Janssen Research & Development

Synopsis
[Protocol RIS-AUT-JPN-01]

R064766 (Risperidone)

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SYNOPSIS

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Protocol No.: RIS-AUT-JPN-01

Title of Study: A Double-blind, Placebo-controlled Study, Followed by an Open-label Extension Study Evaluating the Efficacy and Safety of Risperidone (R064766) in Children and Adolescents with Irritability Associated with Autistic Disorder

NCT No.: NCT01624675

Clinical Registry No.: CR100877

Principal Investigator(s): [redacted] M.D. ([redacted], Japan), and others

Study Center(s): Japan (18 study sites)

Publication (Reference): Not applicable

Study Period: 28 August 2012 (date of first subject informed consent) - 9 October 2014 (date of last observation for last subject)

Phase of Development: 3

Objectives:

Primary Objectives

- To evaluate the efficacy of risperidone compared with placebo in children and adolescents with irritability associated with autistic disorder in the double-blind phase as measured by the Aberrant behavior checklist-Japanese version (ABC-J) Irritability subscale.
- To evaluate the safety of risperidone in the double-blind phase and open-label phase.

Secondary Objectives

- To evaluate the efficacy of risperidone compared with placebo in the double-blind phase as measured by the ABC-J subscales other than the Irritability subscale, clinical global impression-severity (CGI-S), Clinical global impression-change (CGI-C), and Children's global assessment scale (C-GAS).
- To evaluate the efficacy of risperidone in the open-label phase as measured by the subscale of ABC-J, and CGI-S, CGI-C, and C-GAS.
- To evaluate the caregiver's satisfaction with risperidone therapy in the double-blind phase and open-label phase as measured by Parent satisfaction questionnaire (PSQ).
- To measure the plasma concentrations of risperidone and 9-Hydroxy-risperidone (9-OH-risperidone) after administration of risperidone to children and adolescents with irritability associated with autistic disorder, and explore the relationship between the plasma concentrations of the active moiety (calculated by summation of risperidone and 9-OH-risperidone) and efficacy or safety parameters.

Methodology: This is a randomized, 8-week, double-blind, placebo-controlled, parallel-group, flexible-dose, multicenter study, followed by a 48-week, flexible-dose, open-label extension, to evaluate the efficacy and safety of risperidone in children and adolescents aged between 5 and 17 years with a

diagnosis of autistic disorder based on the Diagnostic and statistical manual of mental disorders, 4th edition, text revision (DSM-IV - TR) who had associated irritability.

The study consisted of up to a 2-week screening phase, an 8-week double-blind phase, a 48-week open-label phase, and a 1-week follow-up phase.

During the screening phase, eligibility of each subject for the study was reviewed for up to 2 weeks. The subjects, who were confirmed to be eligible, were randomly assigned (1:1 ratio) to receive either risperidone or placebo.

During the double-blind phase, risperidone or placebo was administered for 8 weeks, and the efficacy and safety of the study drug were evaluated.

During the open-label phase, risperidone was administered to all subjects, and the safety and efficacy of the study drug were evaluated.

Number of Subjects (planned and analyzed):

Planned: At least 38 subjects were to be enrolled in order to assign 19 subjects to each group.

Analyzed:

Double-blind phase

Thirty-nine subjects were enrolled and randomly assigned to the risperidone (RIS) group (n=21) or placebo (PLA) group (n=18). The safety analysis set and the full analysis set (FAS) consisted of all 39 subjects randomized and received the study drug..

Open-label phase

Thirty-five subjects received risperidone in the open-label phase, comprising 17 subjects from the placebo group in the double-blind phase (PLA/RIS group) and 18 subjects from the risperidone group (RIS/RIS group). The safety analysis set and FAS consisted of all 35 subjects.

Pharmacokinetics

The pharmacokinetic analysis set consisted of all 21 risperidone–treated subjects in the double-blind phase and all 35 risperidone–treated subjects in the open-label phase.

Pharmacokinetics/pharmacodynamics

The pharmacokinetic/pharmacodynamic analysis set for both efficacy and safety endpoints consisted of all 18 subjects in the double-blind phase and 32 subjects in the open-label phase.

Diagnosis and Main Criteria for Inclusion: The target population for the study was males and females between the ages of 5 and 17 years with a DSM-IV-TR diagnosis of autistic disorder.

Among children or adolescents diagnosed with autistic disorder, those who fulfilled all of the following 3 inclusion criteria were eligible for the study: (1) CGI-S score of ≥4, (2) ABC-J Irritability subscale score of ≥18 points, and (3) mental age or development age of >18 months as measured by the Tanaka-Binet Intelligence Scale or the Kyoto Scale of Psychological Development 2001, or Full-scale intelligence quotient (FIQ) of ≥35 as measured by the Wechsler preschool and primary scale of intelligence (WPPSI), Wechsler intelligence scale for children-third edition (WISC-III), or Wechsler intelligence scale for children-fourth edition (WISC-IV).

