-2.8 ± 4.36	-7.0 [-13.4, -0.5]
		Risperidone	11	32.8 ± 4.47	22.9 ± 10.10	-9.9 ± 7.23	

Mean ± standard deviation

a) Based on an analysis-of-covariance model using treatment groups as factors, and baseline values as covariates.

b) Stratified by median

As risperidone is classified as an antipsychotic drug, the impact of AEs related to sedation¹⁴⁾ on the efficacy of risperidone was evaluated. The change from baseline in ABC-J irritability (agitation) subscale score in the risperidone group did not differ substantially between subjects with and without sedation-related AEs (Table 12). In subjects without sedation-related AEs, the change was larger in the risperidone group than in the placebo group (Table 12). In subjects with sedation-related AEs, the change was larger in the placebo group than in the risperidone group; however, no clear conclusion could be drawn regarding this finding because of the small number of subjects in the placebo group. In the long-term extension phase of the Japanese phase III study and in foreign clinical studies (Study RIS-USA-150 and Study RIS-CAN-23), the efficacy of risperidone was shown regardless of occurrence of sedation-related AEs.

14) AEs coded to the following MedDRA PTs: Somnolence, sedation, lethargy, hypersomnia, asthenia, apathy, malaise, fatigue, depressed level of consciousness, stupor, coma, sopor, decreased activity, listless, and sluggishness.

Table 12. Change in ABC-J irritability (agitation) subscale score from baseline to the last assessment in the double-blind phase of the Japanese phase III study in subjects with and without adverse events related to sedation (FAS, LOCF)

		Treatment group	No. of subjects assessed	Subscale score		Change from baseline	Difference from placebo [95% CI] ^{a)}
				Baseline	Last assessment		
AEs related to sedation	Yes	Placebo	2	25.5 ± 3.54	11.5 ± 4.95	-14.0 ± 1.41	4.7 [-8.6, 18.0]
		Risperidone	11	29.4 ± 5.10	20.3 ± 9.11	-9.1 ± 7.41	
	No	Placebo	16	27.8 ± 5.47	26.3 ± 8.61	-1.4 ± 5.55	-8.8 [-14.0, -3.5]
		Risperidone	10	27.0 ± 7.59	16.6 ± 12.17	-10.4 ± 7.50	

Mean ± standard deviation

a) Based on an analysis-of-covariance model using treatment groups as factors, and baseline values as covariates

On the basis of the above, the applicant considers that the efficacy of risperidone is unlikely to be affected by occurrence of AEs related to sedation.

Patients previously treated with antipsychotic drugs including risperidone were eligible for the Japanese phase III study. Table 13 summarizes the change in ABC-J irritability (agitation) subscale score by prior treatment. Because of the small number of patients receiving prior treatment with antipsychotic drugs including risperidone, it was difficult to evaluate the impact of prior treatment with antipsychotic drugs including risperidone on the efficacy of risperidone. The applicant also evaluated the change in ABC-J irritability (agitation) subscale score in subjects with and without prior treatment with antiepileptic drugs (Table 13). Because of the small number of patients with prior treatment with antiepileptic drugs, it was difficult to evaluate the impact of prior treatment with antiepileptic drugs on the efficacy of risperidone.

Table 13. Change in ABC-J irritability (agitation) subscale score from baseline in the double-blind phase of the Japanese phase III study in subjects with and without prior treatment (FAS, LOCF)

		Treatment group	No. of subjects assessed	Subscale score		Change from baseline	Between-group difference [95% CI] ^{a)}
				Baseline	Last assessment		
Prior treatment with antipsychotic drugs ^{b)}	Yes	Placebo	1	31.0	29.0	-2.0	-10.4 [-85.6, 64.9]
		Risperidone	4	26.5 ± 2.65	20.3 ± 9.64	-6.3 ± 10.24	
	No	Placebo	17	27.3 ± 5.35	24.4 ± 9.70	-2.9 ± 6.82	-8.1 [-12.7, -3.5]
		Risperidone	17	28.6 ± 6.95	18.1 ± 11.01	-10.5 ± 6.57	
Prior treatment with risperidone	Yes	Placebo	1	31.0	29.0	-2.0	22.0
		Risperidone	2	24.5 ± 0.71	25.0 ± 2.83	0.5 ± 2.12	
	No	Placebo	17	27.3 ± 5.35	24.4 ± 9.70	-2.9 ± 6.82	-8.4 [-12.9, -3.9]
		Risperidone	19	28.6 ± 6.57	17.8 ± 10.88	-10.8 ± 6.79	
Prior treatment with antiepileptic drugs	Yes	Placebo	3	24.7 ± 6.51	21.3 ± 13.28	-3.3 ± 8.08	-4.6 [-20.0, 10.9]
		Risperidone	6	26.0 ± 4.38	18.3 ± 8.52	-7.7 ± 8.29	
	No	Placebo	15	28.1 ± 5.05	25.3 ± 9.00	-2.7 ± 6.62	-8.2 [-13.1, -3.2]
		Risperidone	15	29.1 ± 6.92	18.6 ± 11.56	-10.5 ± 7.00	

Mean ± standard deviation

a) Based on an analysis-of-covariance model using treatment groups as factors, and baseline values as covariates

b) Risperidone, aripiprazole, olanzapine, quetiapine, or levomepromazine

PMDA's view:

The submitted clinical study data suggest that the baseline characteristics evaluated are unlikely to have substantial impact on the efficacy of risperidone. However, because of the small number of subjects evaluated, the applicant should continue to collect information on factors that may affect the efficacy of risperidone via post-marketing surveillance.

As a result of the above review, PMDA has concluded that the Japanese phase III study showed the

superiority of risperidone over placebo and demonstrated the efficacy of risperidone on irritability associated with autistic disorder in Japanese children and adolescents.

3.(ii).B.(2) Safety of risperidone

PMDA asked the applicant to explain whether the safety profile of risperidone differs between children and adolescents with autistic disorder and irritability and patients with schizophrenia (the approved indication).

The applicant's explanation:

Incidence of AEs in Japanese and foreign clinical studies in patients with autistic disorder¹⁵⁾ and in adults with schizophrenia¹⁶⁾ is summarized in Tables 14 and 15. The incidence of somnolence, increased appetite, and weight increased was higher in children and adolescents with autistic disorder than in adults with schizophrenia. Pyrexia was the only AE related to neuroleptic malignant syndrome¹⁷⁾ observed in the Japanese clinical studies of risperidone in children and adolescents with autistic disorder. (Pyrexia occurred in 1 of 35 patients [2.9%] in the Japanese long-term study.)

15) (a) Japanese short-term study = The double-blind phase of the Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01) (8 weeks)
(b) Japanese long-term study = The long-term extension phase of the Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01) (48 weeks)
(c) Foreign short-term studies = Pooled data from Study RIS-USA-150 Part 1 (8 weeks; Reference 5.3.5.1.2), Study RIS-CAN-23 (8 weeks; Reference 5.3.5.1.4), and the double-blind phase of Study RIS-AUT-4002 (6 weeks; Reference 5.3.5.1.5; excluding subjects who received risperidone at low doses in the double-blind phase)
(d) Foreign long-term studies = Pooled data from Study RIS-USA-150 Part 2 (4 months; Reference 5.3.5.1.3; including data from the open-label extension phase following Part 1), and the open-label phase (26 weeks) of Study RIS-AUT-4002 (5.3.5.1.5).

16) (a) Japanese short-term studies = Pooled data from the risperidone groups in a clozapamine-controlled phase III study (8 weeks) (Initial New Drug Application Data *G-4* [only in Japanese]) and a haloperidol-controlled phase III study (8 weeks) (Initial New Drug Application Data *G-5* [only in Japanese]);
(b) Japanese long-term study = Long-term study (≥ 6 months) (Initial New Drug Application Data *G-11* [only in Japanese]);
(c) Foreign short-term studies = Pooled data from the risperidone groups in Study RIS-INT-3 (8 weeks), Study RIS-USA-1 (6 weeks), and Study RIS-USA-72 (4 weeks);
(d) Foreign long-term studies = Pooled data from Study RIS-USA-6 (1 year), Study RIS-USA-9 (1 year), and Study RIS-INT-4 (1 year)

17) AEs included in the standardized MedDRA query (SMQ) search for "neuroleptic malignant syndrome."

