# STATISTICAL DOCUMENTATION

*Long-Term Risperidone Treatment vs Prolactin Pooled Analysis*

**Protocols**

RIS-CAN-19/20, RIS-USA-93/97 and RIS-INT-41

Sponsor

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# INTRODUCTION - ANALYSIS PLAN

This document is a brief technical report of the post-hoc analyses conducted on the pooled data from five clinical studies to assess the effect of risperidone associated increases in prolactin levels in children with long-term risperidone treatment and explore any relationship with side effects hypothetically attributable to prolactin (SHAP).

The objectives were:

1. To characterize changes in serum prolactin levels over one year of risperidone treatment
2. To determine the association/correlation between prolactin levels and age
3. To explore the relationship between prolactin levels and prolactin-related side effects (SHAP)
4. To explore the relationship between prolactin levels and extrapyramidal symptoms (EPS)
5. To determine the association/correlation between the Conduct Problem Subscale score of the N-CBRF and prolactin levels

## Methods

Five study databases of risperidone-treated children were pooled ('analysis' dataset). The table below summarizes the study design and duration of each trial.

| Study ID | Design | Duration |
|---|---|---|
| RIS-CAN-19 | Double-blind, placebo controlled | 6 weeks |
| RIS-CAN-20 | Open label follow-up to RIS-CAN-19 | 48 weeks |
| RIS-USA-93 | Double-blind, placebo controlled | 6 weeks |
| RIS-USA-97 | Open label follow-up to RIS-USA-93 | 48 weeks |
| RIS-INT-41 | Separate open label trial to collect safety data | 48 weeks |

### Analysis Populations

Intent-to-Treat Population (ITT): The ITT population consisted of patients who received at least one dose of risperidone.

Primary Analysis Population (PA): This population is a subset of the ITT patients with pre-dose and at least one post-dose prolactin observation at or after week 4.

Fixed N Subsets. The PA dataset was grouped into five subsets in order to determine if dropout had an effect on the trend in prolactin levels over the one year period of study. The five fixed subsets were defined as follows:

(1) Patients with a prolactin observation at pre-dose and weeks 4 to 7

(2) Patients with a prolactin observation at pre-dose, weeks 4 to 7 and 8 to 12

(3) Patients with a prolactin observation at pre-dose, weeks 4 to 7, 8 to 12 and 16 to 24

(4) Patients with a prolactin observation at pre-dose, weeks 4 to 7, 8 to 12, 16 to 24 and 28 to 36

(5) Patients with a prolactin observation at pre-dose, weeks 4 to 7, 8 to 12, 16 to 24, 28 to 36 and 40 to 48

## Key Variables Analyzed

- Prolactin concentrations. Concentrations were determined under a slightly different schedule in the five studies. To standardize sampling, observations taken during 4-7, 8-12, 16-24, 28-36, 40-48 and 52-55 were grouped together.
- Prolactin-related side effects (SHAP). SHAP are adverse events classified under the WHO system organ class as "Endocrine disorders" or "Reproductive disorders". SHAP classified under preferred term as "Balanoposthitis", "Dysmenorrhoea", "Growth Hormone Excess", "Hernia Inguinal", "Hyperprolactinaemia", "Penis Disorder", "Sexual Function Abnormal", "Sialoadenitis", "Testis Disorder", "Thyroiditis", "Thyroid Stim. Hormone Decreased" or "Vaginitis Atrophic" were not included. To be classified as SHAP, the duration of Amenorrhoea had to be at least one week. Females with Gynaecomastia were included if it had occurred for at least successive 31 days, and males were included if they were less than 10 years of age.
- Extrapyramidal Symtoms (EPS). EPS are adverse events classified under the WHO system organ class as "Central and Peripheral Nervous System Disorders". EPS classified under the WHO preferred term as "Agitation", "Akathesia", "Bradykinesia", "Dyskinesia Tardive", "Dystonia", "Extrapyramidal Disorder", "Hyperkinesia", "Hyperreflexia", "Hypertonia", "Hypokinesia", "Hypotonia", "Muscle Contractions Involuntary", "Oculogyric Crisis", "Parkinsonism", "Rigidity", "Shuffling Gait", "Stiffness", "Tics" or "Tremor" were included.
- Conduct Problem Subscale on Nisonger Conduct Behavior Rating Form (N-CBRF). Non-imputed scores provided in the 'analysis' datasets were used. Responders were defined as patients with >=25%, >=35% and >= 50% improvement from pre-dose to each of the study periods.

# Documentation of Statistical Tables and Graphs

## Analysis Population

A total of 700 patients were enrolled and received study medication (ITT population). Table 1 shows the number of patients in the ITT and PA populations. Table 2 summarizes the number of patients at key assessment time-points that qualified for analysis of the long-term risperidone effect on prolactin (PA population). Table 3 identifies all patients in the ITT population and provides a patient-by-patient listing of prolactin levels plus gender, DSM-IV Axis II, IQ, pre-dose age, Tanner stage, height [cm], weight [kg] and BMI (possible stratification variables).

## Demographic and Pre-dose Characteristics

In Table 4, patient demographics and screening characteristics are summarized for the ITT, PA and Non-PA populations. To determine if PA and Non-PA populations are comparable with respect to demographic and pre-dose variables, p-values are provided for categorical variables (chi-square test) and continuous variables (two sample t-test). Descriptive statistics for study drug dosing variables (exposure [mg], duration [days], daily dose [mg/day]) in the ITT, PA and Non-PA populations are summarized in Table 5.

