TOPLINE RESULTS

Date: 18-SEP-2002			
Protocol Number:	RIS-INT-70	**Clinical Phase:**	3
Title:	The long-term safety and efficacy of Risperdal® in conduct disorders in children with borderline, mild or moderate mental retardation - a follow up trial of RIS-INT-41.		
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Trial Design:

- Multicenter, Phase 3, open-label, uncontrolled trial: flexible dose of 0.02 to 0.06 mg/kg/day of oral Risperdal® treatment in conduct and other disruptive behaviour disorders in children with borderline, mild or moderate intellectual impairment (defined as an IQ of 35 to 84) aged 5 to 15 years inclusive. This trial is an extension trial to RIS-INT-41, which was a one-year open label trial.
- Treatment duration/Trial duration: 12 months Risperdal® treatment/ 12 months trial duration.
- Primary safety assessments include adverse events monitoring (with special attention to serious AE's, and EPS-, prolactin-, and glucose-related AE's), plasma prolactin levels, body weight and Body Mass Index, and ECG. Incidence of AE's will be summarized for children (<12 years) and adolescents (≥12 years).
- All safety assessments will be based on all subjects who received at least one dose of study medication (all subjects analysis set).
- Primary efficacy variable/Primary Timepoint: Conduct Problem subscale of the Nisonger Child Behaviour Rating Form (N-CBRF) after 24 months of Risperdal® treatment (RIS-INT-41 and RIS-INT-70).
- Efficacy analyses will be based on all subjects who took at least one dose of study medication in this trial and had at least one post-baseline assessment of the primary efficacy variable (intent-to-treat analysis set).
- Since this is a follow up of an open-label trial, no sample size calculations were performed.

Primary Objective:

The primary objective of this trial is to acquire additional long-term safety data for an additional year of Risperdal® treatment in subjects who completed RIS-INT-41. A secondary objective of this trial is to collect additional long-term open-label efficacy data.

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EXHIBIT P-14 Date: M.L. GRAY, CSR, RPR

Topline Results Summary

Forty-eight subjects entered this trial and took at least one dose of study medication. Two subjects did not have post-baseline efficacy assessments. Therefore, safety analyses are based on 48 and efficacy analyses on 46 subjects. The subjects who enrolled in this study showed no marked differences in demographic characteristics and disease status (assessed at the start of RIS-INT-41) compared to subjects who did not continue Risperdal® treatment. Forty-two male subjects entered this trial. Most subjects (39) had a diagnosis of Conduct Disorder or Disruptive Behavior Disorder not otherwise specified, either with or without additional Attention Deficit/Hyperactivity Disorder. Mean IQ equaled 64.2. In general, incidence of AE's and change versus baseline of the primary efficacy variable in RIS-INT-41 were similar for subjects who did and did not continue in this trial. However, hyperprolactinaemia appeared to have occurred less frequently in subjects who enrolled in this study (2.1%) relative to those who did not (11.5%). This could indicate that the population of subjects in this trial represents a biased sample with respect to prolactin levels and/or prolactin-related AE's. Therefore, interpretation of prolactin levels should be done with caution. Upper respiratory tract infections also appeared to have occurred less frequently in subjects who enrolled in this study (4.2%) relative to those who did not continue (18.2%). This is an open-label follow-up study where subjects represent a biased sub-sample of all eligible subjects who completed RIS-INT-41. Since this trial was not designed to investigate potential sources of bias due to subject' self-selection into continued treatment or not, we can only attempt to identify potential sources of bias and all results should be interpreted with caution

Overall, the continued treatment of behavior disorders in children with borderline, mild or moderate mental retardation with Risperdal® appeared to be well tolerated in this population of subjects. There were no indications that the therapeutic effect of Risperdal® on the primary efficacy variable changed during the second year of treatment.

No safety concerns arose during the second year of Risperdal® treatment in this study. Incidence of adverse events was somewhat lower during the second year of treatment, prolactin levels remained stable in male subjects (female results were difficult to interpret due to low sample sizes) and BMI did not increase further. No clinically important prolongations of corrected QT intervals were noticed. The three most frequently reported adverse events that occurred during the first year of Risperdal® treatment in RIS-INT-41 showed a marked decrease in incidence during the second year of treatment. Somnolence decreased from 31.3% to 8.3%, rhinitis decreased from 20.8% to 8.3% and headache decreased from 16.7% to 4.2%. Other frequently reported AE's remained relatively stable – including weight increase, upper respiratory tract infection and prolactin related AE's (gynaecomastia and hyperprolactinaemia) – and there were no marked increases in AE incidence.