Table 14. Incidence of adverse events reported in Japanese clinical studies in children and adolescents with autistic disorder or adults with schizophrenia

	Adverse Events			Adverse Events for which a causal relationship to the study drug could not be ruled out ^{a)}				
	Short-term study ^{b)}		Long-term study ^{c)}	Short-term studies			Long-term studies	
Patients	Children/adolescents with autistic disorder		Children/adolescents with autistic disorder	Children/adolescents with autistic disorder ^{b)}		Adults with schizophrenia ^{d)}	Children/adolescents with autistic disorder ^{e)}	Adults with schizophrenia ^{e)}
Treatment group	Placebo	Risperidone	Risperidone	Placebo	Risperidone	Risperidone	Risperidone	Risperidone
No. of subjects assessed	18	21	35	18	21	201	35	83
Overall adverse events	16 (88.9)	19 (90.5)	34 (97.1)	5 (27.8)	14 (66.7)	110 (54.7)	28 (80.0)	53 (63.9)
Commonly observed events								
Somnolence	2 (11.1)	11 (52.4)	17 (48.6)	2 (11.1)	11 (52.4)	11 (5.5) ^{f)}	17 (48.6)	5 (6.0) ^{f)}
Increased appetite	0	5 (23.8)	10 (28.6)	0	5 (23.8)	2 (1.0)	9 (25.7)	3 (3.6)
Weight increased	0	4 (19.0)	12 (34.3)	0	4 (19.0)	2 (1.0)	12 (34.3)	3 (3.6)
Vomiting	0	3 (14.3)	6 (17.1)	0	0	11 (5.5) ^{g)}	0	3 (3.6) ^{g)}
Nasopharyngitis	1 (5.6)	2 (9.5)	10 (28.6)	0	0	0	0	0
Drooling	0	2 (9.5)	2 (5.7)	0	2 (9.5)	23 (11.4) ^{h)}	2 (5.7)	10 (12.0) ^{h)}
Anxiety	0	2 (9.5)	1 (2.9)	0	2 (9.5)	16 (8.0) ⁱ⁾	1 (2.9)	5 (6.0) ⁱ⁾
Dizziness	0	2 (9.5)	1 (2.9)	0	2 (9.5)	9 (4.5) ^{j)} 4 (2.0) ^{k)}	1 (2.9)	3 (3.6) ^{j)} 3 (3.6) ^{k)}
Malaise	0	2 (9.5)	0	0	2 (9.5)	11 (5.5)	0	8 (9.6)
Influenza	0	1 (4.8)	7 (20.0)	0	0	0	0	0
Gastroenteritis	1 (5.6)	1 (4.8)	5 (14.3)	0	0	0	0	0
Enuresis	2 (11.1)	1 (4.8)	2 (5.7)	2 (11.1)	0	0	1 (2.9)	1 (1.2)
Diarrhoea	2 (11.1)	1 (4.8)	2 (5.7)	0	0	0 ^{l)}	0	1 (1.2) ^{l)}
Pyrexia	2 (11.1)	0	1 (2.9)	0	0	0	0	0
Constipation	0	0	5 (14.3)	0	0	14 (7.0)	2 (5.7)	9 (10.8)
Upper respiratory tract inflammation	0	0	5 (14.3)	0	0	0	0	0
Hyperprolactinaemia	0	0	4 (11.4)	0	0	0	4 (11.4)	0
Conjunctivitis	0	0	4 (11.4)	0	0	0	0	0

No. of subjects with AEs (incidence %)

a) This category presents only adverse events for which a causal relationship could not be ruled out, because no other types of AE data are available to date from the studies in adults with schizophrenia (Initial New Drug Application Data Summary *Table G-109* [only in Japanese]).

b) Footnote 15)-(a);

c) Footnote 15)-(b);

d) Footnote 16)-(a);

e) Footnote 16)-(b);

f) sleepiness;

g) nausea/vomiting;

h) salivation;

i) anxiety/feeling irritated;

j) lightheadedness;

k) dizziness;

l) diarrhoea/abdominal pain

Table 15. Incidence of adverse events reported in foreign clinical studies in children and adolescents with autistic disorder or adults with schizophrenia

Patients	Short-term studies				Long-term studies	
	Children/adolescents with autistic disorder ^{a)}		Adults with schizophrenia ^{b)}		Children/adolescents with autistic disorder ^{c)}	Adults with schizophrenia ^{d)}
Treatment group	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone
No. of subjects assessed	126	120	225	564	149	758
Overall adverse events	105 (83.3)	115 (95.8)	162 (72.0)	453 (80.3)	114 (76.5)	506 (66.8)
Most commonly observed events						
Increased appetite	20 (15.9)	53 (44.2)	1 (0.4)	1 (0.2)	47 (31.5)	2 (0.3)
Somnolence	15 (11.9)	51 (42.5)	2 (0.9)	29 (5.1)	27 (18.1)	23 (3.0)
Fatigue	11 (8.7)	36 (30.0)	0	11 (2.0)	33 (22.1)	29 (3.8)
Sedation	2 (1.6)	31 (25.8)	2 (0.9)	17 (3.0)	16 (10.7)	16 (2.1)
Vomiting	19 (15.1)	24 (20.0)	15 (6.7)	33 (5.9)	25 (16.8)	22 (2.9)
Constipation	8 (6.3)	22 (18.3)	14 (6.2)	48 (8.5)	11 (7.4)	28 (3.7)
Cough	15 (11.9)	21 (17.5)	5 (2.2)	14 (2.5)	29 (19.5)	17 (2.2)
Nasopharyngitis	10 (7.9)	21 (17.5)	7 (3.1)	19 (3.4)	16 (10.7)	35 (4.6)
Pyrexia	17 (13.5)	18 (15.0)	3 (1.3)	7 (1.2)	16 (10.7)	6 (0.8)
Enuresis	12 (9.5)	18 (15.0)	0	0	27 (18.1)	2 (0.3)
Headache	12 (9.5)	16 (13.3)	50 (22.2)	113 (20.0)	17 (11.4)	74 (9.8)
Rhinorrhoea	12 (9.5)	15 (12.5)	2 (0.9)	5 (0.9)	8 (5.4)	1 (0.1)
Nasal congestion	4 (3.2)	15 (12.5)	5 (2.2)	25 (4.4)	9 (6.0)	36 (4.7)
Anxiety	13 (10.3)	13 (10.8)	24 (10.7)	80 (14.2)	18 (12.1)	66 (8.7)
Drooling	4 (3.2)	13 (10.8)	1 (0.4)	1 (0.2)	16 (10.7)	3 (0.4)
Diarrhoea	18 (14.3)	11 (9.2)	3 (1.3)	8 (1.4)	21 (14.1)	18 (2.4)
Weight increased	3 (2.4)	10 (8.3)	0	5 (0.9)	10 (6.7)	36 (4.7)
Dizziness	2 (1.6)	10 (8.3)	5 (2.2)	34 (6.0)	7 (4.7)	29 (3.8)

No. of subjects with AEs (incidence %)

a) Footnote 15)-(c);

b) Footnote 16)-(c);

c) Footnote 15)-(d);

d) Footnote 16)-(d)

The following sections present the applicant's view on (1) the AEs commonly reported in children and adolescents with autistic disorder; and (2) the following AEs in the known safety profile of risperidone: sedation, growth and weight gain, extrapyramidal symptoms, cardiovascular events, and events related to suicide or hostility/aggression.

3.(ii).B.(2).1 Adverse events related to sedation

The applicant's explanation:

Table 16 shows the incidence of AEs related to sedation¹⁴⁾ in Japanese and foreign clinical studies in patients with autistic disorder.¹⁵⁾ In Japanese and foreign short-term studies, the incidence of AEs related to sedation was higher in the risperidone group than in the placebo group, but most of the events were mild or moderate. In the Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01), the incidence of AEs related to sedation by modal dose of risperidone was as follows: 55.6% (5 of 9 subjects) for <0.05 mg/kg/day, 50.0% (6 of 12 subjects) for ≥0.05 mg/kg/day in the double-blind phase; and 63.6% (7 of 11 subjects) for <0.05 mg/kg/day, 66.7% (4 of 6 subjects) for ≥0.05 mg/kg/day in the long-term extension phase. There was no relationship between the dose of risperidone and the incidence of AEs related to sedation. In the Japanese phase III study, AEs related to sedation occurred more frequently during the initial phase of treatment, and many of the events occurred in the first 28 days of treatment.

Table 16. Incidence of adverse events related to sedation in Japanese and foreign clinical studies of risperidone

	Short-term studies				Long-term studies	
	Japanese study ^{a)}		Foreign studies ^{b)}		Japanese study ^{c)}	Foreign studies ^{d)}
Treatment group	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone
No. of subjects assessed	18	21	126	120	35	149
AEs related to sedation	2 (11.1)	11 (52.4)	28 (22.2)	95 (79.2)	17 (48.6)	56 (37.6)
Commonly observed events						
Somnolence	2 (11.1)	11 (52.4)	15 (11.9)	51 (42.5)	17 (48.6)	27 (18.1)
Malaise	0	2 (9.5)	1 (0.8)	1 (0.8)	0	0
Fatigue	0	0	11 (8.7)	36 (30.0)	0	33 (22.1)
Sedation	0	0	2 (1.6)	31 (25.8)	0	16 (10.7)
Lethargy	0	0	2 (1.6)	6 (5.0)	0	4 (2.7)
Sluggishness	0	0	0	3 (2.5)	0	0
Hypersomnia	0	0	4 (3.2)	2 (1.7)	0	1 (0.7)
Listless	0	0	0	2 (1.7)	0	0

No. of subjects with AE (incidence %)

a) Footnote 15)-(a);

b) Footnote 15)-(c);

c) Footnote 15)-(b);

d) Footnote 15)-(d)

Among subjects who experienced AEs related to sedation in the Japanese phase III study, none had AEs related to injury.¹⁸⁾ Table 17 summarizes the incidence of AEs related to injury in subjects in foreign clinical studies¹⁵⁾ by occurrence of AEs related to sedation. Only a small number of subjects experienced both sedation-related and injury-related AEs.