Test Product, Dose and Mode of Administration, Batch No.:

Test Product: Risperidone 1 mg/mL Oral Solution (liquid containing 1 mg of risperidone per mL) was used during the double-blind phase. Risperidone 1 mg/mL Oral Solution or Risperidone 0.5 mg Orally-disintegrating (OD) Tablet (tablet containing 0.5 mg of risperidone in each tablet) was used during the open-label phase.

Dose and Mode of Administration:

During the double-blind phase, subjects were treated with risperidone or placebo. The dose was adjusted depending on the weight of each subject at each study visit. For subjects weighing <20 kg, study medication was started with 0.25 mg/day once daily in the evening. The dose was increased to 0.5 mg/day on Day 4 (0.25 mg twice daily in the morning and evening). The dose was titrated by the increment of 0.25 mg/day (up to the daily dose of 1.0 mg) at the scheduled study visit thereafter. For subjects weighing ≥20 kg, study medication was started with 0.5 mg/day once daily in the evening. The dose was increased to 1.0 mg/day on Day 4 (0.5 mg twice daily in the morning and evening). The dose was titrated by the increment of 0.5 mg/day (up to 2.5 mg/day) at the scheduled study visit thereafter. For subjects weighing ≥45 kg, the maximum daily dose was 3.0 mg.

During the open-label phase, all of the subjects were treated with risperidone. The dose was adjusted depending on the weight of each subject at each study visit. Study medication was started with 0.25 mg/day once daily in the evening for subjects weighing <20 kg or 0.5 mg/day once daily in the evening for subjects weighing ≥20 kg. The dose was increased to 0.5 mg/day (0.25 mg twice daily in the morning and evening) or 1.0 mg/day (0.5 mg twice daily in the morning and evening) respectively on Day 4. Based on the response and tolerability of each subject, the dose was subsequently titrated by the increment of 0.25 mg/day up to 1.0 mg/day or 0.5 mg/day up to 2.5 mg/day respectively at the scheduled study visit. For subjects weighing ≥45 kg, the maximum daily dose was 3.0 mg.

The dose could be reduced to the minimum of 0.25 mg/day because of occurring an adverse event without titrating at any time throughout the study period.

Batch No.:

Double-blind phase: Risperidone 1 mg/mL Oral Solution CEB1C01

Open-label phase: Risperidone 1 mg/mL Oral Solution CBB1700, Risperidone 0.5 mg OD Tablet J02586

Reference Therapy, Dose and Mode of Administration, Batch No.: A placebo was used only in the double-blind phase.

Reference Therapy: Risperidone Oral Solution placebo (liquid containing no active ingredient that is identical with Risperidone 1 mg/mL Oral Solution in appearance and odor)

Dose and Mode of Administration: Dose was titrated in the same manner as that of the test product.

Batch No.: Risperidone Oral Solution placebo 12F18/F071

Duration of Treatment: 2 weeks in the screening phase, 8 weeks in the double-blind phase, 48 weeks in the open-label phase, and 1 week in the follow-up phase

Criteria for Evaluation: Efficacy: The primary efficacy endpoint in the study was the change from baseline in the ABC-J Irritability subscale score at the end point in the double-blind phase (Week 8 or at the time of discontinuation).

The secondary efficacy endpoints were as follows:

- Changes from baseline in ABC-J subscale score at each assessment time point in the double-blind phase and open-label phase
- Changes from baseline in CGI-S score and C-GAS score at each assessment time point in the double-blind phase and open-label phase
- CGI-C scores and PSQ scores at each assessment time point in the double-blind phase and open-label phase

Pharmacokinetics: The plasma concentrations of risperidone and 9-OH-risperidone were determined after administration of risperidone to children and adolescents with irritability associated with autistic disorder. It was further assessed whether there was correlation between the plasma concentration of the active moiety and the efficacy or safety parameter (change from baseline in ABC-J Irritability subscale score and QT interval corrected for heart rate [QTc]).

Safety: The safety profile of study medication was assessed by monitoring adverse events, clinical laboratory tests, heights, weights, body mass index (BMI), vital signs, and Electrocardiogram (ECG). In addition, occurrence of extrapyramidal symptoms (EPS) was assessed using the Drug-induced extrapyramidal symptoms scale (DIEPSS).

Statistical Methods:

Efficacy:

The efficacy analysis set in the double-blind phase was based on the FAS population, which included all subjects who were randomly assigned and received at least 1 dose of the double-blind study drug, and have efficacy data at baseline of the double-blind phase and at least 1 post-baseline time point during the double-blind phase. The efficacy analysis set in the open-label phase included all subjects who were enrolled in the open-label phase and received at least 1 dose of the open-label study drug, and have efficacy data at the open-label baseline and at least 1 post-baseline time point during the open-label phase.

The primary efficacy endpoint in the double-blind phase was the change from baseline in the ABC-J Irritability subscale score at the end point in the double-blind phase. The primary analysis was performed as follows: The mean change from baseline in ABC-J subscale score at the end point in the double-blind phase was analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor, and baseline score as a covariate. The last-observation-carried-forward (LOCF) method was used to impute the missing data. The treatment effect was determined based on the difference of the least-squares mean change from baseline. The analysis of between-group comparison was performed at the two-sided significance of 0.05.

