PLAINTIFF'S EXHIBIT 27

From: Deloria, Carmen [JANUS]
Sent: Thursday, August 22, 2002 1:56 PM
To: Lin, Joseph [JANUS]
Subject: FW: pooled prolactin manuscript

Follow Up Flag: Follow up
Flag Status: Completed


pooled prolactin manuscript Au...

For your review.

-----Original Message-----
From: Pandina, Gahan [JANUS]
Sent: Wednesday, August 21, 2002 10:36 AM
To: Binder, Carin [JOI]; De Smedt, Goedele [PRDBE]; Nys, Vincent [JanBe]; Reyes-Harde, Magali [JANUS]; Deloria, Carmen [JANUS]; Jacko, Mary [PRDUS]; Braendle, Daniel [JACCH]; Rupnow, Marcia [JANUS]
Cc: Derivan, Albert [PRDUS]; Caers, Ivo [PRDBE]
Subject: RE: pooled prolactin manuscript

Dear Team,

Attached please find my comments. I think the paper is overall constructed well and well-written. I think we need to include the lack of association between Tanner/height delay and PRL level or SHAP, as our advisors tell us that this is one serious concern about prolactin. If we can demonstrate that the transient rise in PRL does not result in abnormal maturation or SHAP, this would be most reassuring to clinicians. I realize that these manuscripts are being developed in parallel, but the relationship here is important. We have also had many concerns about patients who are maintained on stimulants, as this might affect PRL level, and no subanalyses were included. Perhaps we can discuss prior to the next revision. Congratulations on the Tanner data being accepted. Great news! Maybe this will make it easier for us to include this as a subanalysis in this paper.

Gahan

-----Original Message-----
From: Binder, Carin [JOI]
Sent: Thursday, August 15, 2002 11:06 AM
To: De Smedt, Goedele [PRDBE]; Nys, Vincent [JanBe]; Reyes-Harde, Magali [JANUS]; Deloria, Carmen [JANUS]; Pandina, Gahan [JANUS]; Jacko, Mary [PRDUS]; Braendle, Daniel [JACCH]; Rupnow, Marcia [JANUS]
Cc: Derivan, Albert [PRDUS]; Caers, Ivo [PRDBE]
Subject: pooled prolactin manuscript

Dear Pediatric Publication Team,

May I ask you to please review the attached draft manuscript within the next 2 weeks if possible. Since this is holiday time - leeway will be extended to early September. I have inserted some comments in yellow for our authors to clarify - please ignore these. Remember that the growth/Tanner analysis is being written as a separate paper (Brief Report format)which is why we did not look at Tanner staging/growth in this prolactin paper.

Key message- prolactin rise is transient and not related to side effects hypothetically attributed to prolactin, EPS or efficacy response.

Did we ever discuss which Journal to submit to? Your choices will be welcomed!

Note - the Tanner/Growth abstract to AACAP was accepted!

Exhibit
Pandina – 11
5.21.13

EXHIBIT
Date: P-27
M.L. GRAY, CSR, RPR

Regards,
Carin

PS If this needs to be sent to other people to review - please forward. Thanks

<< File: pooled prolactin manuscript 08.02.doc >>

Title: **Prolactin Levels in Children and Adolescents with Long-Term Risperidone Use**

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[Journal requirements: 1) contributions that need acknowledging but do not justify authorship, such as general support by a departmental chairperson, critical review of study proposal, or data collection; 2) acknowledgments of technical help; 3) acknowledgments of financial and material support, specifying the nature of the support; and 4) indications of previous presentation. Authors must secure written permission to be cited from acknowledged persons.]

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ABSTRACT

Background

This analysis was designed to investigate prolactin levels in children with long-term risperidone treatment and explore any relationship with side effects hypothetically attributable to prolactin (SHAP).

Method

Data from five clinical trials were pooled for this post-hoc analysis. Children aged 5 to 15 years with had subaverage IQs and conduct or other disruptive behaviour disorders received risperidone treatment for up to 55 weeks. Outcome measures analyzed included serum prolactin levels, adverse events, and the Conduct Problem subscore of the NCBRF.

Results

Mean prolactin levels rose from 7.8 ng/ml at baseline to a peak of 29.4 ng/ml at Weeks 4 to 7, then progressively decreased to 16.1 ng/ml at Weeks 40 to 48. There was no relationship between prolactin levels and age. Girls returned to a mean value within the normal range (≤30 ng/ml) by Weeks 8 to 12 and boys were close to normal values (≤18 ng/ml) by Weeks 16 to 24. SHAP were reported by 4.7% of the children; the most common was gynecomastia (3.4%). There was no direct correlation between prolactin elevation and SHAP. Whether prolactin levels were within the normal range or above the upper limit of normal (ULN), patients who experienced extrapyramidal symptoms (EPS), or had improvement in behavioral symptoms were no more likely to have higher prolactin levels than those without symptoms or improvement.