Table 17. Incidence of adverse events related to injury in subjects with and without adverse events related to sedation in foreign clinical studies

	Short-term studies ^{a)}				Long-term studies ^{b)}	
	Yes		No		Yes	No
Treatment group	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone
No. of subjects assessed	28	95	98	25	56	93
AEs related to injury	1 (3.6)	5 (5.3)	4 (4.1)	0	4 (7.1)	1 (1.1)

No. of patients with AEs (incidence %)

a) Footnote 15)-(c);

b) Footnote 15)-(d)

Based on the above, the applicant considers that sedation induced by risperidone probably had no effect on the occurrence of AEs related to injury.

In the foreign post-marketing safety information (data cut-off on May 31, 2015), the incidence rate of AEs related to sedation by age was 972 events in 7,369,983 person-years (0.1319 events per 1000 person-years) in children/adolescents 5 to 17 years of age, and 5440 events in 29,573,809 person-years (0.1839 events per 1000 person-years) in adults ≥ 18 years of age. Thus the incidence rate did not substantially differ between children/adolescents and adults. The incidence rate of AEs related to sedation in children/adolescents by therapeutic indication was 99 events in 77,024 person-years (1.2853 events per 1000 person-years) for schizophrenia, 96 events in 4,306,936 person-years (0.0223 events per 1000 person-years) for autistic disorder, and 763 events in 2,986,025 person-years (0.2555 events per 1000 person-years) for other indications. There was no trend of a particularly high incidence rate in patients with autistic disorder.

The applicant's conclusion:

18) AEs included in the standardized MedDRA SMQ "accidents and injuries (narrow terms) "

No additional precautionary statement regarding sedation-related AEs is required for the following reasons: (1) Sedation-related AEs occurred regardless of risperidone dose level in children and adolescents with autistic disorder and irritability. However, sedation has a low risk of causing injury or other events, and the risk of sedation-related AEs in such children/adolescents is unlikely to exceed the risk in adults with schizophrenia. (2) The current package insert includes a precautionary statement about drowsiness and decline of attention/concentration/reflex action ability.

3.(ii).B.(2).2) Effects on growth and body weight gain

The applicant explained the incidence of AEs related to growth disorder (i.e., AEs related to physical growth, psychological development, and sexual maturity) in Japanese and foreign clinical studies in patients with autistic disorder¹⁵⁾:

The applicant's explanation:

No subjects in the Japanese phase III study experienced AEs related to growth disorder. In foreign short-term studies, AEs related to sexual maturity occurred only in 1 of 126 subjects (0.8%) receiving placebo (dysmenorrhea) and 5 of 120 subjects (4.2%) receiving risperidone (amenorrhoea, menstrual disorder, menstruation irregular, oligomenorrhoea, and vaginal disorder in 1 subject each). In foreign long-term studies, AEs related to sexual maturity occurred only in 3 of 149 subjects (2.0%) (menstruation irregular, scrotal pain, and hydrocele in 1 subject each). Although hyperprolactinaemia has been reported to affect sexual maturation,¹⁹⁾ there was no AEs related to hyperprolactinaemia in the Japanese short-term studies. In the Japanese long-term studies, AEs related to hyperprolactinaemia occurred in 4 of 26 male subjects (15.4%; hyperprolactinaemia) and 1 of 9 female subjects (11.1%; blood prolactin increased), but none exhibited clinical symptoms. Table 18 shows the incidence rates of AEs related to growth disorder in children and adolescents by therapeutic indication in the foreign post-marketing safety information. In all event categories, the incidence rates are low and do not tend to be higher in patients with autistic disorder than in those with other target diseases.

Table 18. Incidence rate of adverse events related to growth and development in foreign post-marketing safety information

	Autistic disorder	Schizophrenia	Other indications
Estimated total exposure (person-years)	4,306,936	77,024	2,986,025
AEs related to physical development	10 (0.0023)	4 (0.0519)	59 (0.0198)
AEs related to mental development	0	0	2 (0.0007)
AEs related to sexual maturity	30 (0.0070)	56 (0.7270)	284 (0.0951)

No. of patients with AEs (incidence rate [number of events per 1000 person-years]), Data cut off on May 31, 2015

The applicant presented changes from baseline in body weight and height in subjects in the Japanese and foreign clinical studies¹⁵⁾ in percentile values calculated using database from Japan and overseas²⁰⁾

19) Peuskens J et al. *CNS Drugs*. 2014;28:421-53; Maranghi F et al. *Expert Opin Drug Metab Toxicol*. 2013;9:1309-16; Rosenbloom AL. *Int J Pediatr Endocrinol*. 2010;pii:159402; Talib HJ, Alderman EM. *J Pediatr Adolesc Gynecol*. 2013;26:7-15; Eren E et al. *J Clin Res Ped Endo*. 2011;3:65-69.

20) Percentile values were calculated using the following reference data:

Japan: Data published by the Japanese Society for Pediatric Endocrinology (<http://jspe.umin.jp/medical/files/fuhyo1.pdf>).

Overseas: Data published by the Centers for Disease Control and Prevention (http://www.cdc.gov/growthcharts/html_charts/wtage.htm [for body weight], http://www.cdc.gov/growthcharts/html_charts/stage.htm [for height]).

(Table 19). In the short-term studies, body weight tended to increase more in the risperidone group than in the placebo group, but the change in height did not differ substantially between the groups. The long-term studies showed a trend of increase in both body weight and height. Table 19 summarizes the percentile values of body weight and height in patients with and without AEs related to increased appetite.²¹⁾ In Japanese clinical studies, the change in percentile body weight or height did not differ substantially by occurrence of AEs related to increased appetite. In the foreign clinical studies, however, body weight percentile tended to increase more clearly in subjects with AEs related to increased appetite than in those without such AEs; this finding suggests that increased appetite may affect body weight.

21) AEs coded to the following MedDRA PTs: Increased appetite, hyperphagia, binge eating, food hoarding, food craving, bulimia nervosa, and lack of satiety

Table 19. Changes from baseline in height and body weight percentile in Japanese and foreign clinical studies

Treatment group	Short-term studies				Long-term studies			
	Japanese study ^{a)}		Foreign studies ^{b)}		Japanese study ^{c)}	Foreign studies ^{d)}		
	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone		
Body weight	Overall population							
	Baseline	48.14 ± 29.16 (18)	42.34 ± 29.45 (21)	63.51 ± 30.32 (125)	61.74 ± 31.00 (114)	44.39 ± 29.47 (35)	64.11 ± 31.71 (141)	
	Last assessment	49.56 ± 28.55 (18)	51.08 ± 28.49 (21)	64.47 ± 29.52 (123)	70.76 ± 27.00 (118)	54.93 ± 27.88 (35)	73.39 ± 28.07 (148)	
	Change from baseline	1.43 ± 4.87 (18)	8.73 ± 5.06 (21)	1.17 ± 6.89 (122)	9.34 ± 11.27 (112)	10.54 ± 11.52 (35)	9.47 ± 12.77 (140)	
	Subjects with AEs related to increased appetite							
	Baseline	-	33.73 ± 37.51 (5)	64.54 ± 30.80 (20)	59.36 ± 31.03 (49)	41.17 ± 37.57 (10)	64.25 ± 31.63 (75)	
	Last assessment	-	40.11 ± 35.74 (5)	66.66 ± 30.22 (20)	69.08 ± 27.05 (54)	51.35 ± 36.56 (10)	75.29 ± 27.20 (81)	
	Change from baseline	-	6.39 ± 3.73 (5)	2.12 ± 3.65 (20)	11.34 ± 12.67 (49)	10.18 ± 13.55 (10)	11.68 ± 14.34 (75)	
	Subjects without AEs related to increased appetite							
	Baseline	48.14 ± 29.16 (18)	45.04 ± 27.37 (16)	63.31 ± 30.38 (105)	63.53 ± 31.10 (65)	45.68 ± 26.36 (25)	63.95 ± 32.04 (66)	
	Last assessment	49.56 ± 28.55 (18)	54.50 ± 26.24 (16)	64.04 ± 29.51 (103)	72.19 ± 27.09 (64)	56.36 ± 24.34 (25)	71.10 ± 29.12 (67)	
	Change from baseline	1.43 ± 4.87 (18)	9.46 ± 5.29 (16)	0.99 ± 7.36 (102)	7.78 ± 9.88 (63)	10.68 ± 10.91 (25)	6.92 ± 10.21 (65)	
	Height	Overall population						
		Baseline	40.66 ± 28.00 (18)	37.80 ± 29.09 (21)	54.30 ± 30.73 (83)	49.44 ± 33.40 (74)	36.26 ± 26.82 (35)	52.10 ± 32.52 (138)
		Last assessment	42.00 ± 27.84 (18)	38.05 ± 28.81 (21)	55.22 ± 29.58 (84)	50.56 ± 31.86 (77)	42.49 ± 27.85 (35)	54.61 ± 31.54 (148)
Change from baseline		1.34 ± 3.38 (18)	0.25 ± 4.28 (21)	0.85 ± 7.26 (80)	-0.56 ± 11.37 (72)	6.23 ± 6.64 (35)	2.47 ± 10.56 (137)	
Subjects with AEs related to increased appetite								
Baseline		-	22.50 ± 21.71 (5)	43.97 ± 28.79 (16)	47.22 ± 35.86 (41)	33.80 ± 31.69 (10)	49.97 ± 33.35 (72)	
Last assessment		-	22.16 ± 19.67 (5)	44.26 ± 28.71 (16)	46.86 ± 31.71 (45)	38.51 ± 33.22 (10)	51.90 ± 31.99 (81)	
Change from baseline		-	-0.34 ± 2.57 (5)	0.29 ± 8.17 (16)	-1.23 ± 14.25 (41)	4.72 ± 7.43 (10)	2.35 ± 11.92 (72)	
Subjects without AEs related to increased appetite								
Baseline		40.66 ± 28.00 (18)	42.58 ± 30.00 (16)	56.77 ± 30.87 (67)	52.21 ± 30.37 (33)	37.25 ± 25.28 (25)	54.41 ± 31.67 (66)	
Last assessment		42.00 ± 27.84 (18)	43.02 ± 29.89 (16)	57.80 ± 29.40 (68)	55.77 ± 31.84 (32)	44.08 ± 25.99 (25)	57.89 ± 30.90 (67)	
Change from baseline		1.34 ± 3.38 (18)	0.43 ± 4.75 (16)	0.99 ± 7.08 (64)	0.32 ± 5.81 (31)	6.83 ± 6.35 (25)	2.60 ± 8.90 (65)	