For the secondary endpoints in the double-blind phase, the following analyses were performed.

A Subject was considered a responder if he/she had “much improved” or “very much improved” rating on the CGI-C scale. The percentages of responders at each assessment time point and at the end point in the double-blind phase were compared between the risperidone and placebo groups using the chi-square test.

In terms of changes from baseline in CGI-S score, ABC-J subscale scores other than Irritability, and C-GAS score at each assessment time point and at the end point in the double-blind phase, between-group comparison was performed using the ANCOVA model with treatment as a factor, and baseline score as a covariate.

In terms of PSQ parameters at each assessment time point and at the end point in the double-blind phase, between-group comparison was performed using the Wilcoxon rank-sum test.

The efficacy endpoints in the open-label phase were summarized descriptively.

Pharmacokinetics:

The pharmacokinetic analysis set for the double-blind phase included subjects who received at least 1 dose of the study drug in the double-blind phase and had data on plasma concentration of risperidone and 9-OH-risperidone. The pharmacokinetic analysis set for the open-label phase included subjects who received at least 1 dose of the study drug in the open-label phase and had data on the plasma concentration of risperidone and 9-OH-risperidone.

Descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation, median, minimum, and maximum) of actual and dose-normalized (based on the dose used just before blood sampling) plasma concentration of the active moiety, risperidone and 9-OH-risperidone at each pharmacokinetics assessment time point were calculated.

Pharmacokinetics/pharmacodynamics:

The plasma concentration of the active moiety was calculated at the end point in the double-blind phase defined as assessment time points for the primary efficacy endpoint, Week 24 and end point in the open-label phase. Correlation between the plasma concentrations of the active moiety at these time points and the efficacy or safety parameter (change from baseline in ABC-J subscale score and QTc interval) was assessed visually by plotting the data overtime.

Safety:

The safety analysis set in the double-blind phase included all of the subjects who were randomly assigned and received at least 1 dose of the double-blind study drug. The safety analysis set in the open-label phase included all subjects who were enrolled in the open-label phase and received at least 1 dose of the open-label study drug.

Adverse events were coded in accordance with the Medical dictionary for regulatory activities (MedDRA). Adverse events occurred during the treatment period (double-blind phase and open-label phase) were included in the safety analysis. Adverse events occurred during the double-blind phase and those during the double-blind phase were separately compiled. The percentage of subjects with at least 1 specific adverse event was calculated by the treatment groups. In terms of laboratory tests, ECG, vital signs, and physical examination results, change from baseline at each time point were summarized using descriptive statistics. For the DIEPSS parameters, frequency distribution and descriptive statistics at each assessment time point are presented.

RESULTS:

STUDY POPULATION:

Double-blind phase

A total of 44 subjects signed informed consent, and 39 of them were confirmed to be eligible for the study. These subjects were randomly assigned to placebo group (n=18) or risperidone group (n=21) in the 1:1 ratio and all randomized subjects received study medication. Eleven of the 18 placebo-treated subjects (61.1%) and 18 of the 21 risperidone-treated subjects (85.7%) completed the double-blind phase. A total of 10 subjects discontinued the double-blind phase (placebo group: 7 subjects [38.9%], RIS group: 3 subjects [14.3%]). The reason for discontinuation was “insufficient response” in all of the subjects (placebo group: 7 subjects, RIS group: 1 subject), except 2 subjects who withdrew the consent in the RIS group.

Most of the subjects enrolled were males in both of the two groups (placebo group: 14/18 [77.8%], RIS group: 16/21 [76.2%]). The median age was 7.0 years in the placebo group and 8.0 years in the RIS group, and subjects of 5 to 8 years old accounted for the highest proportion in the both groups. The two treatment

groups were comparable with respect to age, BMI, ABC-J Irritability subscale score at baseline, intelligence quotient (IQ) score, medical history, complication, and prior and concomitant medications.

Three subjects were found to have major deviations from the protocol (placebo group: 2 subjects, RIS group: 1 subject) as follows. The study drug was administered before the randomization date in one of the 2 placebo-treated subjects, and the study drug that had been returned was re-dispensed in the other placebo-treated subject. One risperidone-treated subject used antiparkinson drugs with action on the dopamine receptor (levodopa, amantadine hydrochloride, etc.) that were defined as prohibited concomitant medications. For the subject treated from a date before randomization, the investigator initiated the study medication before a randomization code number was issued by the Web enrollment center, because there was only one study drug available for assignment at the study site at the time of entry of the subject, so the investigator could know the drug number to be assigned already before the drug number was actually notified from the enrollment center.

The median duration of study medication (range) was 56.5 (28–60) days in the placebo group and 57.0 (12–63) days in the RIS group, being similar between the two treatments. The median mode dose in the RIS group was 2.000 mg/day. The median mode dose per kg of body weight was 0.067 mg/kg/day in the placebo group (1 mL in placebo calculated as 1 mg) and 0.054 mg/kg/day in the RIS group, showing lower in the RIS group than in the placebo group.