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Conclusion

With long-term risperidone treatment in children, serum prolactin levels tended to rise and peak within the first month or two, and then steadily decline to values within the normal range by three to five months. There was no relationship between the occurrence of SHAP, EPS or improvement on the Conduct Disorder subscale of the NCBRF and prolactin elevation.

KEY WORDS

prolactin, children, risperidone, hyperprolactinemia, antipsychotic

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INTRODUCTION

Antipsychotic drugs are thought to exert their therapeutic effect through antidopaminergic action in the mesolimbic system.[1] Blocking dopamine D_2 receptors can also cause side effects commonly seen with typical antipsychotics, including extrapyramidal symptoms (EPS) and elevated serum prolactin levels. The introduction of atypical antipsychotics has provided therapeutic benefit with a reduction in these side effects.

While EPS have been emphasized as an antipsychotic-related side effect, there is increasing clinical and scientific interest in the effects of elevated prolactin levels. Prolactin is a hormone synthesized by lactotrophs of the anterior pituitary gland and its primary biologic role includes breast tissue development and stimulation of lactation.[2] Prolactin is under inhibitory dopaminergic control and the elevation of prolactin associated with antipsychotic drugs is thought to be mediated by blockade of dopamine D_2 receptors on pituitary lactotrophs. (do we want to mention that there are different types of prolactin, some bioactive and some not, and little is known about variability of prolactin in the developing child? Do we have information on the specific prolactin assay used here, as this could be questioned later? Gahan)

Persistent and marked hyperprolactinemia is associated with hypogonadism in both genders, mainly by inhibiting hypothalamic gonadotrophin-releasing hormone secretion.[3] (VK-should we quote University web reference re: prolactin prolonged >

500?) This can lead to a decrease in bone mineral density and increased risk for osteoporosis.[4] Elevated prolactin has also been associated with gynecomastia, galactorrhea and menstrual disturbances.[1,3] The long-term consequences of chronic hyperprolactinemia in children with prolactinomas can include menstrual irregularities, infertility, short stature, and osteopenia and/or osteoporosis.[5] The importance of studying the longitudinal and long-term trends in serum prolactin in patients treated with antipsychotics is clear. It is especially relevant in children and adolescents because of growth and sexual development (if we comment on this, it would make sense to include correlations with Tanner staging. This relationship was highlighted by our national ad board as a primary concern with prolactin, rather than just tumor risk, etc. Gahan). Based on higher than expected rates of EPS in children and adolescents treated with antipsychotics, Wudarsky and colleagues hypothesized the possibility of a more robust drug-related prolactin elevation in this age group—possibly reflecting a greater sensitivity of the dopamine systems in young patients.[2]

As such, they conducted a 6-week trial in 35 children and adolescents with early onset psychosis who were treated with one of three different antipsychotics (haloperidol, clozapine, or olanzapine).[2] They did find more robust prolactin elevation in pediatric patients than observed in adults; with the typical antipsychotic, haloperidol, and with the atypical antipsychotic, olanzapine.[2] They noted that these results justified longer observation intervals with bigger samples to establish treatment safety of antipsychotics in this age group. There has also been a report of prolactin elevation in children after 10 weeks of treatment with the atypical antipsychotic, risperidone.[6] None of the children

showed clinical signs of hyperprolactinemia, but the authors noted the paucity of available data on potential effects of long-term hyperprolactinemia in children during treatment with antipsychotics.

Risperidone is a novel atypical antipsychotic that binds with a high affinity to serotonin 5-HT_2 receptors, dopamine D_2 receptors and α_1-adrenergic receptors. Double blind, placebo controlled trials with risperidone have demonstrated efficacy in several disorders, including the management of symptoms associated with conduct and other disruptive behaviour disorders in children, adolescents and adults with subaverage intellectual functioning or mental retardation in whom destructive behaviours (e.g., aggression, impulsivity, and self-injurious behaviours) are prominent. We decided to pool several studies in children and adolescents aged 5 to 15 years of age. Two 6-week double-blind placebo-controlled trials with 48-week open-label extensions, plus one additional open-label 48-week trial, included measurements of serum prolactin at several time periods, and provides us with the opportunity to evaluate prolactin levels in children and adolescents with long-term risperidone treatment (up to 55 weeks).

There is controversy concerning prolactin levels that warrant further investigation in children. Consultation with pediatric endocrinologists indicated that prolactin levels above 18 ng/ml but below 30 ng/ml, and without any clinical problems, do not require extensive investigation. They suggested that prolactin levels >100 ng/ml for extended periods of time should be investigated by the practitioner (personal communication) (this may be questioned, as there are other "experts" presenting regularly for other

companies suggesting that any sustained elevation outside the normal range should be of concern - Gahan.