Mean ± standard deviation (Number of subjects);

-: No applicable subjects

a) Footnote 15)-(a);

b) Footnote 15)-(c);

c) Footnote 15)-(b);

d) Footnote 15)-(d)

The applicant's conclusion:

Subjects receiving risperidone in Japanese and foreign clinical studies tended to have a larger body weight gain than the general population. Therefore, the applicant will advise healthcare professionals to periodically monitor the safety and efficacy of risperidone in pediatric patients with autistic disorder, and not to use the drug for a long period aimlessly in the population. However, no additional precautionary statement about other AEs related to growth disorder is necessary because the incidence of such AEs is low.

3.(ii).B.(2).3 Adverse events related to extrapyramidal symptoms

The applicant's explanation:

Table 20 summarizes the incidence of AEs related to extrapyramidal symptoms²²⁾ in the Japanese and foreign clinical studies in patients with autistic disorder.¹⁵⁾ No subjects in the Japanese studies experienced clinically significant AEs related to extrapyramidal symptoms. In the foreign short-term studies, the incidence of AEs related to extrapyramidal symptoms tended to be higher in subjects receiving risperidone than in subjects receiving placebo; the events occurred more frequently during the initial phase of treatment. No tardive dyskinesia was reported in any of the Japanese and foreign clinical studies. Risperidone may pose a risk of AEs related to extrapyramidal disorder or tardive dyskinesia in children and adolescents with autistic disorder. However, no additional precautionary statements are necessary because the risk is already mentioned in the current package insert.

Table 20. Incidence of AEs related to extrapyramidal symptoms in Japanese and foreign clinical studies

	Short-term studies				Long-term studies	
	Japanese study ^{a)}		Foreign studies ^{b)}		Japanese study ^{c)}	Foreign studies ^{d)}
Treatment group	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone
No. of subjects assessed	18	21	126	120	35	149
AEs related to extrapyramidal symptoms	0	2 (9.5)	24 (19.0)	38 (31.7)	3 (8.6)	29 (19.5)
Commonly observed events						
Drooling	0	2 (9.5)	4 (3.2)	13 (10.8)	2 (5.7)	16 (10.7)
Tremor	0	0	1 (0.8)	11 (9.2)	0	7 (4.7)
Dyskinesia	0	0	3 (2.4)	5 (4.2)	0	4 (2.7)
Musculoskeletal stiffness	0	0	2 (1.6)	4 (3.3)	0	4 (2.7)
Restlessness	0	0	6 (4.8)	3 (2.5)	0	1 (0.7)
Akathisia	0	0	2 (1.6)	3 (2.5)	0	1 (0.7)
Muscle rigidity	0	0	0	3 (2.5)	0	1 (0.7)
Psychomotor hyperactivity	0	0	2 (1.6)	2 (1.7)	0	3 (2.0)
Extrapyramidal disorder	0	0	0	2 (1.7)	0	0
Masked facies	0	0	0	2 (1.7)	0	0
Movement disorder	0	0	0	2 (1.7)	0	0
Hypertonia	0	0	3 (2.4)	1 (0.8)	0	1 (0.7)

No. of subjects with AEs (incidence %)

a) Footnote 15)-(a);

b) Footnote 15)-(c);

c) Footnote 15)-(b);

d) Footnote 15)-(d)

3.(ii).B.(2).4 Effects on the cardiovascular system

The applicant's explanation:

Table 21 summarizes the incidence of QT/QT_C interval prolongation and proarrhythmic events²³⁾ in patients with autistic disorder in Japanese and foreign clinical studies.¹⁵⁾ The incidence did not differ substantially between subjects receiving risperidone and those receiving placebo. No subjects in the Japanese or foreign clinical studies showed a QTcF interval of >450 ms. In the Japanese phase III study and the foreign short-term studies, no subjects had a >60 ms change in QTcF interval from baseline. In the foreign long-term studies, a >60 ms change in QTcF interval from baseline was observed in only 1 subject at Month 4 and 1 subject at the last assessment. Risperidone has been known to induce

22) AEs included in the standardized MedDRA query (SMQ) search for "extrapyramidal syndrome" (excluding tardive dyskinesia)

23) AEs included in the standardized MedDRA query (SMQ) search for "torsade de pointes/QT prolongation," and AEs coded to the following MedDRA PTs: Convulsions, epilepsy, and sudden unexplained death in epilepsy.

cardiovascular effects such as thromboembolism, orthostatic hypotension, and cerebrovascular disorder, but no such AEs were observed in the Japanese or foreign clinical studies.

Table 21. Incidence of AEs related to QT/QTc interval prolongation and proarrhythmic effect in Japanese and foreign clinical studies

	Short-term studies				Long-term studies	
	Japanese study ^{a)}		Foreign studies ^{b)}		Japanese study ^{c)}	Foreign studies ^{d)}
Treatment group	Placebo	Risperidone	Placebo	Risperidone	Risperidone	Risperidone
No. of subjects assessed	18	21	126	120	35	149
AEs related to long QT/QTc interval and proarrhythmic effect	1 (5.6)	1 (4.8)	2 (1.6)	1 (0.8)	2 (5.7)	3 (2.0)
Electrocardiogram QT prolonged	1 (5.6)	1 (4.8)	1 (0.8)	0	0	0
Epilepsy	0	0	0	0	2 (5.7)	0
Fainting	0	0	0	1 (0.8)	0	0
Convulsions	0	0	1 (0.8)	0	0	3 (2.0)

No. of subjects with AEs (incidence %)

a) Footnote 15)-(a);

b) Footnote 15)-(c);

c) Footnote 15)-(b);

d) Footnote 15)-(d)

The applicant's conclusion:

While there is a risk of cardiovascular AEs in children and adolescents receiving risperidone for the treatment of autistic disorder, no additional precautionary statement is necessary because the current package insert already mentions the risk of cardiovascular AEs.

3.(ii).B.(2).5 Adverse events related to suicide or hostility/aggression

The applicant's explanation:

According to a study on suicidal ideation and suicide attempt in patients with autistic disorder (Mayes SD et al. *Res Autism Spectrum Disord.* 2013;7:109-19), the percentage of patients with suicidal ideation and suicide attempt²⁴⁾ is 13.8% in patients with autistic disorder 1 to 16 years of age, 0.5% in typically developing children 6 to 12 years of age, and 42.9% in patients with depression 8 to 16 years of age. The risk of suicide in children/adolescents with autistic disorder is lower than that in patients with depression, but tends to be higher than that in the general population. With regard to the Japanese and foreign clinical studies of risperidone,¹⁵⁾ AEs related to suicide²⁵⁾ was not reported in the Japanese study, while self-injurious behavior was reported in 1 of 126 subjects (0.8%) receiving placebo in the foreign short-term studies and 2 of 149 subjects (1.3%) in the foreign long-term studies. In the foreign post-marketing safety information, the incidence rate of AEs related to suicide by age group was 229 events in 7,369,983 person-years (0.0311 events per 1000 person-years) in children and adolescents 5 to 17 years of age and 1883 events in 29,573,809 person-years (0.0637 events per 1000 person-years) in adults ≥18 years of age; no substantial difference was found between the 2 age groups. The incidence rate in children/adolescents by therapeutic indication was 13 events in 77,024 person-years (0.1688 events per 1000 person-years) in patients with schizophrenia, 19 events in 4,306,936 person-years (0.0044 events

24) The percentage of patients who answered "sometimes," "frequently," or "very frequently" to a question asking them to rate the frequency of suicide ideation or suicide attempt as "never," "sometimes," "frequently," or "very frequently" (4 answer options).

