

# Statistical Review & Evaluation - XYNTHA

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**STN 125264/0**

**SPONSOR:**

Wyeth Pharmaceutical

**TITLE:**

Antihemophilic Factor VIII (Recombinant)B-Domain Deleted Recombinant Factor VIII (BDDrFVIII, ReFacto AF)[moroctocog alfa], submitted for the treatment of hemophilia A.

**DOCUMENT REVIEWED:**

BLA Supplement

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**INTENDED USE**

BRANDNAME: Antihemophilic Factor (Recombinant), Plasma/Albumin-Free, Kit, for Intravenous Use.

BRANDNAME is an anti-hemorrhagic blood coagulation factor VIII indicated for:

- Control and prevention of bleeding episodes in patients with hemophilia A
- Surgical prophylaxis in patients with hemophilia A
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## **BACKGROUND**

The Moroctocog alfa (AF-CC) BB IND ----- was submitted to the Office of Blood Research and Review on 21 September 2001, to support the development program for Moroctocog alfa (AF-CC). Wyeth has had several interfaces with the Agency over the course of the development program. Communications with the Agency were conducted to address key aspects of the clinical development program to meet FDA requirements for approval of Moroctocog alfa (AF-CC). Wyeth and the Agency held a pre-BLA meeting to discuss the content and format of the submission.

## **OBJECTIVES**

Data from study 3082B2-310-WW will serve as the primary data to demonstrate efficacy and safety of moroctocog alfa (AF-CC) to control and prevent bleeding. The primary safety objective of this study was to determine the incidence rate of FVIII inhibitors associated with the use of moroctocog alfa (AF-CC) in the study patient population. The primary efficacy objective in study 3082B2-310-WW was to establish the bioequivalence between moroctocog alfa (AF-CC) and a recombinant FVIII product (Advate) in the PK period.

## **PRIMARY ENDPOINTS:**

The primary safety endpoint of the study is the incidence of de novo Factor VIII inhibitors in the study population. The primary PK endpoints include the areas under the curve from zero to the last measurable concentration ( $AUC_t$ ), and from zero to infinity ( $AUC_\infty$ ), and incremental recovery (K value, IU/dL per IU/kg).

**DESIGN:** This study is a multi-national, multi-center trial. The study will consist of two parts: a pharmacokinetic period and a safety and efficacy period. The first period of the study was designed as a randomized, two-way blinded, crossover pharmacokinetic evaluation in 30 patients using the one stage Factor VIII activity assay. In the second period, the open-label part of the study, the rate of inhibitor development and other clinical safety and efficacy parameters are assessed in the patients taking Moroctocog alfa (AF-CC) for at least 50 exposure days over 6 months.

**SAMPLE SIZE:** Ninety-four (94) patients were enrolled and treated with at least 1 dose of Moroctocog alfa (AF-CC) in both the intent-to-treat (ITT) and modified intent-to-treat (mITT) populations (the mITT population consists of subjects who receive at least 1 dose of study drug); 89 patients were part of the efficacy-evaluable population (i.e., achieved  $\geq 50$  EDs to test article); 30 patients were in the per-protocol populations for bioequivalence testing.

## **PHARMACOKINETIC ANALYSIS AND RANDOMIZATION:**

Thirty one (31) patients who met requirements for the PK period were randomized 1:1 to receive a sequence of a single infusion of Moroctocog alfa (AF-CC) followed by Advate or a single infusion of Advate followed by Moroctocog alfa (AF-CC). Thirty (30) patients completed PK1 and PK2 assessments and were included in the per-protocol population

for bioequivalence testing.

### **STATISTICAL METHODS:**

All efficacy and safety endpoints were summarized with descriptive statistics. Descriptive statistics were used to summarize demographic and baseline data on the study population, as well as data on hemostatic efficacy, treatment-emergent adverse events (TEAEs) and treatment-emergent hemophilia events, and annualized bleeding episodes. For continuous variables, number, mean, standard deviation, median, minimum, and maximum are provided. Interquartile ranges and 95% confidence intervals are provided where meaningful. For categorical variables, frequency and percentage are presented for each category.

The sample size was determined in the context of the primary safety endpoint of this study, i.e., inhibitor risk assessment, and was selected to ensure at least 81 evaluable patients would complete the trial. It was determined using an agreed upon Bayesian statistical model that at least 81 patients would be required to insure with at least 95% probability that the true population inhibitor development rate with Moroctocog alfa (AF-CC) was less than 4.4% (a predefined maximum population limit), should a maximum of 2 cases of inhibitors develop in the study sample population. The sample size is also based on regulatory advice regarding the design of pivotal studies for FVIII replacement products that target at least 80 patients for assessment of safety and efficacy.

### **EFFICACY RESULTS:**

#### **Based on the central laboratory potency assessment:**

The 90% CIs about the ratios of Moroctocog alfa (AF-CC) to Advate geometric means of AUC<sub>t</sub>, AUC<sub>∞</sub>, and incremental recovery (K-value) were within the bioequivalence window of 80% to 125%, indicating the bioequivalence of Moroctocog alfa (AF-CC) and Advate. The 90% CIs about the ratios of Moroctocog alfa (AF-CC) month-6-to-baseline geometric means of AUC<sub>t</sub>, AUC<sub>∞</sub>, and K-value were also within the bioequivalence window of 80% to 125%, indicating that there were no time-dependent changes in the PK parameters of Moroctocog alfa (AF-CC).

#### **Based on the manufacturer's labeled potency:**

The 90% CIs about the ratios of Moroctocog alfa (AF-CC)-to-Advate geometric means of AUC<sub>t</sub> and AUC<sub>8</sub> met the bioequivalence criteria. The upper bound of the 90% CI for K-value exceeded 125% (**the 90% CI was 117% to 138%**). The 90% CIs about the ratios of moroctocog alfa (AF-CC) month 6 to baseline AUC<sub>t</sub>, AUC<sub>∞</sub>, and K-value were within the bioequivalence window of 80% to 125%, indicating Moroctocog alfa (AF-CC) PK remained unchanged after repeated use for 6 months, consistent with the results based on the central laboratory potency assessment.

### **SAFETY RESULTS:**

The primary safety endpoint was met, in that transient low-titer inhibitors that were clinically asymptomatic were detected in only 2 out of 94 patients (2.1% of the study population). Results from the Bayesian analysis indicate the rate of inhibitor development is less than 4.4% with 96.7% probability and the 95% upper limit of the true (population) inhibitor rate (the maximum rate calculated with at least 95%

probability) is 4.07%.

**REVIEWER'S COMMENTS TO CBER:**

The primary efficacy endpoint of this study has been met: Moroctocog alfa (AF-CC) is bioequivalent to full-length recombinant FVIII (Advate)

The primary safety endpoint of the study was met: the population (true) inhibitor rate for the test article is below the predefined acceptable value of 4.4%.