The objective of this post-hoc analysis was to investigate serum prolactin levels in children and adolescents with long-term risperidone treatment, and to explore any possible correlation with side effects hypothetically attributable to elevated prolactin levels (SHAP). Because many of these children would have been going through puberty, and symptoms associated with hyperprolactinemia, such as gynecomastia and menstrual disturbances, can also be seen with puberty, possible associations with age and gender were also explored.

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METHODS

Pooled Study Databases

Five study databases of risperidone-treated children and adolescents were merged. There were two double blind (DB), placebo-controlled trials of 6 weeks duration (RIS-CAN-19, RIS-USA-93) and three 48-week open-label (OL) follow-on studies; RIS-CAN-20 followed RIS-CAN-19 and RIS-USA-97 followed RIS-USA-93. RIS-INT-41 was designed as an open-label trial to collect safety data. Children were permitted to enter the open-label 48-week extension trials (RIS-CAN-20, RIS-USA-97) provided they had at least 2 weeks of treatment during the double-blind trial. The same sponsor designed the studies to be consistent with one another, including identical patient selection criteria, medication dosing and outcome measures. All studies were conducted in accordance with the Declaration of Helsinki as revised in 1983 and approved by the institutional review boards at each participating centre and by the appropriate regulatory bodies in the respective countries.

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Patients

The studies enrolled children, aged 5 to 14 years inclusive, who had: 1) a DSM-IV Axis I diagnosis of conduct disorder (CD), oppositional defiant disorder (ODD), or disruptive behavior disorder not otherwise specified (DBD-NOS); 2) a parent-assessed rating of ≥24 in the Conduct Problem subscale of the Nisonger-Child Behavior Rating Form (NCBRF)[7]; 3) a DSM-IV Axis II diagnosis of mild or moderate mental retardation or borderline intellectual functioning with an IQ ≥36 and ≤84; and 4) a score of ≤84 on the

Vineland Adaptive Behavior Scale.[8] In addition, subjects had to be outpatients who were physically healthy and had a behavioral problem sufficiently severe that the investigator felt antipsychotic treatment was warranted at entry to the DB trial and to the open-label extension trial RIS-INT-41. Individuals with attention deficit/hyperactivity disorder (ADHD) were eligible provided they met all other selection criteria. A responsible person was required to accompany the subject at clinic visits, provide reliable assessments, and dispense medications.

Subjects were excluded if they had a diagnosis of pervasive development disorder, schizophrenia, other psychotic disorder, head injury or seizure disorder, history of tardive dyskinesia, neuroleptic neuropathy, known hypersensitivity to neuroleptics or risperidone, tested positive for HIV, abnormal laboratory values, or were using a prohibited medication. Subjects were excluded from the open label follow-on studies if more than three weeks had elapsed since their participation in the previous DB trial or, if during that trial, they experienced a hypersensitivity reaction to trial medication, extrapyramidal symptoms (EPS) not controlled by medication, an adverse event possibly related to risperidone for which they were withdrawn. Subjects provided verbal and, if capable, written informed consent; signed consent was also obtained from the subject's legal representative.

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Study and Other Medications

Participants who were randomized to risperidone treatment during the DB study could receive a maximum of 55 weeks of risperidone therapy (6 weeks during the DB study plus 48 weeks during the OL extension).

Risperidone was provided by Janssen Research Foundation as an oral solution of 1.0 mg/ml to be administered once daily in the morning at an initial dose of 0.01 mg/kg on Days 1 and 2, and increased to 0.02 mg/kg on Day 3. Thereafter, the dose could be adjusted by the investigator at weekly intervals to a maximal allowable dose of 0.06 mg/kg/day; increments were not to exceed 0.02 mg/kg/day. For those with breakthrough symptoms, the dosing schedule could be changed to a bid regimen.

Medications used to treat EPS were to be discontinued at DB trial entry. For those with emergent EPS during the trials, the dose of risperidone could be reduced; the rate of dose reduction was not limited. Anticholingeric agents were permitted only in cases where dose reduction resulted in deterioration of behavioral symptoms or failed to improve EPS and the Extrapyramidal Symptoms Rating Scale (ESRS) had been completed.[9]

Prohibited medications included any antipsychotics other than the study medication, anticonvulsants, antidepressants, lithium, clonidine, guanfacine, carbamazepine, valproic acid or cholinesterase inhibitors. Psychostimulants, including methlyphenidate, pemoline and dexedrine, were allowed for the treatment of ADHD provided the subject

was already taking them at a stable dosage for at least 30 days prior to trial entry and every attempt was made to keep the dose constant throughout the DB and OL extension trials. Sedative/hypnotic medications were allowed provided that the dose and frequency of use were kept to a minimum. Behavior intervention therapies were also allowed during the OL extension trial.