Open-label phase

Thirty-seven subjects newly signed the informed consent prior to entry in the open-label phase, and 35 of these subjects who were confirmed to be eligible were treated with risperidone (PLA/RIS group: n=17, RIS/RIS group: n=18). Twenty-six subjects completed the open-label phase (26/35 [74.3%], PLA/RIS group: n=14, RIS/RIS group: n=12). Nine subjects discontinued the open-label phase (9/35, 25.7%). The reason for discontinuation was non-compliance with the study drug for at least 7 consecutive days in 3 subjects, insufficient response in 3 subjects, safety concern (AE, etc.) in 1 subject, ineligible condition found after the start of the open-label phase in 1 subject, and other in 1 subject.

The demographic and other baseline characteristics of subjects in the open-label phase were similar to that of subjects in the double-blind phase, because these parameters of subjects in the open-label phase were calculated by use of the data of subjects in the open-label phase collected before the start of study medication in the double-blind phase.

Major protocol deviation was found in 1 subject (PLA/RIS group). This subject used protocol-specified, prohibited concomitant drugs (sedative and hypnotic) under a condition violating the protocol requirement.

The median duration of study treatment was 336 days (PLA/RIS group: 336 days, RIS/RIS group: 336 days).The median mode dose was 1.5 mg/day, and the median mode dose per kg of body weight was 0.044 mg/kg/day.

EFFICACY RESULTS:

Double-blind phase

For the primary efficacy endpoint, the least-squares mean (standard error) change from baseline in the ABC-J Irritability subscale score at the end point (Week 8 or at the time of discontinuation) was -2.7 (1.63) in the placebo group and -9.8 (1.51) in the RIS group, with the difference [95% confidence interval (CI)] being -7.1 (-11.6, -2.6). This result revealed statistically significant improvement in Irritability score for the RIS group compared with the placebo group (ANCOVA, p=0.0030).

For the secondary efficacy endpoints, the least-squares mean change from baseline in the ABC-J Irritability subscale score at each assessment time point showed the following differences (95% CI) between the RIS group and placebo group: -6.4 (-10.8, -1.9) at Week 2, -8.4 (-13.3, -3.5) at Week 4, -7.2

(-11.6, -2.8) at Week 6, and -7.1 (-11.6, -2.6) at the end point in the double-blind phase (Week 8 or at the time of discontinuation). Thus, the ABC-J Irritability subscale score was statistically significantly improved in the RIS group compared with the placebo group as early as at 2 weeks of treatment (ANCOVA, p=0.0063, without adjustment for multiplicity), and the improvement was maintained at 4 weeks and onwards during the double-blind phase.

With respect to ABC-J subscales other than Irritability (Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech), no statistically significant between-group difference was found in the change of the Lethargy/Social Withdrawal subscale score from baseline to the end point (ANCOVA, p=0.6409), while other 3 subscale scores showed statistically significant improvements in the RIS group compared with the placebo group (p=0.0353 on the Stereotypic Behavior, p=0.0042 on the Hyperactivity/Noncompliance, and p=0.0364 on the Inappropriate Speech).

In terms of CGI-C at the end point, the percentage of subjects who were assessed as “much improved” or “very much improved” (CGI-C responders) showed no statistically significant difference between the two treatment groups, although the percentage of CGI-C responders was 14.3% (3/21 subjects) in the RIS group while there was no CGI-C responder in the placebo group (Chi-square test, p=0.0951). The frequency distribution of CGI-C at the end point showed statistically significant difference between the two treatment groups (Wilcoxon rank-sum test, p=0.0017). The between-group difference in the frequency distribution of CGI-C was shown as early as after 1 week of treatment and was maintained up to the end of double-blind phase.

In terms of the least-squares mean change from baseline in CGI-S score to the end point, the difference (95% CI) of RIS group from placebo group was -0.3 (-0.7, 0.1). The change (improvement) was larger in the RIS group than in the placebo group, although there was no statistically significant difference between the two groups (ANCOVA, p=0.1288).

The change in C-GAS score from baseline to the end point showed statistically significant improvement for the RIS group compared with the placebo group (ANCOVA, p=0.0045).

The frequency distribution of the responses to PSQ at the end point showed a statistically significant between-group difference in the response to Question 2 (benefit of the study drug for autism) (Wilcoxon rank-sum test, p=0.0052), but no statistically significant between-group difference was found in the responses to Question 1 (satisfaction with the study drug) and Question 3 (recommendation for other autistic patients).

The above results showed that risperidone improves the irritability symptom in subjects with irritability associated with autistic disorder aged between 5 and 17 years, compared with placebo.

Open-label phase

Baseline was defined as a time before the start of study medication in the open-label phase for subjects in the PLA/RIS group and as a time before the start of study medication in the double-blind phase for subjects in the RIS/RIS group. The mean change (SD) in the ABC-J Irritability subscale score from baseline at the end point (Week 48 or at the time of discontinuation) was -13.3 (10.27) as analyzed in all subjects treated during the open-label phase (PLA/RIS group: -11.4 [10.70], RIS/RIS group: -15.1 [9.81]). The Irritability subscale score improved up to Week 8 in both of PLA/RIS and RIS/RIS groups in the open-label phase, and the improvement in the irritability score was maintained until the end of the open-label phase.

