Prolactin Revised Analysis
Outcome of Jan 22, 2002 meeting

Analysis to be on the full dataset (patients with < 6 weeks prolactin and patients with> 6 weeks prolactin included i.e. approx n=163 from the double blind trials plus n= 409 from openlabel).

Nomenclature:

- event name refers to the side effect related to prolactin. As per the meeting, dysmenorrhea and balanoposthitis will not be considered a prolactin side effect. Sialodenitis and thyroiditis are to be deleted.
- N=163 refers to all subjects with prolactin at baseline and endpoint plus subjects in open label trials with baseline and post baseline prolactin values.
- AE = adverse event.

Requested Analyses

1) Calculate Normative values of prolactin: at baseline DB (and OL baseline) calculate mean $\pm$ 2 SD, broken down into gender and age ($\geq$9 yrs for girls and $\geq$10 yrs for boys)

2) Data listings

For the placebo arm of DB trials (RIS-USA-93, RIS-CAN-19):

generate a table with the following information: CRF number, male/female, age, weight, BMI, Tanner stage, adverse event name, adverse event days from treatment start at each time period (separated out as 4-6 weeks) and prolactin value, event days at event stop (separated out as 4-6 weeks) and prolactin values, mean dose of risperidone within each time period i.e. 4-6 weeks, weight change at each time period, BMI change at each time period, listing of concomitant meds during each time period

generate table with all risperidone DB data and open label data (RIS-USA-97, RIS-CAN-20, RIS-INT-41) Formatted: Bullets and Numbering

generate a table with the following information: CRF number, male/female, , age, weight, BMI, Tanner stage adverse event name, adverse event days from treatment start at each time period (separated out as 4-6 weeks, 10-12 weeks, etc up to week 54) and prolactin value (at event start), event days at event stop (separated out as 4-6 weeks, 10-12 weeks etc.) and prolactin values at event stop, mean dose of risperidone within each time period i.e. 4-6 weeks, weight change at each time period, BMI change at each time period, listing of concomitant meds during each time period

2) Generate a list of all prolactin related side effects (galactorrhea, lactation, amenhorea, menorrhagia, gynecomastia, testis and penis disorder, atrophic vaginitis, sexual function

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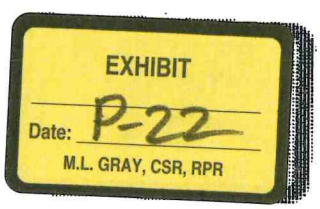

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abnormal) in ITT population but exclude subjects in the "matching prolactin (n=163) database".

3) Verbatim list correlated to side effects i.e. request physician verbatims on "testis disorder; penis disorder; vaginitis atrophic;sexual function abnormal, breast enlargement etc..."... This list will be circulated for review and identification of prolactin related Aes.

4) List all subjects with prolactin ≥30: how many of them had side effects . Can we determine if these patients are different from other subjects who did not have this occur (dose, weight gain, gender, etc..). Can we list how many subjects had transient prolactin > 30 (and for how long) and how many had sustained prolactin (more than 1 measure of prolactin >30 and prolactin >30 at End of Study. *(assumption: there will be a substantial "n" of transient prolactin elevation and a more modest "n" for subjects with sustained prolactin elevation*). E

Examine to see how these 2 groups might differ (dose, demographics, weight, etc). List subjects who discontinued trial due to prolactin related AEs and list prolactin levels.

5) List of concomitant meds in subjects with prolactin related side effects (a) ITT population minus subjects in matching prolactin and in (b) subjects with matching prolactin.

6) Compare matching prolactin data (N=163) subjects with no matching prolactin data subjects in terms of baseline prolactin, duration of exposure to risperidone to ensure the sample is similar.

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