

CMC Review - Novoeight

To: File of STN 125466/0, Natalya Ananyeva and Leigh Pracht
From: Zuben E. Sauna (OBRR/DH/LH)
Through: Tim Lee, Acting Chief, LH/DH/OBRR
Basil Golding, MD,
Director of Division of Hematology/OBRR

Subject: Final Review of assays used to assess immunogenicity in patients treated with Antihemophilic Factor (Recombinant) [Novoeight] in studies conducted by Novo Nordisk to support the licensure of the BLA
CC: Lisa Faulcon

Summary

This memorandum summarizes the review of the assays used to assess the incidence of inhibitory anti-drug antibodies to turoctocog alfa (Novo Nordisk's recombinant analogue of human coagulation factor VIII [FVIII] that contains only 21 amino acids of the FVIII B-domain). Based on my review, I conclude that the assay development and validation are performed adequately, and the assays are suitable to be used in clinical studies to assess the levels of antibodies against the product.

The product

Turoctocog alfa (also called Novoeight or N8) is a recombinant analogue of FVIII, intended to be administered to patients with hemophilia A. The molecule is a so-called third generation antihemophilic factor, i.e., it is formulated and manufactured without animal or human proteins. Moreover, Turoctocog alfa is an engineered form of the FVIII protein with a truncated B-domain. The recombinant protein is produced in Chinese hamster ovary (CHO) cells using cell culture medium without serum- or animal-derived components followed by downstream purification.

Overview

This review pertains to three main classes of assays used to detect antibody responses in the pre-clinical and clinical samples:

- 1) The detection of neutralizing antibodies against FVIII (referred to as "inhibitors")
- 2) The detection of anti-host cell proteins (HCP) antibodies; i.e., antibodies against proteins of CHO cells used to produce the recombinant FVIII protein therapeutic
- 3) The detection of anti-murine IgG antibodies from the affinity column used to purify turoctocog alfa

The key validation parameters for the 3 assays are as follows:

Analysis parameter	Anti-CHO antibodies	Anti-murine IgG antibodies	Anti-FVIII neutralizing antibodies
Sensitivity	-----(b)(4)----- -----	-----(b)(4)----- -----	-----(b)(4)----- -----
Cut point	-----(b)(4)----- -----	-----(b)(4)----- -----	----- (b)(4) -----

Assay variation	----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
-----------------	--------------------	--------------------	--------------------

(b)(4)-----

----- (b)(4) -----

The development of FVIII inhibitors is clinically the most consequential complication of replacement therapy in hemophilia A. Thus, all subjects in all clinical trials were monitored for the development of inhibitors. The applicant has submitted the results of the immunogenicity studies in section 5.3.1.4 of the original BLA. The ----- (b)(4) ----- of the Bethesda assay was the primary assay used to evaluate the development of inhibitors. This is a well established assay that is used extensively in research, in clinical studies as well as in clinical labs after the licensure of all FVIII products. Although Novo Nordisk's general approach for assay validation appeared to be adequate, additional details of the validation studies and SOPs used were not submitted in the original application and had to be requested from the applicant. This assay is significant because the development of inhibitors is the primary end-point of the clinical studies, and no inhibitors were detected in any of the subjects enrolled in the clinical trial.

Review of validation studies for the ----- (b)(4) ----- of the Bethesda assay used to analyze patient samples for presence of FVIII inhibitors

Background

----- (b)(4) -----

----- (b)(4) -----

-----, The validation study by Novo Nordisk evaluates and includes consideration of several factors which may affect the accuracy and reliability of the assay which have been part of the scientific discourse since 1995.

----- (b)(4) -----:

----- (b)(4) -----

-----.

---(b)(4)---:

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----:

----- (b)(4) -----
-----:

----- (b)(4) -----
----- (b)(4) -----

3 pages redacted (b)(4)

- ----- (b)(4) -----

Use of immunogenicity assays in the clinical studies

The reviewer from the CRB will provide the detailed review of the clinical studied. Here I review the assessment of FVIII inhibitors in the clinical samples. The primary objective of the clinical trials was to assess the incidence of FVIII inhibitors (the cut-point for samples to be determined as inhibitor positive was ≤ 0.6 BU/mL). The clinical program for turoctocog alfa was initiated with a pharmacokinetic trial (NN7008-3522) to document the essential pharmacokinetic characteristics of the product and to achieve initial safety information. Two principal trials were then conducted to evaluate the safety and efficacy of the product.