RESULTS

1. GENERAL ANALYSIS SPECIFICATIONS

Changes in safety and efficacy variables will be analyzed relative to two baseline values: (i) BASELINE(1): value at start of RIS-INT-41; (ii) BASELINE(2): value at start of this study (i.e. last assessment in RIS-INT-41 or new assessment at start of RIS-INT-70 if available)

Results from follow-up trials are difficult to interpret because subjects enrolled in such can represent a biased sample. It can be expected that subjects showing a good therapeutic response and/or favorable treatment tolerability are more likely to continue treatment. To anticipate potential sources of bias in follow-up trials, it is important to identify differences between subjects who do or do not continue treatment. Therefore, baseline characteristics, safety profiles and efficacy of treatment during the previous trial will be compared for subjects who did and those who did not roll over into RIS-INT-70. It is important to note that this trial was not designed to study potential sources of bias and this presentation of the data only attempts to identify them. Therefore, all results should be interpreted keeping in mind that the subject population represents a self-selected group. Specific potential sources of bias – as suggested by our exploratory comparisons and important for the interpretation of the results presented in this document – will be emphasized in the text.

2. SUBJECT AND TREATMENT INFORMATION

2.1. Study Completion/Withdrawal Information

A total of 504 subjects entered RIS-INT-41, 23 of which enrolled from RIS-CAN-19 (a double-blind placebo-controlled trial). Of the 481 newly recruited subjects, 351 completed RIS-INT-41. Forty-eight subjects enrolled in this trial, all of which took at least one dose of study medication (i.e. safety analysis set). The low number of subject enrolling in this study is to a large extent attributable to the late approval of the protocol in some countries. As a consequence many subjects became ineligible to participate in this study, or started using commercial medication. About 70% of the subjects completed this trial (Table 1).

Table 1: Trial termination reasons
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

State of Termination Term. Reason	RISPERIDONE (N=48) n (%)
Completed	33 (69)
Discontinued	15 (31)
Due to adverse event	6 (13)
Due to insufficient response	2 (4)
Subject ineligible to continue the trial	2 (4)
Subject withdrew consent	2 (4)
Subject non-compliant	1 (2)
Due to other reason	2 (4)

2.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics at the start of RIS-INT-41 are provided for subjects who did (INT-41/INT-70) or did not enroll from RIS-INT-41 in this study (INT-41) (Table 2). There were no marked differences in age, sex and disease status. A nearly equal number of children (<12 years) and adolescents (≥12 years) enrolled in this study.

Table 2: Demographic data, baseline characteristics and psychiatric history (RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

	INT-41 (N=433)	INT-41/INT-70 (N=48)
Age, years		
N	433	48
Mean (SD)	9.7 (2.47)	9.9 (2.32)
Median	10.0	10.0
Range	4 - 14	6 - 14
Age, years (at start int-70)		
N		48
Category, n (%)		
<12 years		25 (52)
>=12 years		23 (48)
Mean (SD)		11.0 (2.35)
Median		11.0
Range		7 - 15
Sex, n (%)		
N	433	48
Female	75 (17)	6 (13)
Male	358 (83)	42 (88)
DSM-IV AXIS I, n (%)		
N	433	48
ADHD	9 (2)	1 (2)
ADHD+BD NOS	37 (9)	12 (25)
ADHD+CD	86 (20)	10 (21)
ADHD+ODD	84 (19)	6 (13)
BD NOS	29 (7)	3 (6)
CD	104 (24)	14 (29)
ODD	84 (19)	2 (4)
DSM-IV AXIS II, n (%)		
N	432	48
Borderline intellectual functioning	158 (37)	20 (42)
Mild mental retardation	188 (44)	18 (38)
Moderate mental retardation	86 (20)	10 (21)
IQ-rating		
N	432	48
Mean (SD)	64.0 (13.62)	64.2 (14.14)
Median	65.0	68.0
Range	35 - 84	36 - 84

ADHD: Attention Deficit/Hyperactivity Disorder, BD NOS: Disruptive Behavior Disorder not otherwise specified; CD: Conduct Disorder; ODD: Oppositional Defiant Disorder

2.3. Extent of Exposure

Mean dose of trial medication and treatment duration are summarized below.