Outcome measures

The outcome measures relevant to this analysis included serum prolactin levels, adverse events, and scores on the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (NCBRF).

Prolactin levels were measured at baseline to DB entry and at Week 6 or early discontinuation, and then at OL entry, Week 4, and at Months 3, 6, 9 and at the beginning of Month 12. Serum prolactin levels were measured by Quest Diagnostics Clinical Trials using an ACS:180 Automated Chemiluminescence System, manufactured by Ciba Corning at the time of the studies. Ciba Corning followed NCCLS (National Committee for Clinical Laboratory Standardization) recommended protocols to determine reference ranges, with calculations based on 95% confidence intervals. The normal ranges used by Quest Diagnostics were used to define the upper limit of normal (ULN) for male and female patients in this analysis. For males, the ULN was 18 ng/ml and for females it was 30 ng/ml.

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Adverse events were assessed at each study visit, with study visits scheduled at entry and weekly during the DB studies and at entry then weekly for the first month, and monthly for the remaining 11 months of the OL extension studies. For those subjects who entered the OL extension study within 10 days of completing the DB study, the final safety and efficacy assessments made during the earlier trial served as baseline data at entry for this study. Otherwise, subjects were reassessed. Side effects hypothetically attributable to prolactin (SHAP) were captured from the adverse event database using the broad criteria of those events classified under WHO System Organ Class as "endocrine disorders" or "reproductive disorders". Upon consultation with pediatric endocrinologists, any adverse events under the following Preferred Terms were not included: balanoposthitis, dysmenorrhoea < 31 days, growth hormone excess, hernia inguinal, hyperprolactinemia, penis disorder, sexual function abnormal, sialoadenitis, testis disorder, thyroiditis, thyroid stimulating hormone decreased, and vaginitis atrophic. Patients with less than one week of amenorrhoea, and males 8 years of age or older and females with < 31 days of gynaecomastia were also excluded (this exclusion may be questioned, as we get feedback from advisors that they see the most gynecomastia in adolescent boys; again, a base rate problem, the frequency and course of which is unknown in the normal population- Gahan).

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Similarly, EPS symptoms were captured as those events classified under System Organ Class as "central and peripheral nervous system disorders" with the following Preferred Terms: agitation, akathesia, bradykinesia, tardive dyskinesia, dystonia, extrapyramidal disorder, hyperkinesia, hyperreflexia, hypertonia, hypokinesia, hypotonia, muscle

contractions involuntary, oculogyric crisis, parkinsonism, rigidity, shuffling gait, stiffness, tics and tremor.

The Conduct Problem subscale of the parent/caregiver rated NCBRF was completed at baseline and then weekly during the DB trial, then at OL baseline, at Weeks 1 and 4, and at Months 3, 6, 9 and the beginning of Month 12. The NCBRF was developed for children with developmental disabilities and its subscales were derived by factor analysis.[7] It has been studied independently and has stable factor structure and good inter-rater and test-test reliability.[7],[10] The 16-item Conduct Problem subscale is one of 6 Problem Behaviour subscales. Each problem behavior is rated on a 4-point Likert scale from 1 (*behaviour did not occur or was not a problem*) to 3 (*behaviour occurred a lot or was a severe problem*). A reduction in score therefore represents improvement. Three sets of responder criteria were assessed: improvement ≥25% vs <25%; ≥35% vs <35%; and ≥50% vs <50% versus prolactin levels.

Statistical Analysis

All subjects who took at least one dose of study medication were included in this analysis as part of the intent-to-treat (ITT) population. Those subjects with pre-dose and at least one post-dose prolactin observation at or after 4 weeks of risperidone exposure were classified as the primary analysis (PA) population. Analysis time periods were defined as pre-dose, Weeks 4 to 7, Weeks 8 to 12, Weeks 16 to 24, Weeks 28 to 36, Weeks 40 to 48 and Weeks 52 to 55. The analyses performed on Weeks 52-55 will not be presented due to the small sample size (n=42) which makes it difficult to

compare groups. For the analysis of prolactin levels by age, age groups were defined as 5 to 7, 8 to 9, 10 to 11, and 12 to 15 years. For the analysis of prolactin by age and gender, the children were divided to represent pre-pubertal and post-pubertal ages: for girls <9 years and ≥9 years and for boys <10 years and ≥10 years. The studies enrolled children up to 14 years of age, but some participants turned 15 during the long-term trial; hence the 12 to 15 years category.