25) AEs coded to the following MedDRA PTs: Completed suicide, depression suicidal, intentional overdose, intentional self-injury, poisoning deliberate, self-injurious behaviour, self-injurious ideation, suicidal behaviour, suicide ideation, and suicide attempt.

per 1000 person-years) in patients with autistic disorder, and 88 events in 2,986,025 person-years (0.0295 events per 1000 person-years) in patients receiving risperidone for other indications; there was no trend of a higher incidence rate in patients with autistic disorder.

AEs related to hostility/aggression²⁶⁾ were not observed in subjects in the Japanese clinical studies. In the foreign short-term studies, the incidence of such AEs was lower in the risperidone group than in the placebo group (Table 22). In the foreign post-marketing safety information, the incidence rate of AEs related to hostility/aggression by age group was 756 events in 7,369,983 person-years (0.1026 event per 1000 person-years) in children and adolescents 5 to 17 years of age and 2998 events in 29,573,809 person-years (0.1014 event per 1000 person-years) in adults ≥ 18 years of age; no substantial difference was found between the 2 age groups. The incidence rate in children/adolescents by therapeutic indication was 50 events in 77,024 person-years (0.6491 event per 1000 person-years) in patients with schizophrenia, 144 events in 4,306,936 person-years (0.0334 event per 1000 person-years) in patients with autistic disorder, and 555 events in 2,986,025 person-years (0.1859 event per 1000 person-years) in patients receiving risperidone for other indications; there was no trend of a higher incidence in patients with autistic disorder.

Table 22. Incidence of adverse events related to hostility/aggression in foreign clinical studies

Treatment group	Short-term studies ^{a)}		Long-term studies ^{b)}
	Placebo	Risperidone	Risperidone
No. of subjects assessed	126	120	149
AEs related to hostility/aggression	22 (17.5)	12 (10.0)	17 (11.4)
Commonly observed events			
Aggression	9 (7.1)	4 (3.3)	4 (2.7)
Irritability	9 (7.1)	3 (2.5)	7 (4.7)
Agitation	6 (4.8)	3 (2.5)	3 (2.0)
Psychomotor hyperactivity	2 (1.6)	2 (1.7)	3 (2.0)
Abnormal behaviour	2 (1.6)	2 (1.7)	2 (1.3)
Laceration	2 (1.6)	1 (0.8)	1 (0.7)

No. of subjects with AEs (incidence %)

a) Footnote 15)-(c);

b) Footnote 15)-(d)

The applicant's conclusion:

Children and adolescents with autistic disorder who receive risperidone may experience AEs related to suicide or hostility/aggression. However, the risk in this population is unlikely to exceed the risk in patients with schizophrenia (the approved indication). No additional precautionary statement is considered necessary because the risk of AEs related to suicide or hostility/aggression is already mentioned in the current package insert.

PMDA's view:

The submitted clinical study data suggest that risperidone may affect the growth (particularly body weight gain) of children and adolescents with autistic disorder and irritability. Therefore, it is appropriate to provide a precaution in the package insert to prevent aimless long-term treatment with risperidone.

26) AEs included in the standardized MedDRA query (SMQ) search for "hostility/aggression"

As patients with autistic disorder are known to be at a high risk of suicide, the applicant should appropriately inform healthcare professionals of the suicide risk, including the risk of AEs related to hostility/aggression, using educational materials. Other AEs discussed here may also develop in children and adolescents with autistic disorder and irritability, but no additional precautions are necessary for the following reasons: (1) the risk of these AEs in children and adolescents with autistic disorder is unlikely to exceed the risk in patients with schizophrenia (the approved indication); (2) the risk of these AEs is already mentioned in the current package insert. The applicant should collect information on the occurrence of extrapyramidal and cardiovascular AEs, sedation, growth, body weight gain, and AEs related to suicide or hostility/aggression via post-marketing surveillance.

3.(ii).B.(3) Clinical positioning and indications

3.(ii).B.(3).1 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of risperidone in the treatment of autistic disorder.

The applicant's explanation:

Patients with autistic disorder present with not only core features (impairment in social reciprocity, deficits in communication, repetition, ritualistic behavior, and perseveration) but also associated symptoms such as seizures, gastrointestinal disorders, sleep disorder, and challenging behaviors including aggression and self-injurious behavior (Myers SM et al. *Pediatrics*. 2007;120:1162-82). Non-pharmacotherapy and pharmacotherapy are used in the treatment of autistic disorder. Core features are usually managed by non-pharmacotherapy, namely treatment and education, such as therapeutic education from infancy and special needs education (Sugiyama T, *The Japanese Journal of Psychiatric Treatment* 2008;23;178-82); core features are not expected to respond to pharmacotherapy. Problematic psychiatric symptoms associated with autistic disorder (e.g., aggression, temper tantrums, irritability, hyperactivity, and self-injurious behavior) may be alleviated by pharmacotherapy (*American Academy of Pediatrics. Am Fam Physicians*. 2008;78;1399-404). In case these symptoms do not respond to, or interfere with non-pharmacotherapy, supportive pharmacotherapy may be considered (*Rutter's Child and Adolescent Psychiatry, Japanese translation supervised by Nagao K, et al. Akashi Shoten, 2007;739-69*). In conclusion, risperidone may offer a pharmacotherapy option for the management of problematic behaviors (e.g., self-injurious behavior and aggression due to irritability) associated with autistic disorder, in the current situation where (1) pharmacotherapy is a supportive treatment for associated symptoms in autistic disorder, and (2) in Japan pimozide is the only medication approved for indications related to autistic disorder.

PMDA's view:

According to the efficacy and safety data of risperidone from the clinical studies on irritability associated with autistic disorder, risperidone may become a pharmacotherapy option for irritability associated with autistic disorder. As pharmacotherapy of irritability is only a supportive symptomatic treatment, a

precaution should be made not to administer the drug aimlessly for a long period. In order to promote the proper use of risperidone, the applicant should prepare educational materials to appropriately inform healthcare professionals that risperidone is not expected to be effective against the core features of autistic disorder, and that the drug should be used as supportive treatment for irritability associated with autistic disorder.

3.(ii).B.(3).2 Indications

PMDA asked the applicant to explain the appropriateness of the wording "autistic disorder in pediatric patients" in the proposed indication.

The applicant's explanation:

The term "autistic disorder" in DSM-IV-TR was replaced by "autism spectrum disorder" in 2013, when the diagnostic criteria by the American Psychiatric Association were revised in the DSM-5. "Autism spectrum disorder" is a comprehensive term that includes autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified, and Childhood disintegrative disorder. DSM-5 uses the new term for the following reasons: (1) There is no evidence that "autistic disorder," "Asperger's disorder," and "pervasive developmental disorder not otherwise specified," are independent disease entities. (2) Childhood disintegrative disorder is rare and difficult to diagnose.²⁷⁾ In addition, irritability is seen in association with autistic disorder, childhood disintegrative disorder, and Asperger's disorder; antipsychotic drugs are the main pharmacotherapy for irritability.²⁸⁾ In clinical practice, the diagnostic criteria of "autism spectrum disorder" in the DSM-5 are expected to become more common in the future. However, the term "autistic disorder" is appropriate for the indication of risperidone, for the following reasons: (1) The Japanese phase III clinical study (5.3.5.1.1: Study RIS-AUT-JPN-01) was conducted in patients diagnosed with "autistic disorder" according to DSM-IV-TR. (2) The classification in DSM-IV-TR is similar to that in the latest version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) published by the World Health Organization; ICD-10 is also used in clinical practice.

In the Japanese phase III study, the efficacy and safety of risperidone were assessed in patients ≥ 5 to < 18 years of age, because the eligible age for the foreign clinical studies was between 5 years (the lower limit) and 12 years to 17 years 2 months (the upper limit). Nevertheless, patients < 5 years or ≥ 18 years of age may require risperidone therapy, because autistic disorder may be diagnosed in patients < 5 years old,²⁹⁾ and because a foreign guideline on autistic disorder in adults (National Collaborating Centre for

27) Kanba S, ed. Reading and Understanding DSM-5 - A new era in diagnosis of mental disorders based on traditional psychopathology, DSM-IV, and ICD-10: Neurodevelopmental disorder, feeding and eating disorders, elimination disorders, disruptive, impulse-control, and conduct disorders, suicidal behavior [in Japanese]. Nakayama Shoten 2013;68-74

28) The Editorial committee of Japanese Journal of Psychiatric Treatment. Guidelines for the Treatment of Mental Disorders in Children and Adolescents (New Edition). Seiwa Shoten 2008;178-82; Yamazaki K, et al. ed. Current Child & Adolescent Psychiatry. Nagai Shoten 2002;137-44; The Editorial committee of the Japanese Journal of Psychiatric Treatment. Guidelines for the Treatment of Mental Disorders in Children and Adolescents (New Edition). Seiwa Shoten 2008;187-90.