Table 3: Duration of trial medication and mean dose (mg/kg/day)
(RIS-INT-70, a Follow up trial of RIS-INT-41; All Subjects Analysis Set)

	RISPERIDONE (N=48)
Treatment duration, days	
N	48
Mean (SD)	330.5 (92.92)
Median	367.5
Range	47 - 457
Mean dose (days on drug only)	
N	48
Category, n (%)	
0 - < 0.01	1 (2)
0.01 - < 0.02	1 (2)
0.02 - < 0.03	10 (21)
0.03 - < 0.04	13 (27)
0.04 - < 0.05	11 (23)
0.05 - < 0.06	8 (17)
>= 0.06	4 (8)
Mean (SD)	0.041 (0.0160)
Median	0.039
Range	0.01 - 0.09

3. SAFETY

3.1. Adverse Events (ALL AE's analysis)

The incidence of adverse events – either new in onset or ongoing – are summarized in Table 4. AE's that occurred in >10% of the subjects in any of the subgroups are displayed. This table displays AE's for two groups of subjects and in two periods of treatment, resulting in three subgroups. The first column displays AE's for newly recruited subjects in RIS-INT-41 that did not enroll into RIS-INT-70 while column two depicts AE's from subjects that did continue in this study. Both columns consider the first year of Risperdal® treatment (i.e. treatment in RIS-INT-41). While the incidence of most adverse events appeared to be similar for both groups, hyperprolactinaemia showed a lower incidence in subjects who enrolled in this study. Therefore, especially the prolactin-related results should be interpreted with great caution. Additionally, respiratory system disorders -

and upper respiratory tract infection in particular – appear to have occurred at a lower frequency in subjects who continued treatment in this trial.

The last column displays adverse events occurring during the second year of Risperdal® treatment. The incidence of AE's appeared somewhat lower in general during the second year of treatment. More specifically, several adverse events that occurred relatively frequently during the first year in RIS-INT-41 showed marked decreases during the second year of Risperdal® treatment (somnolence, rhinitis, headache).

Table 4:Incidence of all adverse events
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

AE System Organ Class Adverse Event Preferred Term	INT-41 (N=433) n (%)	INT-41/INT-70 (N=48) n (%)	INT-70 (N=48) n (%)
Total no. subjects with adverse events	396 (91.5)	43 (89.6)	37 (77.1)
Psychiatric disorders	207 (47.8)	24 (50.0)	16 (33.3)
Agitation	20 (4.6)	3 (6.3)	6 (12.5)
Appetite increased	46 (10.6)	7 (14.6)	4 (8.3)
Somnolence	123 (28.4)	15 (31.3)	4 (8.3)
Aggressive reaction	23 (5.3)	7 (14.6)	3 (6.3)
Centr & periph nervous system disorders	191 (44.1)	21 (43.8)	10 (20.8)
Hyperkinesia	14 (3.2)	5 (10.4)	3 (6.3)
Headache	95 (21.9)	8 (16.7)	2 (4.2)
Metabolic and nutritional disorders	92 (21.2)	13 (27.1)	10 (20.8)
Weight increase	72 (16.6)	11 (22.9)	9 (18.8)
Respiratory system disorders	234 (54.0)	15 (31.3)	10 (20.8)
Rhinitis	118 (27.3)	10 (20.8)	4 (8.3)
Coughing	57 (13.2)	5 (10.4)	2 (4.2)
Pharyngitis	67 (15.5)	3 (6.3)	2 (4.2)
Upper resp tract infection	79 (18.2)	2 (4.2)	2 (4.2)
Body as a whole - general disorders	207 (47.8)	22 (45.8)	9 (18.8)
Fatigue	60 (13.9)	8 (16.7)	1 (2.1)
Fever	56 (12.9)	3 (6.3)	1 (2.1)
Injury	43 (9.9)	7 (14.6)	1 (2.1)
Gastro-intestinal system disorders	166 (38.3)	13 (27.1)	9 (18.8)
Vomiting	50 (11.5)	5 (10.4)	0
Endocrine disorders	70 (16.2)	4 (8.3)	6 (12.5)
Gynaecomastia	18 (4.2)	4 (8.3)	6 (12.5)
Hyperprolactinaemia	50 (11.5)	1 (2.1)	1 (2.1)

INT-41: All AE's during RIS-INT-41 for subjects not enrolling in RIS-INT-70. INT-41/INT-70: All AE's during RIS-INT-41 for subjects who enrolled in RIS-INT-70. INT-70: All AE's during RIS-INT-70.

