Record of Telephone Conference, April 15, 2013 - Novoeight

From: LEWP (Lewis Pollack) [lewp@novonordisk.com]
Sent: Tuesday, April 16, 2013 1:21 PM
To: Pracht, Leigh
Subject: NovoEight BLA 125466/0: April 15 T-con regarding Statistical Question in April 9, 2013 IR (Item 13)

Dear Leigh,

Thank you for arranging yesterday's t-con with the FDA's statistical reviewer. As discussed, I am providing the list of Novo Nordisk attendees, a summary of the agreements reached, and a timeline for our response. Preliminary response information for question 13(a) also is included.

Please let me know if you have any questions, and also if you would like us to email the responses to 13(a) and 13(c) in advance of the formal submission (see time line below).

Regards,
Lewis

Novo Nordisk attendees:
· Trine Saugstrup - Statistician
· Anders Rosholm – Statistics Specialist
· Jonas Holger Poulsson – Programming Specialist
· Madhusudhan Reddy Mule Venkata – Statistical Programmer
· Frank Bringstrup – Senior Regulatory Project Manager
· Dorte Bjørn-Larsen – Specialist, Regulatory Affairs
· Rafeya Khan – Senior Associate, Regulatory Affairs
· Lewis Pollack - Sr. Director, Regulatory Affairs

Summary of agreements: Novo Nordisk will provide FDA with the information needed to enable the Agency's statistician to verify the inhibitor rate, annualized bleeding rate and demographic data. A program for calculation of the annualized bleeding rate also will be provided.

Inhibitor rate (13a):
o Historical inhibitor results are available in the ADHAEM data set and the inhibitor results obtained in the studies are available via the condition PARAMCD =

'FVIII_NEUT_AB' in ADLAB.   Please see additional details in the preliminary response that follows.

Calculation of annualized bleeding rate and hemostatic response rate (13b)
·   Novo Nordisk will provide a program calculating the annualized bleeding rate using the Poisson model allowing for over dispersion using the pooled data. In addition we will explain how to modify the program for use with data from individual trials.
·   Novo Nordisk will clarify where to find additional information about the bleeding episodes; such as, cause of bleed, site of bleed, number of infusions and hemostatic rating.
·   Calculation of the success rate will be explained in detail.

Demographic data (13c)
·   Variables pertaining to demographic data reside primarily in the ADSL derived data set. Details about variable names and data sets will be provided for relevant baseline characteristics.

Timeline for the response:
Novo Nordisk plans to formally submit our responses to question 13 as an amendment to the BLA by COB April 22, 2013.   Additionally, we expect our responses to 13(a) and 13(c) to be complete by COB Thursday April 18.   If the statistical reviewer would like us to provide responses to 13a and 13c when they are ready via email, we can do so and then include these responses in the formal submission on Monday.

Preliminary response to Inhibitor Rate question (13a)
Historical inhibitor results are available in the ADHAEM data set and the inhibitor results obtained in the studies are available via the condition PARAMCD = 'FVIII_NEUT_AB' in ADLAB.

When calculating the inhibitor rate the following filters are used to identify the relevant samples:
·   FASF = 'Y'
Selects only results for patients in the full analysis set
·   ANFL = 'Y'
Selects only eligible samples. It is e.g. used to select a single value, if two values at the same time point are provided by the lab. A comment is then presented in the ANLRE variable.
·   AVISITN ne 10
Samples with AVISITN =10 is taken before the patients are dosed with turoctocog alfa

The inhibitor test result itself is stored in the variable AVAL. If the value is below 0.6 it is rated as negative and is the result equal or greater than 0.6 the result is rated as positive.

To count the number of patients contributing to the denominator for the inhibitor rate a new variable NDOSE (counting the number of doses of turoctocog alfa per patient) are calculated using the ADEXPOS data set.

The new variable could be calculated by a PROC SQL statement in SAS, see example of a code below. SUBJID refers to subject id number, SAFF refer to the safety analysis set and again the ANFL are used only to use eligible doses (doses taken with previous product before the first dose of turoctocog alfa have a ANFL='N').

```
proc sql;
create table exposures as
    select distinct subjid, count(subjid) as ndose
from adexpos_(where=(SAFF= 'Y' and ANFL = 'Y'))
group by subjid
order by subjid
    ;
quit;
```

The number of patients contributing to the denominator for the inhibitor rate can then be found by counting patients were the new variable NDOSE created via proc sql is equal or greater than 50 (NDOSE>=50) and/or patients with a positive inhibitor result.

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