2. SYNOPSIS

Name of Sponsor/Company: Baxter Innovations GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Investigational Product: Advate (rAHR-PFM)	Volume:	
Name of Active Ingredient: Octocog alfa (recombinant human coagulation factor VIII)	Page:	

Title of Study:

Pharmacokinetic comparison of 3000 IU Advate (rAHF-PFM) (using one 3000 IU potency vial) with 3000 IU Advate (rAHF PFM) (using two 1500 IU potency vials) in previously treated patients with severe hemophilia A: a Phase IV, open-label, prospective, randomized, controlled, crossover, multiple center study

Investigators / Study Sites:

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Publication (reference): None

Study Period: **Initiation:** 29 June 2009 **Completion:** 01 April 2010 **Duration:** Approximately 10 months. Subject participation varied from 4 to 9 weeks.	**Study Phase:** IV

Study Purpose and Objectives:

Study Purpose: This clinical study is a post-licensure commitment to the EMA and its purpose was to compare the PK parameters of 3000 IU Advate using one 3000 IU potency vial dissolved in 5 mL diluent with that of two vials of 1500 IU dissolved in 5 mL diluent each (delivered in 10 mL diluent in total)

Primary Objective: The primary objective was to compare the PK parameters of 3000 IU Advate using one 3000 IU potency vial dissolved in 5 mL diluent with 3000 IU Advate using two 1500 IU potency vials dissolved in 5 mL diluent each (administered in 10 mL diluent in total).

Secondary Objective: The secondary objective was to evaluate and compare the percentage of subjects who experience IP related adverse events (AEs) between the treatment groups

Study Design:

This clinical study is a Phase IV, prospective, controlled, randomized, open label, multicenter study. Male subjects were randomized to receive via infusion 3000 IU Advate using one 3000 IU potency vial dissolved in 5 mL diluent followed by two 1500 IU potency vials dissolved in 5 mL diluent each (administered in 10 mL diluent in total) or the alternate sequence.

Number of subjects

Planned: 16

Analyzed: 23 (to ensure allocating three different lots of investigational product) were included in the ITT, PP and safety analysis datasets.

Diagnosis and main criteria for inclusion

Inclusion Criteria

Male subjects who met **ALL** of the following criteria were eligible for this clinical study:

- Subject was male and 18 to 65 years old at the time of screening.
- Subject provided signed informed consent.
- Subject had severe hemophilia A, defined by a baseline FVIII level <1% of normal (based on the chromogenic and the one stage activated partial thromboplastin time (aPTT) assays), as tested at screening at the central laboratory.
- Subject's weight was between 55-65 kg.

- Subject had been treated with FVIII concentrate(s) for a minimum of 150 exposure days (as estimated by the investigator) prior to study entry.
- If subject was human immunodeficiency virus (HIV) positive, he was immunocompetent as determined with a CD4 count ≥200 cells/mm³ (CD4 count at screening).
- Subject was willing and able to comply with the requirements of the protocol.

Exclusion Criteria

Subjects who met ANY of the following criteria were not eligible for this clinical study:

- Subject has a detectable FVIII inhibitor at screening, with a titer ≥0.4 BU (Nijmegen modification of the Bethesda Assay) measured at the central laboratory.
- Subject had a history of FVIII inhibitors with a titer ≥0.4 BU (by Nijmegen assay) or ≥0.5 BU (by Bethesda Assay) at any time prior to screening.
- Subject has undergone a surgery within 21 days prior to screening or within 6 weeks prior to the anticipated first PK infusion.
- Subject had an abnormal renal function (serum creatinine >1.5 mg/dL).
- Subject had active hepatic disease (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] levels >5 times the upper limit of normal).[i]
- Subject had severe chronic liver disease as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) >1.4, hypoalbuminemia, portal vein hypertension including presence of otherwise unexplained splenomegaly, and history of esophageal varices.
- Subject had clinical and/or laboratory evidence of abnormal hemostasis from causes other than hemophilia A (e.g., late-stage chronic liver disease, immune thrombocytopenia purpura).
- Subject was receiving, or was scheduled to receive during the course of the clinical study, an immunomodulating drug other than anti-retroviral chemotherapy (e.g., α-interferon, or corticosteroid agents at a dose equivalent to hydrocortisone greater than 10 mg/day).
- Subject had a known hypersensitivity to mouse or hamster proteins

[i] Fluctuations of up to 5 times the upper limit of normal during the study period will not require discontinuation of subjects with chronic hepatitis B or hepatitis C.

- Subject had participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment or was scheduled to participate in another clinical study involving an IP or investigational device during the course of this clinical study.
- Subject was identified by the investigator as being unable or unwilling to cooperate with study procedures.

Investigational Product (IP), dose and mode of administration, and batch number:
IP: Advate is formulated as a sterile, nonpyrogenic, lyophilized cake of concentrated rAHF for intravenous injection and is provided in single-dose, glass vials labeled with the AHF activity expressed in IU. A single package contains a vial of lyophilized powder (nominal potencies of 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU), a 5 mL solvent vial and a device for reconstitution (BAXJECT II). For this clinical study, only vials containing 1500 IU and 3000 IU were used for the PK infusions, additional 1000 IU potency vials were used for treatment and prophylactic infusion prior to and between PK infusions.