Descriptive statistics were calculated for demographic and pre-dose patient characteristics, study drug dosing information, and serum prolactin levels in each analysis time period (prolactin levels for all patients and by age and by gender). Descriptive statistics were also calculated for prolactin levels (by time period) in patients with versus those without SHAP, for patients with versus those without EPS at any time, and for responders versus non-responders on the Conduct Problem subscale of the NCBRF.

Patient demographics and pre-dose characteristics were compared between the PA and non-PA populations using the chi-square test (for categorical data) or *t*-test (for continuous data). The chi-square test was also used to compare the percentage of patients who experienced SHAP, EPS, or were responders on the Conduct Problem subscale of the NCBRF in patients with a prolactin level above the upper limit of normal (ULN) versus patients with a prolactin level within the normal range at each study period. Correlation coefficients were calculated to assess the correlation between

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prolactin levels and age and score on the Conduct Problem subscale of the NCBRF.

SAS Release 8.00 was used for all analysis.

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RESULTS

Results are presented for the PA population unless noted otherwise.

Patient and Treatment Information

When data from all five clinical trials were pooled, there were 700 patients who received at least one dose of risperidone and were therefore included in the ITT population. A total of 592 patients who had a pre-dose and at least one post-dose prolactin observation at or after 4 weeks of risperidone exposure were included in the PA population. Patient accounting is detailed for the ITT and PA populations by treatment arm for each trial in Table 1.

Table 1. Patient accounting from five clinical trials: ITT and PA populations

Double-Blind		Open-Label		N (%) of Patients	
Protocol	(Treatment)	Protocol	(Treatment)	ITT	PA
CAN-19	(risperidone)			5 (0.7)	1 (0.2)
CAN-19	(risperidone)	CAN-20	(risperidone)	38 (5.4)	24 (4.1)
CAN-19	(placebo)	CAN-20	(risperidone)	39 (5.6)	28 (4.7)
CAN-19	(risperidone)	INT-41	(risperidone)	10 (1.4)	10 (1.7)
CAN-19	(placebo)	INT-41	(risperidone)	13 (1.9)	12 (2.0)
USA-93	(risperidone)			7 (1.0)	0 (0.0)
USA-93	(risperidone)	USA-97	(risperidone)	48 (6.9)	45 (7.6)
USA-93	(placebo)	USA-97	(risperidone)	59 (8.4)	55 (9.3)
		INT-41	(risperidone)	481 (68.7)	417 (70.4)
TOTAL				700	592

populations: ITT = intent-to-treat, PA = primary analysis

It was confirmed that the 108 patients who were not included in the PA population (non-PA population) had comparable pre-dose patient and disease characteristics with the PA population (including baseline prolactin for those available?-Gahan). There was no

statistical difference in gender, age, height, weight, BMI, Tanner stage[11,12], IQ rating, or DSM-IV Axis II diagnosis of intellectual functioning. The only difference was in ethnicity, with fewer Caucasians and more Black patients in the non-PA population (P=0.03).

The PA population included 489 boys (82.6%) and 103 girls (17.4%) with CD, ODD, or DBD-NOS, with or without ADHD. The mean IQ of the children was 65.1 and mental retardation was considered borderline in 40%, mild in 42% and moderate in 18%. Patients had a mean age of 9.9 years and the majority of children (73%) were in Tanner stage 1 of puberty when they began the study. Mean height was 137.8 cm, mean weight was 35.4 kg, mean BMI was 18.0, and 80% of the patients were Caucasian.

The mean daily dose of risperidone in the ITT population was 1.23 mg. In the PA population the mean daily dose was 1.26 mg and in the non-PA population it was 1.05 mg. The mean duration of study drug was 308 days in the ITT population and 319 days in the PA population.

Prolactin levels

The mean pre-dose prolactin level in the PA population was 7.8 ng/ml. Prolactin levels tended to rise in the first 4 to 7 weeks of risperidone intake to a mean of 29.4 ng/ml. Mean values then steadily decreased to 23.4 ng/ml (SD 17.0) at Weeks 8 to 12, then 19.6 ng/ml (SD 14.5) at Weeks 16 to 24, 18.5 ng/ml (SD 13.5) at Weeks 28 to 36, and 16.1 ng/ml (SD 13.2) at Weeks 40 to 48 (Figure1).