Among the ABC-J subscales other than Irritability, the mean change (SD) of score at the end point from baseline for all subjects treated during the open-label phase were -6.8 (6.98) in Lethargy/Social Withdrawal, -3.7 (4.39) in Stereotypic Behavior, -13.3 (12.30) in Hyperactivity/Noncompliance, -1.9 (2.62) in Inappropriate Speech. The improvement in Lethargy/Social Withdrawal and Hyperactivity/Noncompliance was showed and maintained up to the end point in the open-label phase.

The percentage of CGI-C responders at the end point was 34.3% (12/35 subjects) for all subjects treated during the open-label phase. The percentage of CGI-C responders continued to increase up to Week 8 and was maintained thereafter until the end of the open-label phase.

The mean change (SD) in CGI-S from baseline to the end point was -0.7 (1.04) for all subjects treated during the open-label phase. The frequency distribution of CGI-S showed a tendency toward improvement overall. Improvement in CGI-S score became apparent at Week 3 and was maintained thereafter until the end of the open-label phase.

The mean change (SD) in the C-GAS score from baseline to the end point was 10.6 (13.61) for all subjects treated during the open-label phase. The change from baseline in C-GAS score improved in both PLA/RIS and RIS/RIS groups up to Week 16 during the open-label phase, and the improvement was maintained thereafter until the end of the open-label phase.

With regard to the frequency distribution of the responses to PSQ at the end point, the response to Question 1 (satisfaction with the study drug) was ranked more than "moderately satisfied" and the response to Question 2 (benefit of the study drug for autism) was ranked more than "moderately beneficial" in about 80% of all subjects treated during the open-label phase. The response to Question 3 (recommendation for other autistic patients) was "no" in only 1 subject.

Based on the above results, risperidone maintained the improvement of irritability symptoms in subjects aged between 5 and 17 years with irritability associated with autistic disorder throughout the 48-week treatment period.

Pharmacokinetic/pharmacodynamic relationship

No correlation was found between the change from baseline in the ABC-J Irritability subscale score and the plasma concentration of the active moiety.

PHARMACOKINETIC RESULTS:

When risperidone was administered to subjects with irritability associated with autistic disorder aged between 5 and 17 years at doses of 0.25 to 3.0 mg/day twice daily (0.25 mg or 0.5 mg once daily from Day 1 to Day 3), the postdose (a sampling time of 0 to 8: reflecting more near peak plasma levels) plasma concentrations and the trough (a sampling time of 8 to 30 hours: representative for trough levels) plasma concentrations (dose-normalized to 1 mg b.i.d. and dose/weight-normalized to 0.02 mg/kg b.i.d.) of the active moiety, risperidone, and 9-OH-risperidone were comparable throughout pharmacokinetic assessment time points.

For the exposure (concentrations) of the active moiety, risperidone and 9-hydroxy-risperidone, there is an apparent trend for higher plasma exposure with dose increase. For the exposure of the active moiety, risperidone (postdose), and 9-OH-risperidone plasma concentrations (dose-normalized to 1 mg b.i.d.), there is an apparent trend for higher with younger age, which disappears after correction for body weight (dose/weight-normalized to 0.02 mg/kg b.i.d.). And, the exposure of dose/weight-normalized (to 0.02 mg/kg b.i.d.) plasma concentration was comparable between ages. However, the results should be interpreted with caution, considering the low number of subjects

SAFETY RESULTS:

Double-blind phase

During the double-blind phase, 16/18 (88.9%) placebo-treated subjects and 19/21 (90.5%) risperidone-treated subjects experienced Treatment-emergent adverse events (TEAEs). Drug related TEAE were reported in 5/18 (27.8%) placebo-treated subjects and 14/21 (66.7%) risperidone-treated subjects. Drug related TEAEs thus occurred more frequently in the RIS group than in the placebo group, but none of the events led to permanent discontinuation of the study drug. All of TEAEs reported were

mild or moderate in severity. There was no event leading to death, while serious TEAE (dehydration) occurred in 1 placebo-treated subject. Somnolence occurred in 2/18 (11.1%) placebo-treated subjects and 11/21 (52.4%) risperidone-treated subjects, and 2 risperidone-treated subjects experienced EPS-related TEAE (drooling). Other adverse events of clinical interest, including glucose-related TEAEs, potentially prolactin-related TEAEs, and TEAEs related to suicidality, were not reported. The most common TEAEs in the RIS group (reported at an incidence of ≥10%) were somnolence (11.1% in the placebo group, 52.4% in the RIS group), increased appetite (0% in the placebo group, 23.8% in the RIS group), weight increased (0% in the placebo group, 19.0% in the RIS group), and vomiting (0% in the placebo group, 14.3% in the RIS group). Among these TEAEs, somnolence was the only adverse event that occurred in the RIS group at an incidence higher by 25% or more than in the placebo group. Most of these TEAEs were mild in severity, and no severe TEAEs were observed.