29) Center for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*. 2014;63:1-21; Howlin P et al. *Autism*. 1997;1:135-62; Imai M, Ito T. *Journal of Yokohama Rehabilitation Foundation*. 2012;23:41-5.

Mental Health. *Autism: The NICE guideline on the recognition, referral, diagnosis and management of adults on the autism spectrum*, 2012) describes a growing interest in pharmacotherapy, as well as in psychosocial interventions, for the treatment of irritability, aggression, hyperactivity, and self-injurious behavior. That being said, the efficacy and safety of risperidone have been confirmed only in patients ≥ 5 to < 18 years of age in Japanese and foreign clinical studies, and the use of risperidone cannot be recommended to other age groups.

The applicant's conclusion:

The wording "autistic disorder in pediatric patients" is appropriate for the indication of risperidone. The package insert should include a precautionary statement to the effect that the efficacy and safety of risperidone have not been established in patients < 5 years or ≥ 18 years of age.

PMDA's view on the wording (disease term) for the indication of risperidone:

"Autism spectrum disorder" should be used for the following reasons: (1) the DSM-5 uses "autism spectrum disorder," which is a single disease entity that includes autistic disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified; (2) patients with childhood disintegrative disorder or Asperger's disorder diagnosed according to the DSM-IV-TR are treated with antipsychotic drugs if they exhibit irritability for which pharmacotherapy is indicated. However, this issue will be discussed at the Expert Discussion to make the final decision, taking account of the difference in the concept of "autistic disorder" and "autism spectrum disorder," the prevalence of the DSM-5, and other matters.

The proposed target age group (i.e., "pediatric patients") is appropriate for the proposed indication, because the following facts suggest that there is insufficient evidence to strongly recommend risperidone in patients < 5 years or ≥ 18 years of age. However, the final decision will be made taking account of comments raised in the Expert Discussion.

- In the Japanese phase III clinical study, the efficacy and safety of risperidone have been confirmed in patients ≥ 5 to < 18 years of age.
- According to the DSM-5, symptoms of autism spectrum disorder are usually most pronounced in early childhood and early school age; most patients show improvements over time, except a very small number of patients who experience worsening in behavioral symptoms in adolescence.
- There is no evidence such as clinical study results in Japan or elsewhere to strongly recommend the use of risperidone in patients < 5 years or ≥ 18 years of age. Thus the efficacy and safety of risperidone have not been confirmed in these populations.
- Risperidone should be administered as a supportive, symptomatic treatment for irritability, and should not be administered aimlessly for a long period.

3.(ii).B.(4) Dosage and administration

3.(ii).B.(4).1) Dose by body weight category

PMDA asked the applicant to explain the appropriateness of recommending different doses of risperidone according to body weight categories (<20 kg, ≥20 kg to <45 kg, and ≥45 kg).

The applicant's explanation:

In Foreign Study RIS-USA-150 (Reference 5.3.5.1.2), subjects received different doses according to body weight categories: ≥15 kg to <20 kg, ≥20 kg to <45 kg, and ≥45 kg. In Foreign Study RIS-CAN-23 (Reference 5.3.5.1.4), subjects received a risperidone dose by body weight (mg/kg). The dose range actually used did not differ substantially between the 2 studies. Therefore in the United States, the recommended doses were determined by body weight categories, for the sake of patient convenience and the availability of dosage forms. The Japanese phase III study demonstrated the efficacy and safety of risperidone at doses by body weight category. (The dose categories used in this study are based on the doses used in Foreign Study RIS-USA-150 and the dosage regimens approved in the United States.) Thus there should be no major concerns over doses by body weight category. As patients weighing <15 kg were excluded from the Japanese phase III study, the words "patients weighing <20 kg" in the proposed Dosage and Administration section will be changed to "patients weighing ≥15 kg to <20 kg."

3.(ii).B.(4).2) Starting dose

PMDA asked the applicant to explain the appropriateness of the proposed starting doses of risperidone: 0.25 mg/day in patients weighing <20 kg, and 0.5 mg/day in patients weighing ≥20 kg, both administered orally for 3 days.

The applicant's explanation:

In the Japanese phase III study, the starting doses and duration were selected based on the doses used in Foreign Study RIS-USA-150 and the dosage regimens approved in the United States, in order to ensure the tolerability in the early phase of treatment and to immediately control symptoms of irritability. During the first 3 days of treatment in the Japanese phase III study, AEs occurred in 5 of 18 subjects (27.8%) in the placebo group and 5 of 21 subjects (23.8%) in the risperidone group. Somnolence observed in 1 subject was the only moderate or worse AE in the risperidone group, and there were no AEs leading to discontinuation of study treatment. In summary, patients receiving risperidone showed no tolerability issues in the early phase of treatment. The applicant has therefore proposed the following starting doses: 0.25 mg/kg in patients weighing <20 kg, and 0.5 mg/kg in patients weighing ≥20 kg, both administered orally for 3 days.

3.(ii).B.(4).3) Recommended doses and maximum doses

PMDA asked the applicant to explain the appropriateness of the proposed recommended doses and maximum dose of risperidone.

The applicant's explanation:

In Foreign Study RIS-USA-150, subjects received risperidone in a predetermined dose range (from Day 4 onward, subjects weighing <20 kg received 0.5 to 1.0 mg/day, subjects weighing \geq 20 kg received 1.0 to 2.5 mg/day, and subjects weighing \geq 45 kg received 1.0 to 3.5 mg/day). In 9 subjects treated with a modal dose of \leq 1.0 mg/day at the last assessment, the difference from placebo in the change from baseline in the ABC-J irritability (agitation) subscale score was -10.0 [95% CI: -16.0, -4.0], showing an improvement in irritability. Based on this finding, the minimum recommended doses in the United States are 0.5 mg/day for patients weighing <20 kg, and 1 mg/day for patients weighing \geq 20 kg. In the Japanese phase III study, the efficacy of risperidone was assessed at doses of 0.5 to 1.0 mg/day in subjects weighing <20 kg, 1.0 to 2.5 mg/day in subjects weighing \geq 20 kg to <45 kg, and 1.0 to 3.0 mg/day in subjects weighing \geq 45 kg. (This dose range was defined based on the doses in Foreign Study RIS-USA-150 and the approved dosage regimens in the United States.) In the Japanese phase III study, dose reduction to 0.25 mg/day was allowed in case of tolerability issues.

Table 23 summarizes the change from baseline in the ABC-J irritability (agitation) subscale score in the risperidone group by final dose in the double-blind phase of the Japanese phase III study. The ABC-J irritability (agitation) subscale score improved even in subjects who remained on doses below the maximum dose. In the long-term extension phase of the Japanese phase III study, only 3 subjects were treated with a modal dose of <0.5 mg/day (body weight <20 kg) or <1.0 mg/day (body weight \geq 20 kg). It was therefore difficult to evaluate the efficacy of risperidone at doses below 0.5 or 1.0 mg/day. In total, 7 subjects were treated with a modal dose of 0.5 mg/day (body weight <20 kg) or 1.0 mg/day (body weight \geq 20 kg). Six of the 7 subjects showed an improvement in the ABC-J irritability (agitation) subscale score (-11 to -19).

Table 23. Change in ABC-J irritability (agitation) subscale score from baseline to the last assessment by final dose in the double-blind phase of the Japanese phase III study (FAS, LOCF)

Body weight ^{a)}	Final dose ^{b)}	No. of subjects assessed	Scores		Change from baseline
			Baseline	Last assessment	
<20 kg	0.25 mg/day	1	30.0	30.0	0.0
	1.0 mg/day	1	29.0	16.0	-13.0
	1.5 mg/day	1	39.0	35.0	-4.0
≥20 kg	0.5 mg/day	1	25.0	9.0	-16.0
	1.0 mg/day	1	37.0	28.0	-9.0
	1.25 mg/day	1	15.0	0	-15.0
	1.5 mg/day	2	30.0 ± 1.41	18.5 ± 0.71	-11.5 ± 0.71
	2.0 mg/day	6	26.5 ± 5.61	13.0 ± 7.46	-13.5 ± 8.04
	2.5 mg/day	5	29.4 ± 7.47	24.6 ± 10.31	-4.8 ± 3.77
	3.0 mg/day	2	26.0 ± 1.41	16.5 ± 14.85	-9.5 ± 16.26

Mean ± standard deviation

a) Baseline body weight

b) No subjects weighing <20 kg received a final dose of 0.5, 1.25, 2.0, 2.5, or 3.0 mg/kg. No subjects weighing ≥20 kg received a final dose of 0.25 mg/day.