3.2. Adverse events (Treatment emergent analysis)

Table 5 summarizes the incidence of adverse events in this study that were either new in onset or aggravated in severity. Incidences were summarized by age groupings (children and adolescents). Only AE's that occur in >5% of the subjects in any of the subgroups are displayed. EPS-, Prolactin- and glucose-related adverse events, deaths and serious AE's are displayed separately as well in the next subsections.

Table 5: Incidence of adverse events for all subjects, children and adolescents - Treatment emergent analysis
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

AE System Organ Class Adverse Event Preferred Term	<12 years (N=25) n (%)	>=12 years (N=23) n (%)	Total (N=48) n (%)
Total no. subjects with adverse events	16 (64.0)	18 (78.3)	34 (70.8)
Psychiatric disorders	6 (24.0)	9 (39.1)	15 (31.3)
Aggressive reaction	2 (8.0)	1 (4.3)	3 (6.3)
Agitation	1 (4.0)	4 (17.4)	5 (10.4)
Somnolence	1 (4.0)	3 (13.0)	4 (8.3)
Depression	0	2 (8.7)	2 (4.2)
Respiratory system disorders	6 (24.0)	4 (17.4)	10 (20.8)
Rhinitis	3 (12.0)	1 (4.3)	4 (8.3)
Gastro-intestinal system disorders	5 (20.0)	4 (17.4)	9 (18.8)
Abdominal pain	1 (4.0)	2 (8.7)	3 (6.3)
Saliva increased	1 (4.0)	3 (13.0)	4 (8.3)
Body as a whole - general disorders	3 (12.0)	5 (21.7)	8 (16.7)
Condition aggravated	1 (4.0)	2 (8.7)	3 (6.3)
Pain	0	2 (8.7)	2 (4.2)
Metabolic and nutritional disorders	2 (8.0)	1 (4.3)	3 (6.3)
Weight increase	2 (8.0)	1 (4.3)	3 (6.3)
Skin and appendages disorders	2 (8.0)	3 (13.0)	5 (10.4)
Verruca	0	2 (8.7)	2 (4.2)
Endocrine disorders	1 (4.0)	2 (8.7)	3 (6.3)
Gynaecomastia	1 (4.0)	2 (8.7)	3 (6.3)

3.2.1. EPS-related AE's

EPS was seen in 10.4% of the subjects. There were no cases of tardive dyskinesia.

Table 6: Incidence of EPS-related adverse events for all subjects, children and adolescents - Treatment emergent analysis
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

AE System Organ Class Adverse Event Preferred Term	<12 years (N=25) n (%)	>=12 years (N=23) n (%)	Total (N=48) n (%)
Total no. subjects with EPS related adverse events	2 (8.0)	3 (13.0)	5 (10.4)
Centr & periph nervous system disorders	2 (8.0)	3 (13.0)	5 (10.4)
Hyperkinesia	1 (4.0)	1 (4.3)	2 (4.2)
Muscle contractions involuntary	1 (4.0)	0	1 (2.1)
Hypertonia	0	1 (4.3)	1 (2.1)
Hyporeflexia	0	1 (4.3)	1 (2.1)
Oculogyric crisis	0	1 (4.3)	1 (2.1)
Tremor	0	1 (4.3)	1 (2.1)

3.2.2. Prolactin-related AE's

Gynaecomastia was reported in 3 out of 42 boys and one of 6 girls reported amenorrhoea. These adverse events did not resolve during this trial and led to the permanent termination of treatment in two boys experiencing gynaecomastia.