Summary of Treatment-emergent Adverse Events during the Double-blind Phase (Safety Analysis Set for the Double-blind Phase) (Study RIS-AUT-JPN-01)

	Placebo n (%)	Risperidone n (%)
Analysis set: Safety analysis set (double-blind phase)	18	21
Subjects with TEAEs	16 (88.9%)	19 (90.5%)
Subjects with TEAEs leading to death	0	0
Subjects with serious TEAEs	1 (5.6%)	0
Subjects with Drug related TEAEs[a]	5 (27.8%)	14 (66.7%)
Subjects with TEAEs leading to permanent discontinuation	0	0
Subjects with EPS-related TEAEs	0	2 (9.5%)
Subjects with glucose-related TEAEs	0	0
Subjects with potentially prolactin-related TEAEs	0	0
Subjects with TEAEs related to suicidality	0	0

a Drug related TEAEs were defined as TEAEs assessed by the investigator as being possibly, probably, or very likely related to the study drug.

TEAEs that occurred during the follow-up period in subjects who did not enter the open-label phase are included

TEAE: Treatment-emergent adverse event

Summary of Treatment-emergent Adverse Events and Drug Related Treatment-emergent Adverse Events Occurring in At Least 3 Subjects during the Double-blind Phase (Safety Analysis Set for the Double-blind Phase) (Study RIS-AUT-JPN-01)

SOC[a] PT[a]	All TEAEs Placebo n (%)	All TEAEs Risperidone n (%)	Drug Related TEAEs[b] Placebo n (%)	Drug Related TEAEs[b] Risperidone n (%)
Analysis set: Safety analysis set (double-blind phase)	18	21	18	21
Subject number with TEAEs	16 (88.9%)	19 (90.5%)	5 (27.8%)	14 (66.7%)
Metabolism and nutrition disorders	1 (5.6%)	5 (23.8%)	0	5 (23.8%)
Increased appetite	0	5 (23.8%)	0	5 (23.8%)
Nervous system disorders	2 (11.1%)	13 (61.9%)	2 (11.1%)	13 (61.9%)
Somnolence	2 (11.1%)	11 (52.4%)	2 (11.1%)	11 (52.4%)
Gastrointestinal disorders	5 (27.8%)	4 (19.0%)	0	0
Vomiting	0	3 (14.3%)	0	0
Investigations	1 (5.6%)	4 (19.0%)	1 (5.6%)	4 (19.0%)
Weight increased	0	4 (19.0%)	0	4 (19.0%)

a All TEAEs are coded using MedDRA version 17.0

b Drug related TEAEs were defined as TEAEs assessed by the investigator as being possibly, probably, or very likely related to the study drug.
Adverse events that occurred during the follow-up period in subjects who did not enter the open-label phase are included.

TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term

Clinical laboratory tests revealed no clinically-relevant changes from baseline in either of the two groups, except the prolactin level. Even though potentially prolactin-related TEAEs were not observed, change in the mean prolactin level from baseline to the end point was 41.423 ng/mL in the RIS group, being greater than 6.321 ng/mL in the placebo group (reference range of prolactin: 4.29 to 13.69 ng/mL in male and 4.91 to 29.32 ng/mL in female.

The change in the mean body weight from baseline to the end point was 2.50 kg in the RIS group, being greater than 0.51 kg in the placebo group. The change in the mean BMI from baseline to the end point was 1.09 kg/m^2 in the RIS group, being greater than 0.03 kg/m^2 in the placebo group.

One subject each in the placebo group and RIS group showed a change in the ECG at the end point that was considered by the investigator to be a clinically-relevant abnormal finding. However, these subjects were classified into normal category by the central ECG review. ECG parameters revealed no clinically-relevant changes from baseline, except these subjects. None of the subjects had QTc (corrected using formula of Fridericia, Sagie, Bazett and linear-derived) exceeding 480 msec at the end point or change in QTc from baseline exceeding 60 msec at the end point.

With regard to vital signs and DIEPSS assessment, no clinically-relevant changes were observed in either of the two treatment groups.

Open-label phase

During the open-label phase, 34/35 (97.1%) all subjects treated during the open-label phase experienced TEAEs, comprising 17/17 (100.0%) subjects in the PLA/RIS group and 17/18 (94.4%) subjects in the RIS/RIS group. Thus, the two groups were similar with respect to the incidence of TEAEs. Drug related TEAEs were reported in 28/35 (80.8%) subjects. Most of TEAEs were mild in severity, and moderate and severe TEAEs in severity were shown in 5 subjects(14.3%) and 1 subject (2.9%) respectively. No subject

