

1/8/2008 Email - Rotarix

From: Henschal, Laraine

Sent: Tuesday, January 08, 2008 10:31 AM

To: 'Donna.2.Boyce@gsk.com'

Cc: Vujcic, Luba

Subject: Info request for STN#125265/0

Attachments: Picture (Metafile); Picture (Metafile); Picture (Metafile)

Hi Donna,

Some additional request for information from the review team:

1.) On page 88 of your Rota023 year 1 report, you state that you also performed the Cox proportional-hazard model on the data and "Results of analysis using the Cox proportional-hazard model are available on file at GSK Biologicals, Rixensart." Please submit this analysis to your BLA as soon as possible.

2.) In your Reporting and Analysis Plan for Rota-023, you state:

As of May 18th 2004, a total of 14 IS cases have been observed during the 0-30 days post placebo/HRV vaccination period. This leads to an overall IS incidence rate between 2 and

4 / 10 000, which far exceeds the anticipated definite IS incidence rate of 0,3 / 10 000 subjects that was expected to occur in the placebo group.

Due to the higher overall IS incidence (study remains blinded) the width of the confidence interval (CI) of the Risk Difference has become so large that, under identical IS incidences in both study arms (HRV minus placebo), the upper limit of the 90%CI exceeds the initially specified 2/10 000 limit. Therefore the original criterion for meeting the co-primary safety objective is no longer appropriate.

For this reason, the primary safety objective has been revised so that a vaccine with an identical IS incidence as placebo would meet the objective:

- The upper limit of the two-sided 95% CI of the Risk Difference for definite IS occurring within 0-30 days post vaccination should be below 6/10 000, a limit based on the study sample size and the anticipated IS incidence rate.
- There should be no statistically significant increase in the incidence of definite IS occurring within 0-30 days post vaccination (the lower limit of the two-sided 95% confidence interval of the Risk Difference should be below 0).

Since changing the primary objective of an ongoing trial may affect the integrity of the study and thus must be done with caution, please provide more information on how the decision was made, what the procedures are of making such a change, and the names of all regulatory agencies that concurred with this change. Please respond.

3.) In regard to the Diphtheria and Tetanus serology assays, we have the following requests. We note that this information was provided to STN ----- on -----, so the information provided there can be cross referenced, if applicable, for this STN:

- a. For each critical reagent used in the Diphtheria and Tetanus ELISAs, please submit a summary of the data generated to qualify the batch(es) used in the assays presented in this submission.
- b. Please submit data which supports the precision of the Diphtheria and Tetanus ELISAs over their entire working ranges and indicate the specific GMC/GMT range of samples used to determine assay precision.

Thanks,
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