Table 24 summarizes the incidence of AEs by modal dose category in the Japanese phase III study; no major safety concerns were observed even in subjects who remained on the maximum dose.

Table 24. Incidence of adverse events by modal dose in the Japanese phase III study

Modal dose (mg/day)	Subjects weighing <20 kg			Subjects weighing ≥20 kg			
	≤0.5	>0.5 to ≤1.0	>1.0	≤1.0	>1.0 to ≤2.0	>2.0 to ≤3.0	
Double-blind phase (risperidone)							
No. of subjects assessed	1	1	1	2	10	6	
Adverse events	1 (100)	1 (100)	1 (100)	2 (100)	8 (80.0)	6 (100)	
Commonly observed events	Somnolence	1 (100)	0	1 (100)	2 (100)	5 (50.0)	2 (33.3)
	Weight increased	0	0	1 (100)	0	1 (10.0)	2 (33.3)
	Increased appetite	0	0	1 (100)	2 (100)	2 (20.0)	0
	Gastroenteritis	0	0	0	0	1 (10.0)	0
	Vomiting	1 (100)	0	0	0	2 (20.0)	0
Long-term extension phase							
No. of subjects assessed	2	1	2	8	15	7	
Adverse events	2 (100)	1 (100)	2 (100)	8 (100)	14 (93.3)	7 (100)	
Commonly observed events	Weight increased	0	0	1 (50.0)	1 (12.5)	6 (40.0)	4 (57.1)
	Somnolence	1 (50.0)	0	0	6 (75.0)	7 (46.7)	3 (42.9)
	Increased appetite	1 (50.0)	0	1 (50.0)	2 (25.0)	3 (20.0)	3 (42.9)
	Influenza	0	0	0	0	5 (33.3)	2 (28.6)
	Nasopharyngitis	0	1 (100)	1 (50.0)	3 (37.5)	3 (20.0)	2 (28.6)
	Gastroenteritis	1 (50.0)	0	0	1 (12.5)	1 (6.7)	2 (28.6)
	Hyperprolactinaemia	0	0	0	0	3 (20.0)	1 (14.3)
	Upper respiratory tract inflammation	1 (50.0)	0	0	1 (12.5)	2 (13.3)	1 (14.3)
	Pharyngitis	0	0	0	0	2 (13.3)	1 (14.3)
	Asthma	0	0	0	0	2 (13.3)	1 (14.3)
	Constipation	1 (50.0)	0	2 (100)	0	2 (13.3)	0
	Diarrhoea	0	0	0	0	2 (13.3)	0
	Vomiting	1 (50.0)	0	2 (100)	2 (25.0)	1 (6.7)	0
	Conjunctivitis	1 (50.0)	0	2 (100)	1 (12.5)	0	0

No. of subjects with AEs (incidence %)

The applicant's conclusion:

The following dose ranges should be recommended because they are expected to be effective with no major safety concerns: 0.5 to 1.0 mg/day in patients weighing <20 kg, 1.0 to 2.5 mg/day in patients weighing ≥20 kg to <45 kg, and 1.0 to 3.0 mg/day in patients weighing ≥45 kg. The maximum doses should be 1.0 mg/day in patients weighing <20 kg, 2.5 mg/day in patients weighing ≥20 kg to <45 kg, and 3.0 mg/day in patients weighing ≥45 kg.

PMDA's view:

In view of the submitted data including clinical study results, there is no problem with selecting starting doses and treatment duration by body weight category. Also, there is no major problem with the proposed timing of dose increase (Day 4 of treatment) and the proposed maximum doses, for the following reasons: (1) In the Japanese phase III study, the dose was increased to 0.5 mg/day in subjects weighing <20 kg, and to 1.0 mg/day in subjects weighing ≥20 kg; only a limited number of subjects received a modal or final dose lower than 0.5 or 1.0 mg/day. (2) The symptoms of irritability improved even in subjects who remained on doses lower than the maximum dose. (3) No major safety issues were identified in subjects treated at the maximum dose.

A final decision on this issue will be made taking account of comments raised in the Expert Discussion.

3.(ii).B.(5) Post-marketing investigations

PMDA's view:

Taking account of the results of clinical studies of risperidone and post-marketing safety information from Japan and overseas, PMDA considers that the applicant should continue to monitor and evaluate the following events associated with risperidone in post-marketing settings: QT interval prolongation, extrapyramidal symptoms/dyskinesia, neuroleptic malignant syndrome, hyperglycaemia/diabetic ketoacidosis/diabetic coma, priapism, cerebrovascular disorder, venous thromboembolism, agranulocytosis/leukopenia, rhabdomyolysis, ileus paralytic, inappropriate ADH secretion syndrome, hepatic dysfunction/jaundice, arrhythmia, and hypoglycaemia. In post-marketing surveillance, the applicant should also collect information on (1) the impact of patient characteristics on the efficacy of risperidone, (2) the incidence of sedation induced by risperidone and AEs related to suicide or hostility/agitation, and (3) the effect of risperidone on growth and body weight gain.

The applicant's explanation:

A specified use-results survey (post-marketing surveillance) will be conducted in children and adolescents with autistic disorder and irritability. The target sample size is 330 patients. The observation period is 12 months per patient.

PMDA will draw final conclusions regarding the details of the matters to be investigated in post-marketing settings, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

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 Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (5.3.5.1.1: Study RIS-AUT-JPN-01) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that the clinical study was conducted generally in compliance with GCP and there were no obstacles to conducting its review based on the application documents submitted. The following finding regarding the sponsor was identified and notified to the applicant (sponsor) as area for improvement, although it did not affect the overall evaluation of the study.

Area for improvement

Sponsor

- A part of information regarding serious and unexpected adverse drug reactions was not communicated appropriately to investigators or the heads of study sites.

IV. Overall Evaluation

PMDA has concluded that the data submitted demonstrate the efficacy of risperidone in the treatment of irritability associated with autistic disorder in pediatric patients and show acceptable safety in view of the benefits indicated by the data submitted. Risperidone offers a new treatment option for pediatric patients with irritability associated with autistic disorder. PMDA will make the final conclusions on the indication, dosage and administration, and post-marketing investigations, taking account of comments raised in the Expert Discussion.

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

Review Report (2)

January 15, 2016

I. Products Submitted for Registration

[Brand name]	(1) Risperdal Tablets 1 mg Risperdal Tablets 2 mg (2) Risperdal Fine Granules 1% (3) Risperdal OD Tablets 0.5 mg Risperdal OD Tablets 1 mg Risperdal OD Tablets 2 mg (4) Risperdal Oral Solution 1 mg/mL
[Non-proprietary name]	Risperidone
[Applicant]	Janssen Pharmaceutical K.K.
[Date of application]	April 24, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the products submitted for registration, 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).

The PMDA's conclusions described in Review Report (1) were supported at the Expert Discussion. PMDA conducted an additional review of the following points and took necessary actions.

(1) Efficacy of Risperdal Tablets, Granules, OD Tablets, and Oral Solution (risperidone)

The expert advisors generally supported PMDA's view on the efficacy of risperidone, but made a comment that the efficacy of risperidone should be evaluated comprehensively based not only on the results of the Japanese phase III study (5.3.5.1.1: Study RIS-AUT-JPN-01) but also on the comparison with the results of foreign clinical studies. PMDA explained that risperidone has been shown to have efficacy for irritability associated with autism spectrum disorder in pediatric patients, for the following reasons:

Table 25 summarizes the change in the irritability (agitation) subscale score of the Aberrant Behavior Checklist (ABC) (the Japanese version [ABC-J] was used in the Japanese study) from baseline to the last assessment in the Japanese phase III study and in foreign phase III clinical studies (Reference 5.3.5.1.2, Study RIS-USA-150; Reference 5.3.5.1.4, Study RIS-CAN-23).

According to Table 25, (1) all studies showed statistically significant difference between risperidone and placebo; and (2) the between-group difference (risperidone vs. placebo) did not substantially differ among the studies, although a rigorous comparison between the studies was difficult due to differences in the characteristics of subjects and dosage regimens.

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

Table 25. Change in ABC (or ABC-J) irritability (agitation) subscale score from baseline to the last assessment in Japanese and foreign phase III studies (LOCF)

Study	Treatment group	No. of subjects assessed	Subscale score		Change from baseline	Comparison with placebo ^{a)}	
			Baseline	Last assessment		Between-group difference [95% CI]	P value
Japanese phase III study (FAS)	Placebo	18	27.5 ± 5.26	24.7 ± 9.47	-2.8 ± 6.62	-7.1 [-11.6, -2.6]	0.0030
	Risperidone	21	28.2 ± 6.36	18.5 ± 10.57	-9.7 ± 7.29		
Foreign study RIS-USA-150 (ITT) ^{b)}	Placebo	52	25.0 ± 7.00	21.6 ± 9.52	-3.5 ± 8.12	-10.6 [-13.8, -7.5]	< 0.001
	Risperidone	49	26.1 ± 8.35	11.3 ± 7.39	-14.9 ± 10.42		
Foreign study RIS-CAN-23 (ITT) ^{c)}	Placebo	38	21.2 ± 9.74	14.7 ± 11.46	-6.5 ± 8.41	-6.3 [-9.4, -3.2]	< 0.001
	Risperidone	37	18.9 ± 8.84	6.9 ± 5.52	-12.1 ± 5.81		

Mean ± standard deviation; FAS = Full Analysis Set; ITT = Intention-to-treat; LOCF = Last observation carried forward

a) Japanese phase III study:

Comparisons are based on an analysis-of-covariance model using treatment group as factors and baseline values as covariates.