had an adverse event leading to death. Three serious TEAEs were reported in 2 subjects (mycoplasmal tracheobronchitis and asthma in 1 subject, inguinal hernia in 1 subject), although these serious adverse events were considered to be "not related" or "unlikely related" to the study drug, and were confirmed to have resolved at 6 days after onset. TEAEs leading to discontinuation of the study drug occurred in 2 subjects (epilepsy and abnormal hepatic function in 1 subject each), although causal relationship to the study drug was ruled out for both of these adverse events. With respect to adverse events of clinical interest (somnolence, EPS-related TEAEs, glucose-related TEAEs, potentially prolactin-related TEAEs, and TEAEs related to suicidality), somnolence occurred in 17/35 (48.6%) subjects, extrapyramidal symptom-related TEAEs in 2 subjects (drooling in 2 subjects), and potentially prolactin-related TEAEs in 5 subjects, (hyperprolactinemia in 4 subjects and blood prolactin increased in 1 subject). For all of these TEAEs, the causal relationship to the study drug could not be ruled out. The most common TEAEs (reported at an incidence of ≥10% in all subjects treated during the open-label phase) were somnolence (48.6%), weight increased (34.3%), appetite increased (28.6%), nasopharyngitis (28.6%), influenza (20.0%), vomiting (17.1%), gastroenteritis (14.3%), upper respiratory tract inflammation (14.3%), constipation (14.3%), conjunctivitis (11.4%), and hyperprolactinemia (11.4%).

Summary of Treatment-emergent Adverse Events during the Open-label Phase (Safety Analysis Set for the Open-label Phase) (Study RIS-AUT-JPN-01)

	PLA/RIS n (%)	RIS/RIS n (%)	Risperidone n (%)
Analysis set: Safety analysis set (open-label phase)	17	18	35
Subjects with TEAEs	17 (100.0%)	17 (94.4%)	34 (97.1%)
Subjects with TEAEs leading to death	0	0	0
Subjects with serious TEAEs	1 (5.9%)	1 (5.6%)	2 (5.7%)
Subjects with Drug Related TEAEs[a]	14 (82.4%)	14 (77.8%)	28 (80.0%)
Subjects with TEAEs leading to permanent discontinuation	1 (5.9%)	1 (5.6%)	2 (5.7%)
Subjects with EPS-related TEAEs	1 (5.9%)	1 (5.6%)	2 (5.7%)
Subjects with glucose-related TEAEs	0	0	0
Subjects with potentially prolactin-related TEAEs	4 (23.5%)	1 (5.6%)	5 (14.3%)
Subjects with TEAEs related to suicidality	0	0	0

a Drug related TEAEs were defined as TEAEs assessed by the investigator as being possibly, probably, or very likely related to the study drug.
TEAEs occurred during the follow-up period were included.

TEAE: Treatment-emergent adverse event

Summary of Treatment-emergent Adverse Events and Drug Related Treatment-emergent Adverse Events Occurring at An Incidence of ≥10% in All Subjects Treated during the Open-label Phase (Safety Analysis Set for the Open-label Phase) (Study RIS-AUT-JPN-01)

	All TEAEs			Drug Related TEAEs[b]		
SOC[a] PT[a]	PLA/RIS n (%)	RIS/RIS n (%)	Risperidone n (%)	PLA/RIS n (%)	RIS/RIS n (%)	Risperidone n (%)
Analysis set: Safety analysis set (open-label phase)	17	18	35	17	18	35
Subject number with TEAEs	17 (100.0%)	17 (94.4%)	34 (97.1%)	14 (82.4%)	14 (77.8%)	28 (80.0%)
Infections and infestations	13 (76.5%)	11 (61.1%)	24 (68.6%)	0	0	0
Nasopharyngitis	5 (29.4%)	5 (27.8%)	10 (28.6%)	0	0	0
Influenza	3 (17.6%)	4 (22.2%)	7 (20.0%)	0	0	0
Gastroenteritis	3 (17.6%)	2 (11.1%)	5 (14.3%)	0	0	0
Conjunctivitis	0	4 (22.2%)	4 (11.4%)	0	0	0
Endocrine disorders	3 (17.6%)	1 (5.6%)	4 (11.4%)	3 (17.6%)	1 (5.6%)	4 (11.4%)
Hyperprolactinaemia	3 (17.6%)	1 (5.6%)	4 (11.4%)	3 (17.6%)	1 (5.6%)	4 (11.4%)
Metabolism and nutrition disorders	4 (23.5%)	6 (33.3%)	10 (28.6%)	4 (23.5%)	5 (27.8%)	9 (25.7%)
Increased appetite	4 (23.5%)	6 (33.3%)	10 (28.6%)	4 (23.5%)	5 (27.8%)	9 (25.7%)
Nervous system disorders	11 (64.7%)	9 (50.0%)	20 (57.1%)	11 (64.7%)	8 (44.4%)	19 (54.3%)
Somnolence	11 (64.7%)	6 (33.3%)	17 (48.6%)	11 (64.7%)	6 (33.3%)	17 (48.6%)
Respiratory, thoracic and mediastinal disorders	5 (29.4%)	6 (33.3%)	11 (31.4%)	0	0	0
Upper respiratory tract inflammation	1 (5.9%)	4 (22.2%)	5 (14.3%)	0	0	0
Gastrointestinal disorders	6 (35.3%)	8 (44.4%)	14 (40.0%)	0	2 (11.1%)	2 (5.7%)
Vomiting	1 (5.9%)	5 (27.8%)	6 (17.1%)	0	0	0
Constipation	2 (11.8%)	3 (16.7%)	5 (14.3%)	0	2 (11.1%)	2 (5.7%)
Investigations	6 (35.3%)	7 (38.9%)	13 (37.1%)	6 (35.3%)	7 (38.9%)	13 (37.1%)
Weight increased	5 (29.4%)	7 (38.9%)	12 (34.3%)	5 (29.4%)	7 (38.9%)	12 (34.3%)

a All TEAEs are coded using MedDRA version 17.0

b Drug related TEAEs were defined as TEAEs assessed by the investigator as being possibly, probably, or very likely related to the study drug.
TEAEs occurred during the follow-up period were included.