Trial NN7008-3543 (Safety and efficacy of turoctocog alfa in prevention and treatment of bleeding during surgical procedures in patients with hemophilia A):

A total of 172 patients (adults and adolescents, i.e., 12-18 years old) were screened and 150 of these patients were dosed with turoctocog alfa. Of the 150 patients who were

dosed, 22 patients had previously participated in the first human dose trial (NN7008-3522) and this part of the trial is denoted Part A while the remaining 128 patients, not previously been exposed to turoctocog alfa, were denoted as Part B. The 9 patients from Parts A and B who participated in the surgery sub-trial constituted Part C. These 9 patients were not new patients – they had already participated in either part A or part B and after their surgery, they transferred back to part A or part B again. Of the 150 dosed patients, 24 were adolescents (12 to <18 years old).

Trial NN7008-3545 (A multi-centre, open-label, non-controlled trial on safety and efficacy of turoctocog alfa in previously treated paediatric patients with hemophilia A):

This trial (65 enrolled patients) evaluates the safety of turoctocog alfa in paediatric (< 12 years old) previously treated hemophilia A patients.

Trial NN7008-3568: This trial was designed as an extension, open-label, prospective trial where patients completing the trials NN7008–3543 or NN7008-3545 could continue treatment with turoctocog alfa.

An important inclusion criteria was at least 150 exposure days to any other FVIII product and no prior history of FVIII inhibitors (< 0.6 BU/mL).

The patient visits are tabulated below:

Visit #	1a	1b	2b	3	4	5	6a	6b	7	8	9
Day	0		0	7	12	28		42	56	70	75

All patients were examined for the development of FVIII inhibitors at the visit # marked “X”:

Visit #	1a	1b	2b	3	4	5	6a	6b	7	8	9
	X	X	X		X	X	X	X	X	X	X

A positive inhibitor test was defined as > 0.6 BU/mL. If FVIII inhibitor development was suspected during the course of the trial, additional inhibitor tests could be taken at unscheduled visits. All inhibitor samples were to be drawn at least 48 hours after the last dose of FVIII/turoctocog alfa and analyzed by the central laboratory. In the event that a patient had a positive inhibitor test (> 0.6 BU/mL), the patient had to attend an unscheduled visit as soon as possible or within 1 week after the result was available to take a confirmatory inhibitor test on a separately drawn sample. At this unscheduled visit, a recovery test was performed. This second sample was preferably taken prior to any change of treatment. If the second inhibitor test was also positive, the patient had to be withdrawn by discontinuing trial product and attending the end of trial visit within 1 week after the result was available. The patient was considered to have developed an inhibitor only after a second positive confirmatory test.

Results of clinical trials with respect to immunogenicity

FVIII inhibitor incidence:

The primary endpoint was the incidence rate of FVIII inhibitors (\geq 0.6 BU/mL). No patients developed FVIII inhibitors. Furthermore, no signs of early inhibitor development were observed as evaluated by FVIII activity as the pharmacokinetic results 3-6 month after first injection of turoctocog alfa were comparable with the results obtained after the first dose of turoctocog alfa in NN7008-3522.

Anti-HCP and anti-murine IgG antibodies:

Assessments for the development of anti-HCP or anti-murine IgG antibodies were performed at regular time points during the trial and no noteworthy changes in these antibodies over time were apparent.

Conclusions and recommendations

This memorandum is a review of the original BLA STN 125466/0 with respect to the choice, validation and use of immunogenicity assays. The review has paid particular attention to the validation of the -----(b)(4)----- of the Bethesda assay which was the primary assay used to evaluate the development of inhibitors. It was important to do so for two reasons:

(a) The primary end-point of the clinical trial was the development of inhibitors.

(b) No inhibitors were detected in any of the subjects enrolled in the trial.

Based on data provided by Novo Nordisk and their responses to information requests, I find that Novo Nordisk has used standard assays that have been well characterized in the literature and have developed SOPPs based on well-designed validation studies. These assays are adequate to be used in the evaluation of clinical samples.

In addition, Novo Nordisk has provided details for assays for the detection of anti-HCP and anti-murine IgG antibodies. The validation of these assays was adequate, and suitable for detecting these antibodies in clinical samples.

From the perspective of immunogenicity assays used to detect anti-HCP, anti-murine IgG and inhibitory anti-FVIII antibodies, I recommend approval of STN 125466/0.

Page Last Updated: 01/28/2015

Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

Language Assistance Available: [Español](#) | [繁體中文](#) | [Tiếng Việt](#) | [한국어](#) | [Tagalog](#) | [Русский](#) | [ةيبرعلا](#) | [Kreyòl Ayisyen](#) | [Français](#) | [Polski](#) | [Português](#) | [Italiano](#) | [Deutsch](#) | [日本語](#) | [ىسراف](#) | [English](#)