## Normal Range of Prolactin

Descriptive statistics for prolactin levels at pre-dose (prior to risperidone treatment), including 90% and 95% confidence intervals for individual observations, are provided for gender and Tanner Stage in Table 6. Figures 1 (gender) and 2 (Tanner Stage) illustrate the spread of the data with box-plots (box and whisker plots are used to present percentiles (10%, 25%, 50% (median), 75% and 90%).

## Prolactin Profiles

Descriptive statistics of long-term prolactin levels are given in Table 7 and illustrated graphically in Figure 3 (Note: Weeks 52-55 is not shown on the graph dne to the small sample size in that time period). Mean prolactin values are connected by a solid line while tlie spread of the data is illustrated with a box-plot (box and whisker plots are used to present percentiles (10%, 25%, 50% (median), 75% and 90%).

The incidence of prolactin levels at or above the upper limit of normal (ULN) at each time period is presented in Table 8. ULN for prolactin levels is 18 ng/mL for males and 30 ng/mL for females.

### Evaluation of the Association Between Early Discontinuation vs Prolactin Levels

Table 9 provides descriptive statistics for prolactin levels by time period for the five fixed sub-populations defined by the availability of a prolactin observation at every time point. Mean prolactin levels by time period across the five fixed subsets are presented in Figure 4. In Table 10, the incidence of prolactin levels at or above ULN [ng/mL] is summarized by time period across fixed subsets. Table 11 and Figure 5 present prolactin levels at each time period across the fixed subsets for patients discontinuing vs. continuing in the trial.

### Prolactin Profiles by Gender and Age

Prolactin levels are summarized at each time period for gender, age group, and gender and age group (boys: >= 10, < 10; girls: >= 9, < 9) in Tables 12 to 14, and illustrated graphically in Figures 6 to 8, respectively. Correlations between prolactin levels [ng/mL] and age [years] are provided for observed points on the log base 10 scale to adjust for skewness (Table 15). The slope of the regression curve, and lower and upper 95% confidence intervals of the slope are provided on the log base 10 scale, and then converted to the original scale. The results show that, for each year, there is an approximate 1 ng/mL expected increase in mean prolactin. $R^2$ provides information on the amount of variation in prolactin levels that can be explained by age at each study period. Scatterplots illustrate the relationship between prolactin levels and age at each time period (Figures 9 to 13).

### Prolactin-related Side Effects (SHAP) vs Prolactin Levels

Table 16 shows the frequency of prolactin-related side effects by WHO system organ class and preferred term in the ITT, PA and Non-PA populations. Descriptive statistics for onset of SHAP from pre-dose [days] are provided in Table 17. In Table 18, descriptive statistics of prolactin levels are provided for patients with vs without prolactin-related side effects. Mean prolactin levels are plotted for these two groups in Figure 14. Descriptive statistics of risperidone dosing are provided for patients with and without side effects in Table 19. Frequency tables are presented in Table 20 to summarize prolactin-related side effects by prolactin levels. Chi-square tests are provided at each time period to determine if there is a relationship between SHAP and prolactin levels. A histogram is used to illustrate the incidence

of SHAP for patients at or above the ULN of prolactin. (Figure 15). In Table 21, the number of SHAP is summarized, in the ITT and PA populations, by gender and age group (< 10 vs >= 10 for males; < 9 vs >= 9 for females). The following patient listings are provided in Tables 22 – 25 for patients who had prolactin-related side effects:

- Description of prolactin-related side effects (Table 22)
- Concomitant medication use (Table 23)
- Demographic variables (gender, age, DSM-IV Axis II, IQ) and prolactin levels over time (Table 24)
- Tanner stage, height and weight across the one-year period of study (Table 25)

### Extrapyramidal Symptoms (EPS)

Incidence of EPS by system organ class and preferred term in the ITT, PA and Non-PA populations are summarized in Table 26. Descriptive statistics for duration [days] from pre-dose are provided for the onset of the first extrapyramidal symptom in Table 27. In Table 28, descriptive statistics of prolactin levels are provided for patients with vs without EPS. Mean prolactin levels are plotted for these two groups in Figure 16. Frequency tables of number of EPS by prolactin levels and study period is presented in Table 29. Chi-square tests are provided at each time period to determine if there is a association between EPS and prolactin levels. A histogram is used to illustrate the precentage of patients with EPS at or above ULN at each time period (Figure 17). A description of EPS is provide in a patient data listing (Table 30).

### Conduct Problem Subscale of the N-CBRF

Descriptive statistics of prolactin levels by responders in each time period are provided in Table 31. Mean prolactin levels are plotted for responders at each time period for each of the three response criteria (Figures 18 to 20). Change from pre-dose in prolactin levels by responders in provided in Table 32. Frequency tables summarize responders on the conduct problem subscale by prolactin levels [ng/mL] at or above ULN (Table 33). Chi-square tests are provided at each time period to determine if there is a relationship between responders and prolactin levels. Histograms are presented in Figures 21 to 23 to illustrate the distribution of responders at or above ULN at each time period. Correlations between the Conduct Problem Subscale score and prolactin levels [ng/mL] at each study period are provided for observed points on the log base 10 scale to adjust for skewness in Table 34. The slope of the regression curve, and lower and upper 95% confidence intervals are provided on the log base 10 scale. The results

show that, for every tenfold ng/mL increase in prolactin, there is an approximate one unit expected decrease in the mean conduct disorder subscale score. $R^2$ provides information on the amount of variation in the Conduct Problem subscale score that can be explained by prolactin levels at each study period. Scatterplots illustrate the relationship between the Conduct Problem subscale score and prolactin levels at each time period (Figures 24 to 28).