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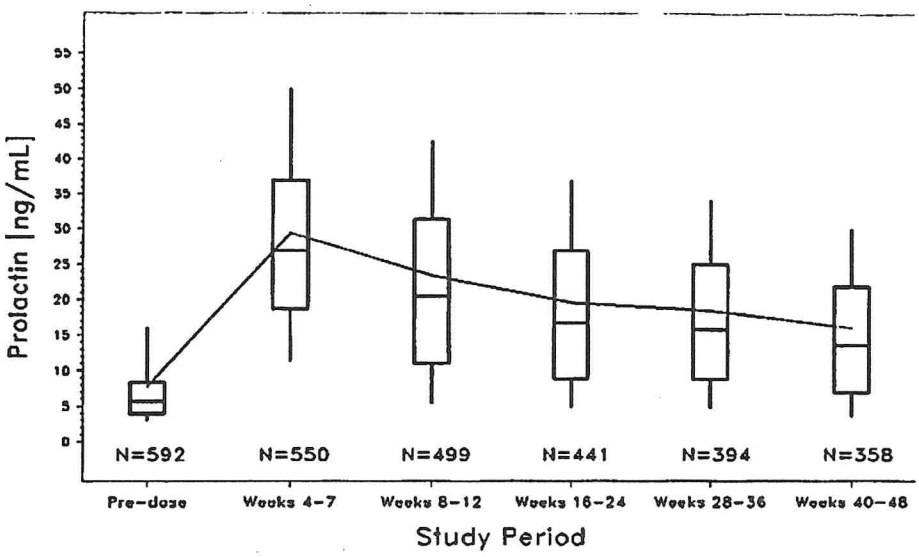
Figure 1. Prolactin Levels

PA – As Observed



The incidence of prolactin levels at or above the ULN followed a similar pattern. At baseline, 4.9% of patients had prolactin levels at or above the ULN. This rose to 70.5% at Weeks 4 to 7 and then steadily declined to 30.7% at Weeks 40 to 48.

The comparability of prolactin levels was assessed at each time period in patients who discontinued the trial versus those who continued to the next time period. This analysis of fixed subsets did not reveal any notable differences in the pattern of mean prolactin levels over time in these two groups. The highest mean value occurred during Weeks 4 to 7: 29.5 ng/ml in the continuing patient group versus 29.4 ng/ml in the discontinuing patient group.

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By gender

The mean pre-dose prolactin level in the boys was 7.3 ng/ml and in the girls, the mean pre-dose level was 10.0 ng/ml. Both genders had peak mean prolactin levels in Weeks 4 to 7; for boys the mean was 28.8 ng/ml and for girls the mean was 32.7 ng/ml (you want to assure everyone that there was variability week to week in PRL-Gahan). Prolactin levels steadily decreased to a mean of 15.1 ng/ml for boys and 21.4 ng/ml for girls at Weeks 40 to 48. The mean value for the girls had returned to the normal range (ULN 30 ng/ml) by Weeks 8 to 12, and the mean for the boys was close to normal by Weeks 16 to 24 (mean 18.9 ng/ml and ULN is 18 ng/ml).

By age

When prolactin levels were assessed by age group there was a similar rise and fall in levels over time for each group. There was no correlation between prolactin levels and age at any time period (correlation coefficient values ranged from 0.01 to 0.13).

By gender and age

Prolactin levels are presented in Figure 2 by gender and age. Girls ≥9 years of age had mean prolactin levels higher than the ULN at Weeks 4 to 7 (34.6 ng/ml) but had returned to within normal limits by Weeks 16 to 24. Pre-pubertal girls (<9 years of age) had mean prolactin levels within normal limits throughout the study. Mean prolactin levels were very similar for pre- and post-pubertal boys throughout the trial.

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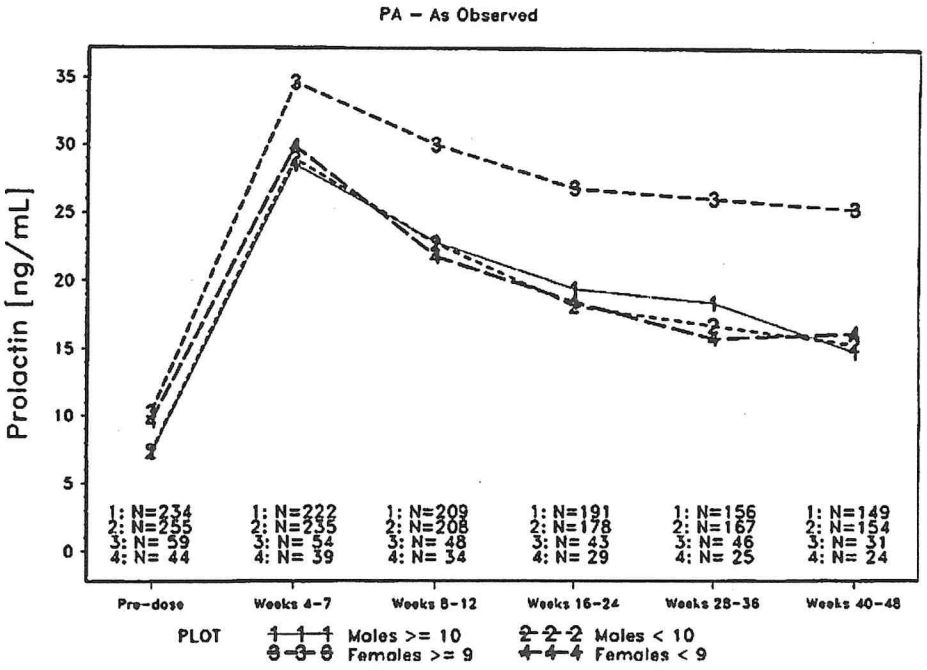
Figure 2. Mean Prolactin Levels by Gender and Age Group