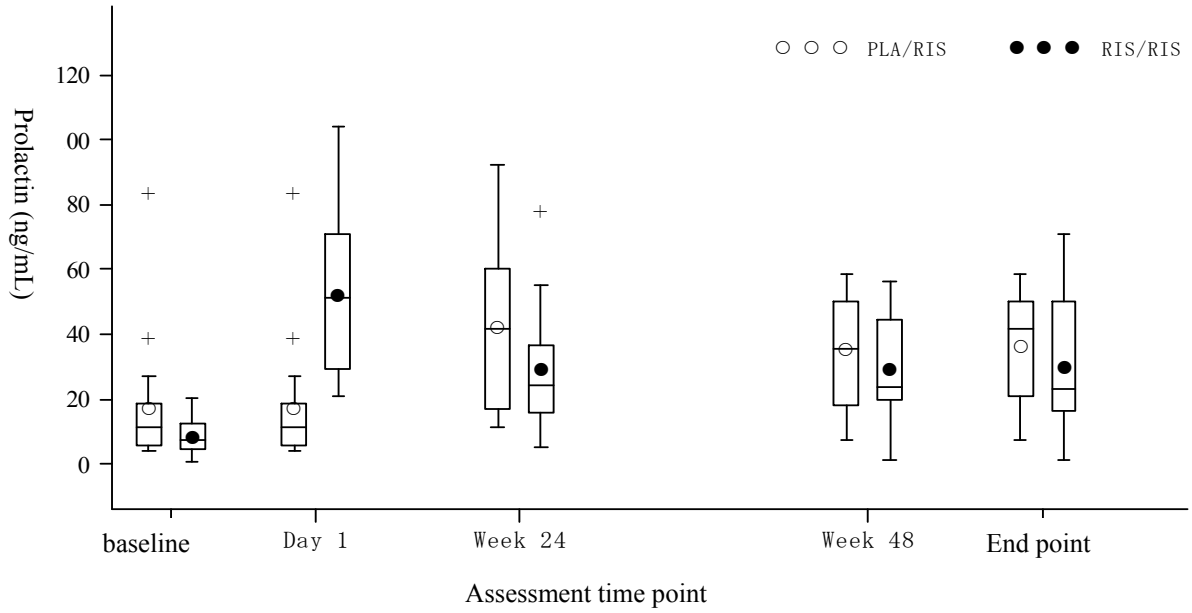
TEAE: Treatment-emergent adverse event, SOC: System organ class, PT: Preferred term

Clinical laboratory tests revealed no clinically-relevant changes from baseline, except the prolactin levels. The change from baseline in prolactin level increased at Week 24 in the PLA/RIS group and tended to decrease at Week 48. The RIS/RIS group showed increased prolactin level at the start of open-label phase, while prolactin tended to decrease somewhat at Week 24 compared with the start of open-label phase, and the decreased prolactin level was maintained at Week 48. Any symptoms or signs related to laboratory findings were not reported.

The mean change (range) from baseline to the end point in all subjects treated during the open-label phase was 5.88 (0.7–15.3) kg in weight and 1.51 (-0.7–4.8) kg/m^2 in BMI. Weight continued to increase up to Week 48, while the BMI showed an increase at Week 24 but did not increase any further at Week 48.

No subjects had QTc exceeding 480 msec in the ECG at Week 24 or the end point. The number of subject with QTc exceeding 60 msec in the change from baseline was 2, but both were below 450 msec.

Vital signs, and DIEPSS assessment showed no clinically-relevant changes.



Baseline was defined as a time before the start of study medication in the open-label phase for subjects in the PLA/RIS group and as a time before the start of study medication in the double-blind phase for subjects in the RIS/RIS group.

A box plot of prolactin during the Open-label Phase (Safety Analysis Set for the Open-label Phase) (Study RIS-AUT-JPN-01)

Pharmacokinetic/pharmacodynamic relationship

No correlation was found between change in QTc (corrected using formula of linear-derived) interval from baseline and the plasma concentrations of the active moiety.

CONCLUSIONS:

When risperidone was administered to the subjects aged between 5 and 17 years with irritability associated with autistic disorder at doses of 0.25–3.0 mg/kg once daily or twice daily for 8-week, risperidone improved the symptom of irritability associated with autistic disorder compared with placebo and continuous risperidone therapy maintained the effect.

Overall, risperidone was well tolerated and no new safety concern of risperidone was identified.

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