Table 7: Incidence of Prolactin-related adverse events for all subjects, children and adolescents - Treatment emergent analysis
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

AE System Organ Class Adverse Event Preferred Term	<12 years (N=25) n (%)	>=12 years (N=23) n (%)	Total (N=48) n (%)
Total no. subjects with Prolactin related adverse events	1 (4.0)	3 (13.0)	4 (8.3)
Endocrine disorders	1 (4.0)	2 (8.7)	3 (6.3)
Gynaecomastia	1 (4.0)	2 (8.7)	3 (6.3)
Reproductive disorders, female	0	1 (4.3)	1 (2.1)
Amenorrhoea	0	1 (4.3)	1 (2.1)

Note: Percentages of Amenorrhoea are calculated with the number of patients as denominator. This AE can only occur in females, and since only 6 females entered this trial, Amenorrhoea occurred in 17% of the female patients

3.2.3. Glucose-related AE's

There were no glucose-related adverse events in this trial

3.2.4. Deaths

There were no deaths in this trial

3.2.5. Serious Adverse Events

Four subjects were hospitalized: three because of a deterioration of their disruptive behavior, one because of a suicide attempt.

Table 8:Incidence of serious adverse events for all subjects, children and adolescents - Treatment emergent analysis
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects Analysis Set)

AE System Organ Class Adverse Event Preferred Term	<12 years (N=25) n (%)	>=12 years (N=23) n (%)	Total (N=48) n (%)
Total no. subjects with serious adverse events	1 (4.0)	3 (13.0)	4 (8.3)
Body as a whole - general disorders	1 (4.0)	2 (8.7)	3 (6.3)
Condition aggravated	1 (4.0)	2 (8.7)	3 (6.3)
Psychiatric disorders	0	1 (4.3)	1 (2.1)
Suicide attempt	0	1 (4.3)	1 (2.1)

3.3. Prolactin levels in male and female subjects

Mean prolactin levels and their changes from Baseline(1) and Baseline(2) are summarized in Tables 9 and 10. Results for males were highly influenced by the high values of a single subject (Figure 1). Therefore, median values and ranges were also included in the tables. Results in females are based on five subjects, and therefore difficult to interpret. A graphical presentation of the individual profiles was added to this document to provide individual data for males and females (Figure 1).

Looking at the median levels and the median changes in male prolactin levels, there appeared to be a relatively stable prolactin-profile during the second year of Risperdal® treatment (Tables 9 and 10). Upper laboratory normal limits in boys and girls are 18 ng/ml and 25 ng/ml respectively. Median prolactin levels stayed within the normal range for boys and remained slightly elevated in girls during this second year of treatment. The graphs of the individual profiles suggest that the prolactin-levels of the subjects in this trial covered the whole range of observed values during RIS-INT-41 (Figure 1). Nevertheless, it should be noted that the incidence of Hyperprolactinaemia appeared to be lower in subjects who enrolled in this

study compared to those who did not continue (Table 4) hereby potentially biasing these results.

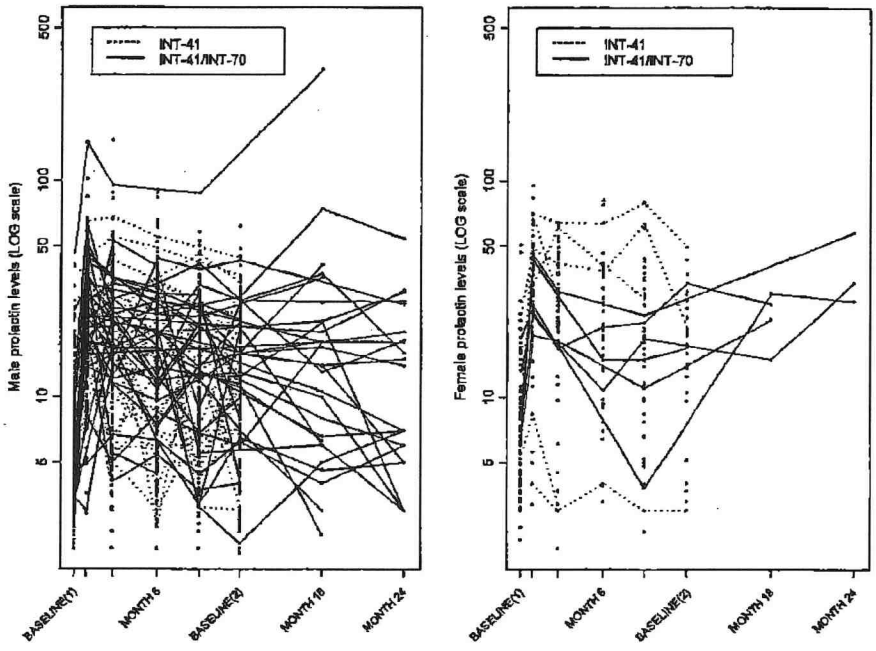
Table 9:Prolactin levels in male and female subjects - Changes from Baseline (RIS-INT-41)
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects (Restricted to Subjects with Visit Baseline(1) Data Only) Analysis Set)