Side effects Hypothetically Attributable to Prolactin (SHAP)

Adverse events corresponding to the analysis definition of SHAP are listed in Table 2. Overall, 31 patients in the ITT population (4.4%), 28 patients in the PA population (4.7%) and 3 patients in the non-PA population (2.8%) had at least one SHAP.

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Table 2. Side effects hypothetically attributable to prolactin: ITT, PA and Non-PA populations

System Organ Class	Preferred Term	N (%) of Patients		
		ITT	PA	Non-PA
Total number of patients		700	592	108
Number of patients with at least one SHAP		31 (4.4)	28 (4.7)	3 (2.8)
ENDOCRINE DISORDERS		22 (3.1)	20 (3.4)	2 (1.9)
	gynecomastia	22 (3.1)	20 (3.4)	2 (1.9)
REPRODUCTIVE DISORDERS, FEMALE		9 (1.3)	8 (1.4)	1 (0.9)
	amenorrhea	4 (0.6)	3 (0.5)	1 (0.9)
	menorrhagia	3 (0.4)	3 (0.5)	0 (0.0)
	breast enlargement	1 (0.1)	1 (0.2)	0 (0.0)
	lactation nonpuerperal	1 (0.1)	1 (0.2)	0 (0.0)
	menstrual disorder	1 (0.1)	1 (0.2)	0 (0.0)
	vaginal haemorrhage	1 (0.1)	1 (0.2)	0 (0.0)

SHAP = side effect hypothetically attributable to prolactin
ITT = intent-to-treat population, PA = primary analysis population, Non-PA = non-primary analysis population

All events were considered mild to moderate in severity. In the ITT population, 22/574 boys (3.8%) and 9/126 girls (7.1%) reported at least one SHAP; the mean age of the boys was 11.5 years and the mean age of the girls was 12.6 years. The most common SHAP was gynecomastia (3.1% of the ITT population) and all reproductive disorders were reported in <1% of the analysis populations. In the ITT population, 19/31 (61.3%) of the patients had recovered from the first reported adverse event before the end of the study.

Within the PA population, onset of the first SHAP was at a mean 123.6 days (minimum 1 day and maximum 260 days). The mean daily dose of risperidone was comparable in patients who experienced SHAP (1.27 mg) and in those who did not (1.26 mg). The

mean age of girls who experienced SHAP in the PA population was 12.8 years and for boys the mean age was 11.4 years.

The percentage of children with SHAP was assessed for patients with prolactin levels above the ULN versus patients with prolactin levels within the normal range at the various analyses time periods. The proportions were all comparable except for Weeks 8 to 12 time period, in which 7.4% of patients who had prolactin above the ULN had SHAP at some point during the trial, while 2.9% of patients with prolactin levels within the normal range at Weeks 8 to 12 experienced SHAP at some time during the study (P=0.02) (this may be notable as this could be seen to suggest that patients who show an initial rise during the "peak" period above ULN do have a higher propensity for SHAP. I think we need to discuss this somewhere in the manuscript. Gahan). There was no statistical difference in the percentage of patients who reported SHAP for any other analysis time period, whether or not prolactin levels were normal or above the ULN (range 3.4% to 6.5% with SHAP).

Prolactin levels exceeded 100 ng/ml at only one measurement during the study in 6/700 patients (values of 101.8, 102.0, 103.0, 150.0, 153.0 and 160.9 ng/ml). These patients did not have any SHAP except for one 12.5-year-old female. She had menorrhagia that the investigator rated mild in severity, and for which the investigator indicated a 'doubtful' relationship to study medication. The prolactin level of 160.9 ng/ml did not coincide with the menorrhagia; it occurred at least 10 months after the patient's reported 'excessive menstrual bleed'. No action was taken and the event resolved in 13 days.

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Prolactin levels and extrapyramidal symptoms (EPS)

Altogether, 129/592 patients in the PA population (21.8%) reported at least one extrapyramidal symptom. The mean onset of the first EPS was 64.5 days (SD 99.3). There was no significant difference in the percentage of patients who experienced EPS whether or not mean prolactin levels were within the normal range or above the ULN.