Foreign Studies RIS-USA-150 and RIS-CAN-23:

Comparisons are based on an analysis-of-covariance model using treatment group and investigator as factors and baseline values as covariates.

b) Patients with autistic disorder (ABC irritability [agitation] subscale score ≥18) who were 5 years to 17 years 2 months of age received risperidone at a dose between 0.25 and 3.5 mg/day based on body weight category.

c) Patients with autistic disorder or other pervasive developmental disorder who were 5 to 12 years of age received risperidone at a dose between 0.01 and 0.06 mg/kg/day.

(2) Indication, dosage and administration

The expert advisors supported PMDA's view on the indication, dosage and administration of risperidone. The expert advisors made a comment concerning the proposed indication: "The Japanese version of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) lists both *Jihe Spectrum Sho* (a Japanese translation of autism spectrum disorder) and *Jihe Spectrum Shogai* (another Japanese translation of autism spectrum disorder). The term *Jihe Spectrum Sho* should be used for the indication of risperidone, because *Jihe Spectrum Sho* has been used increasingly in the academic meetings of relevant societies since the publication of the Japanese version of the DSM-5, and because *Jihe Spectrum Shogai* will probably be replaced by *Jihe Spectrum Sho* in the future." The expert advisors also made a comment concerning the target age group: "Irritability associated with autism spectrum disorder may occur after 18 years of age." However, the expert advisors has concluded that the indication should include the term "pediatric patients," and that the "Precautions for Indications" section in the package insert should include a precautionary statement that advises healthcare professionals to use risperidone basically in patients ≥5 to <18 years of age, for the following reasons: (1) The symptoms of autism spectrum disorder probably differ between pediatric patients and adults. (2) No clinical studies have evaluated the efficacy of risperidone for irritability associated with autism spectrum disorder in patients ≥18 years of age.

Following the discussion, PMDA instructed the applicant to amend the wording in Indications, Precautions for Indications, and Dosage and Administration as shown below. The applicant responded appropriately. In the original Japanese text, the wording for the dosage and administration for schizophrenia has been modified, in accordance with the wording for the dosage and administration for irritability associated with autism spectrum disorder in pediatric patients. (The modification does not affect the English translation):

[Indications]

Schizophrenia

Irritability associated with autism spectrum disorder in pediatric patients

Precautions for Indications

Risperidone is basically indicated for patients ≥ 5 to < 18 years of age when used for the treatment of irritability associated with autism spectrum disorder in pediatric patients.

[Dosage and administration] (Underline denotes changes from the proposed wording.)

Risperdal Tablets 1 mg, Risperdal Tablets 2 mg;

Risperdal Fine Granules 1%;

Risperdal OD Tablets 0.5 mg, Risperdal OD Tablets 1 mg, and Risperdal OD Tablets 2 mg:

(a) Schizophrenia

The usual adult starting dose is 1 mg of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day, usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg.

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 0.5 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day at intervals of at least 1 week. The daily dose should not exceed 1 mg.

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day at intervals of at least 1 week. The daily dose should not exceed 2.5 mg in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg in patients weighing ≥ 45 kg.

Risperdal Oral Solution 1 mg/mL:

(a) Schizophrenia

The usual adult starting dose is 1 mg (1 mL) of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day (2 to 6 mL/day), usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg (12 mL).

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg (0.25 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 0.5 mg (0.5 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day (0.25 mL/day) at intervals of at least 1 week. The daily dose should not exceed 1 mg (1 mL).

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg (0.5 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg (1 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day (0.5 mL/day) at intervals of at least 1 week. The daily dose should not exceed 2.5 mg (2.5 mL) in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg (3 mL) in patients weighing ≥ 45 kg.

(2) Risk management plan (draft)

In view of the discussions presented in "3.(ii).B.(5) Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA concluded that the current risk management plan (draft) should include the safety and efficacy specifications presented in Table 26, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 27.

Table 26. Safety and efficacy specifications in the risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
<ul style="list-style-type: none">- Neuroleptic malignant syndrome- Extrapyramidal symptoms, dyskinesia- Ileus paralytic- Inappropriate ADH secretion syndrome- Hepatic dysfunction, jaundice- Rhabdomyolysis- Arrhythmia- Cerebrovascular disorder- Hyperglycaemia, diabetic ketoacidosis, diabetic coma- Hypoglycaemia- Agranulocytosis, leukopenia- Venous thromboembolism- Priapism	<ul style="list-style-type: none">- QT prolongation	None
Efficacy Specification		
<ul style="list-style-type: none">- Efficacy in routine clinical practice		

Table 27. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
- Early post-marketing phase vigilance - Specified use-results survey	- Early post-marketing phase vigilance - Preparation and delivery of educational materials for healthcare professionals - Preparation and delivery of patient education materials

PMDA instructed the applicant to conduct post-marketing surveillance to evaluate the above issues, and to design survey items and a case report form so that the following issues are covered:

- Impact of patient characteristics on the efficacy of risperidone
- Incidence of AEs related to sedation induced by risperidone; and
Incidence of AEs related to suicide or hostility/aggression
- Effect of risperidone on the growth and body weight gain in pediatric patients

The applicant proposed its plan for a specified use-results survey in pediatric patients with irritability associated with autism spectrum disorder (Table 28).

Table 28. Outline of specified use-results survey (draft)

Objective	Confirm the safety and efficacy of risperidone for the treatment of irritability associated with autism spectrum disorder in pediatric patients in the clinical setting.
Survey method	Central registration system
Population	Pediatric patients with autism spectrum disorder who have started the first risperidone therapy
Observation period	12 months
Planned sample size	330
Main survey items	- Patient characteristics (e.g., gender, age, height, body weight, duration of illness, and medical history) - Exposure to risperidone (e.g., dose, dosage form, and duration of treatment) - Prior treatment, concomitant medication and therapies - Incidence of adverse events - Laboratory measurements, serum prolactin levels, height, body weight - CGI

PMDA accepts the above plans and considers that the survey should be promptly initiated to confirm the safety and efficacy of risperidone as a treatment of irritability associated with autism spectrum disorder in pediatric patients, and that the results of the surveillance should be appropriately communicated to healthcare professionals.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved after modifying the indication and the dosage and administration statements as shown below. As the present application falls under the category of drugs with a new indication and new dosage, the re-examination period for the proposed indication and dosage should be 4 years.

[Indications]

Schizophrenia

Irritability associated with autism spectrum disorder in pediatric patients

(Underline denotes additions.)

[Dosage and administration]

- (1) Risperdal Tablets 1 mg, Risperdal Tablets 2 mg;
- (2) Risperdal Fine Granules 1%;
- (3) Risperdal OD Tablets 0.5 mg, Risperdal OD Tablets 1 mg, and Risperdal OD Tablets 2 mg:

(a) Schizophrenia

The usual adult starting dose is 1 mg of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day, usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg.

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 0.5 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day at intervals of at least 1 week. The daily dose should not exceed 1 mg.

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg, divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day at intervals of at least 1 week. The daily dose should not exceed 2.5 mg in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg in patients weighing ≥ 45 kg.

- (4) Risperdal Oral Solution 1 mg/mL:

(a) Schizophrenia

The usual adult starting dose is 1 mg (1 mL) of risperidone administered twice daily, and the dose should be increased gradually. The usual maintenance dose is 2 to 6 mg/day (2 to 6 mL/day), usually divided into 2 oral doses. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 12 mg (12 mL).

(b) Irritability associated with autism spectrum disorder in pediatric patients

Patients weighing ≥ 15 kg to < 20 kg:

The usual starting dose is 0.25 mg (0.25 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be

increased to 0.5 mg (0.5 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.25 mg/day (0.25 mL/day) at intervals of at least 1 week. The daily dose should not exceed 1 mg (1 mL).

Patients weighing ≥ 20 kg:

The usual starting dose is 0.5 mg (0.5 mL) of risperidone administered once daily. From Day 4 onward, the daily dose should be increased to 1 mg (1 mL), divided into 2 oral doses. The dose may be adjusted according to the patient's symptoms. In patients requiring dose escalation, the dose should be increased in increments of 0.5 mg/day (0.5 mL/day) at intervals of at least 1 week. The daily dose should not exceed 2.5 mg (2.5 mL) in patients weighing ≥ 20 kg to < 45 kg, and should not exceed 3 mg (3 mL) in patients weighing ≥ 45 kg.

(Underline denotes additions.)

[Conditions for approval]

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