								Change from Baseline(1)					
	N	Mean	SD	Median	Min	Max	Base mean	N	Mean change	SD	Median change	Min	Max
Prolactin													
RISPERIDONE													
Female													
Baseline(1)	6	10.08	5.03	7.70	6.3	18.9							
Month 24	3	40.00	15.88	34.00	28.0	58.0	11.43	3	28.57	20.41	26.80	9.1	49.8
End point	5	34.00	13.98	28.00	23.0	58.0	10.78	5	23.22	16.22	16.70	9.1	49.8
Male													
Baseline(1)	38	7.65	8.27	4.60	2.6	47.7							
Month 24	20	15.87	13.18	14.50	3.0	54.0	5.57	20	10.30	14.17	6.85	-5.7	51.0
End point	33	25.47	55.10	15.00	2.3	324	7.59	33	17.88	48.72	6.40	-18	276

Table 10:Prolactin levels in male and female subjects - Changes from Baseline (RIS-INT-70)
(RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects (Restricted to Subjects with Visit Baseline(2) Data Only) Analysis Set)

								Change from Baseline(2)					
	N	Mean	SD	Median	Min	Max	Base mean	N	Mean change	SD	Median change	Min	Max
Prolactin													
RISPERIDONE													
Female													
Baseline(2)	6	18.58	10.09	17.85	3.8	34.0							
Month 24	3	40.00	15.88	34.00	28.0	58.0	15.50	3	24.50	9.35	24.20	15.3	34.0
End point	5	34.00	13.98	28.00	23.0	58.0	18.90	5	15.10	15.54	15.30	-7.0	34.0
Male													
Baseline(2)	42	17.93	14.57	16.00	2.1	87.7							
Month 24	21	15.45	12.99	14.00	3.0	54.0	17.40	21	-1.95	11.60	-2.00	-23	25.0
End point	35	24.30	53.67	14.00	2.3	324	18.19	35	6.11	42.01	-1.50	-23	236

Figure 1. Individual prolactin levels for male and female subjects over a two-year period of Risperdal® treatment. Observations are provided for subjects that did (INT-41/INT-70) and did not (INT-41) enroll in RIS-INT-70. For clarity of the figure only a random selection (10%) of subjects that did not continue Risperdal® treatment is plotted.



3.4. Body weight and Body Mass Index

Weight increased by 12.2 kg over the two year period of Risperdal® treatment while the BMI increased by 2.7 kg/cm^2 (Table 11). There appeared to be a normalization of weight increase during the second year. During this

trial (Table 12) weight increased with 4.2 kg while BMI increased with 0.3 kg/cm^2. The weight increase during the second year can be attributed to developmental growth.

Table 11: Weight and BMI - Changes from Baseline (RIS-INT-41) (RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects (Restricted to Subjects with Visit Baseline(1) Data Only) Analysis Set)

	RISPERIDONE					
					Change from Baseline(1)	
	N	Mean	SD	Base mean	Mean change	SD
Weight, kg						
Open						
Baseline(1)	47	36.9	14.43			
Month 24	34	47.0	17.20	35.3	11.6	7.17
End point	47	49.1	18.03	36.9	12.2	8.37
Body mass index						
Open						
Baseline(1)	46	18.2	3.77			
Month 24	33	20.3	4.70	17.6	2.7	2.82
End point	46	20.9	5.03	18.2	2.7	3.02

Table 12: Weight and BMI - Changes from Baseline (RIS-INT-70) (RIS-INT-70, a Follow up trial of RIS-INT-41: All Subjects (Restricted to Subjects with Visit Baseline(2) Data Only) Analysis Set)

	RISPERIDONE					
					Change from Baseline(2)	
	N	Mean	SD	Base mean	Mean change	SD
Weight, kg						
Open						
Baseline(2)	48	45.1	16.46			
Month 24	34	47.0	17.20	42.8	4.2	3.39
End point	48	49.3	17.91	45.1	4.2	4.48
Body mass index						
Open						
Baseline(2)	48	20.7	4.74			
Month 24	34	20.3	4.64	20.0	0.3	1.38
End point	48	20.9	4.95	20.7	0.2	1.77

3.5. ECG observations

ECG parameters did not show significant changes, including QTc. At endpoint there was one male subject with a prolonged (i.e. >450 ms for

males and >470 for females) QTcLD value (QTcLD = 455 ms) and there were no subjects with pathological QTcLD values (i.e. >500 ms).