Prolactin levels and score on the Conduct Problem Subscale of the NCBRF

Although behavioural symptom responders tended to have slightly higher mean prolactin levels (maximum 4.1 ng/ml difference) than non-responders, there was no correlation between the Conduct Problem subscale score of the NCBRF and prolactin levels (correlation coefficients ranged from -0.10 to 0.02). Whether responders were defined as improvement of at least 25%, 35% or 50% on the Conduct Problem subscale of the NCBRF, there was no significant difference in the proportion of individuals who were responders whether or not prolactin levels were within the normal range or above the ULN.

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DISCUSSION

Combining the databases from five clinical trials has enabled the unique opportunity to assess prolactin levels with long-term risperidone therapy in 592 children with conduct or other disruptive behaviour disorders. Mean serum prolactin levels were 7.8 ng/ml at baseline and they increased to a peak of 29.4 ng/ml at Weeks 4 to 7, then progressively decreased to a mean of 16.1 ng/ml at Weeks 40 to 48. Masi and colleagues reported a mean serum prolactin level of 25.92 ng/ml during the tenth week of treatment in his study of 25 young autistic children (3.9 to 7 years) who were treated with risperidone for 10 weeks.[6] The mean 23.4 ng/ml prolactin level determined for the Weeks 8 to 12 time period of this analysis is similar to his results.

In the current analysis of long-term risperidone treatment, prolactin values had returned to the normal range at the Weeks 8 to 12 analysis time period for girls (ULN 30 ng/ml) and were close to normal at Weeks 16 to 24 for boys (ULN 18 ng/ml). The initial rise in prolactin levels seen with risperidone therapy in children appears to be transient and levels return to the normal range with continued use.

There was no significant correlation between prolactin levels and age. When age and gender were combined to categorize pre-pubertal versus post-pubertal boys (<10 years and ≥10 years) and girls (<9 years and ≥9 years), the pattern of rise and fall of prolactin levels was similar in all four groups although, not surprisingly, the post-pubertal girls tended to have higher prolactin levels throughout the study.

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Adverse events that are usually associated with hyperprolactinemia include gynecomastia, galactorrhea and menstrual disturbances. For this analysis, side effects hypothetically attributable to prolactin (SHAP) included gynecomastia (in the WHO System Organ Class of 'Endocrine disorders'), plus amenorrhea, menorrhagia, breast enlargement, lactation nonpuerperal, menstrual disorder and vaginal haemorrhage (within the System Organ Class of 'Reproductive disorders, female'). Many of these are also events that are can occur during puberty.

Adverse events that fit the analysis definition of SHAP were reported in 28/592 patients in the PA population (4.7%). All of these events were considered mild or moderate in severity and over half of the patients had recovered from the adverse event before the end of the study. The most common SHAP was gynecomastia, reported in 20/592 patients (3.4%). Gynecomastia is frequently seen in boys going through puberty (but if I read correctly, gynecomastia was excluded for boys >9 years. Gahan). The mean age of boys who experienced SHAP was 11.4 years and for girls the mean age was 12.8 years. This is higher than the mean age for the whole PA population (9.9 years), suggesting the possibility of a link between puberty and SHAP. Even in six children who had a single prolactin value that exceeded 100 ng/ml, only one 12.5-year-old girl reported a SHAP (menorrhagia). Her 'excessive menstrual bleed' occurred and resolved months before her single prolactin level of 160.9 ng/ml with no action taken. The event was rated mild in severity and the investigator indicated a 'doubtful' relationship to study medication.

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There was no direct correlation between prolactin elevation above the upper limit of normal and the occurrence of SHAP. Within the PA population, the first onset of SHAP was at a mean 123.6 days. At this time, girls had mean prolactin levels that had returned to the normal range and boys had mean prolactin levels approaching normal.

It is interesting to note that children with prolactin levels at or above the upper limit of normal did not have a propensity to greater efficacy response on the Conduct Problem subscale of the NCBRF, nor did they have more EPS than children with normal prolactin levels. (Vivek, Bob, Goedele – is this a good place to insert clarification about different dopamine pathways (i.e. the dopaminergic pathways in the mesofundibular system are affected by risperidone but prolactin affected by other dopaminergic pathways)

As a post-hoc analysis of pooled data, these results should be considered exploratory in nature. However, the fact that the initial rise in prolactin levels with risperidone was transient and subsided to normal values reduces the safety concerns regarding long-term treatment in children. This is reinforced by the lack of direct correlation between elevated prolactin levels and SHAP and EPS. (If possible, this would be the place to specifically mention/discuss the lack of correlation between Tanner delay and prolactin level or SHAP. I believe that if we are unable to include this, it will hurt the overall impact of the paper. Gahan)

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