Table 13:Distribution of increases from open-label baseline 1 (RIS-INT-41) in ECG values (RIS-INT-70 - The long-term safety and efficacy of risperdal in conduct disorder in children - A follow up trial of RIS-INT-41: All Subjects Analysis Set)

		RISPERIDONE (N=48)	
Parameter	Total	– Category, n (%) –	
Time Interval	n	<30 ms	30-60 ms
QTcLD change from baseline(1)			
Month 24	27	25 (93)	2 (7)
End point	40	37 (93)	3 (8)

Note: Percentages of sub-groups calculated with the no. of subjects per time interval as denominator.

Table 14:Distribution of increases from open-label baseline 2 (RIS-INT-70) in ECG values (RIS-INT-70 - The long-term safety and efficacy of risperdal in conduct disorder in children - A follow up trial of RIS-INT-41: All Subjects Analysis Set)

		RISPERIDONE (N=48)	
Parameter	Total	– Category, n (%) –	
Time Interval	n	<30 ms	30-60 ms
QTcLD change from baseline(2)			
Month 24	29	26 (90)	3 (10)
End point	45	40 (89)	5 (11)

Note: Percentages of sub-groups calculated with the no. of subjects per time interval as denominator.

4. EFFICACY

4.1. Change in conduct problem subscale of N-CBRF scores from the two baselines

Of the 48 subjects that enrolled in this study, two had no post-baseline assessment of efficacy. That leaves 46 subjects in the Intent-To-Treat dataset, the primary dataset for efficacy. Strong decreases in the conduct problem subscale of N-CBRF occurred during the first weeks of Risperdal® treatment in RIS-INT-41 and remained relatively stable over the two year period (Table 15, Table 16). A graphical inspection of the N-CBRF conduct problem subscale over the two-year period of Risperdal® treatment - for subject who did (INT-41/INT-70) or did not enroll in this study - indicates that the subject population treated for a second year did not show strong

differences in efficacy compared to those not continuing Risperdal® treatment (Figure 2).

Table 15: Summary of Conduct Problem Subscale of N-CBRF - Changes from Baseline (RIS-INT-41) (RIS-INT-70, a Follow up trial of RIS-INT-41: Intent-to-treat (Restricted to Subjects with Visit Baseline(1) Data Only) Analysis Set)

Lower scores indicate better condition

	RISPERIDONE						
					Change — from Baseline(1) —		
	N	Mean	SD	Base mean	Mean change	SD	P (a)
Conduct disorder(imputed)							
Open							
Baseline(1)	46	32.3	7.10				
Month 24	31	12.8	8.51	32.6	-19.8	10.64	<0.001
End point	46	16.5	11.62	32.3	-15.7	12.55	<0.001

(a) Two sided P-value for paired t-test on change from baseline(1).

Table 16: Summary of conduct problem subscale of N-CBRF - Changes from Baseline (RIS-INT-70) (RIS-INT-70, a Follow up trial of RIS-INT-41: Intent-to-treat (Restricted to Subjects with Visit Baseline(2) Data Only) Analysis Set)

Lower scores indicate better condition

	RISPERIDONE						
					Change — from Baseline(2) —		
	N	Mean	SD	Base mean	Mean change	SD	P (a)
Conduct disorder(imputed)							
Open							
Baseline(2)	46	15.2	10.01				
Month 24	31	12.8	8.51	14.6	-1.8	7.66	0.199
End point	46	16.5	11.62	15.2	1.3	10.48	0.388

(a) Two sided P-value for paired t-test on change from baseline(2).

Figure 2. Conduct problem subscale of N-CBRF (Mean ± SE) over a two-year period of Risperdal® treatment for subject who did (INT-41/INT-70) or did not enroll in this trial (INT-41).