For the first PK infusion, either one 3000 IU vial of Advate dissolved and administered in 5 mL diluent or two 1500 IU vials of Advate dissolved in 5 mL diluent, each (administered in 10 mL in total) were infused followed by the second PK infusion in the alternate sequence according to the randomization list. Infusions were performed by intravenous bolus in a peripheral vein using a 21- or 23-gauge butterfly catheter at a maximum infusion rate of 10 mL/minute.

Mode of Administration: Advate is administered intravenously after reconstitution with the provided sterilized water for injections.

Lot number(s): LE01J519AN, LE01J522BJ, LE01J023AM, LE01J524AF, LE01J535AP, LE01J535AR, LE01J537BB, LE01J545AD, LE01J025AS and LE01J537BF were used for PK infusions, prophylaxis and bleeding episodes.

Duration of treatment:

The overall duration of the clinical study was approximately 10 months. Subject participation varied from 4 to 9 weeks.

Reference therapy, mode of administration, and batch number:

None.

Criteria for evaluation

Pharmacokinetics:

Primary Pharmacokinetic Endpoint:

The primary endpoint was the area under the plasma concentration versus time curve from 0 to 48 hours (AUC_{0-48h}).

Secondary Endpoint(s):

- Total AUC
- Mean residence time (MRT)
- Clearance (CL)
- Incremental recovery (IR) determined as the peak level recorded within the three hours after infusion and reported as [(IU/dL)/(IU/kg)]
- Elimination phase half-life
- C_{max}

Safety:

Secondary Safety Endpoint:

- Investigational drug related adverse events (AEs)

Statistical Methods:

A total of 23 male subjects were to be randomized to provide data from a planned number of at least 15 evaluable subjects. An additional 7 subjects were to be added from the original 16 subjects to ensure allocating a total of 3 different lots of Advate 3000 IU potency and Advate 1500 IU potency (one per infusion) per CPMP guidelines (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products). Based on data from previous Advate studies, 20 subjects should provide about 90% power to detect a 5% difference in AUC using a paired data two-sided t-test on the logs of the AUC_{0-48h} at an alpha level of 5%.

PK analysis:

Subjects with an inhibitor level ≥0.4 BU (assessed by Nijmegen assay, *Verbruggen et al., 1985*) were to be excluded from PK assessment.

Primary Pharmacokinetic Endpoint

Formal statistical comparison were to be made for $AUC_{0\text{-}48h}$ using a paired data t-test on the logs of the $AUC_{0\text{-}48h}$ at an alpha level of 5%. All the other PK parameters were to be reported using descriptive statistics for each of the two infusions but no formal statistical comparison were to be made. Specifically but not exclusively, arithmetic mean, geometric mean, medians, standard deviations, minimum, maximum, frequency counts, 25^{th} and 75^{th} percentiles, and the 95% confidence intervals of select point estimates were to be used to describe the data.

Secondary Pharmacokinetic Endpoints

The following parameters are reported using descriptive statistics for each of the two infusions, without formal statistical comparison:

- total AUC
- mean residence time (MRT)
- clearance (CL)
- incremental recovery (IR, determined as the peak level recorded within the 3 hours ±10 minutes after completion of the infusion and reported as (IU/dL)/(IU/kg)
- elimination phase half-life

Specifically but not exclusively, arithmetic mean, geometric mean, medians, standard deviations, minimum, maximum, frequency counts, 25^{th} and 75^{th} percentiles, and the 95% confidence intervals of selected point estimates are used to describe the data.

Adjusting for Pre Infusion Factor VIII Levels

The calculation of the PK parameters was to ensure that any FVIII present at baseline is not attributed to the IP. Therefore, a baseline adjustment was to be performed by calculating the percentage of the pre infusion FVIII concentration relative to the FVIII concentration achieved at C_{max}. The corresponding FVIII concentration was to be subtracted from the FVIII concentration at each time measurement. Thus, the adjusted FVIII measurement at time t, $FVIII_{corrected,t}$ used to calculate the PK parameters is determined as follows:

$$FVIII\,corrected,t = \left(1 - \frac{pre - \inf\ FVIII\ concentration}{C\max\ FVIII\ concentration}\right) * Measured\ FVIII\ concentration\ at\ time\ t$$

Pharmacokinetic Analysis Method

The following PK parameters are computed using actual sampling times rather than nominal times, whenever possible. Actual sampling times are defined as time from end of infusion to collection time of blood draw.

- Incremental recovery is determined as the peak level recorded within 3 hours ±10 minutes after completion of the infusion and reported as (IU/dL)/(IU/kg).
- $AUC_{0\text{-}48\ h}$ is computed using the linear trapezoidal method.
- Total AUC is defined as the total area under the plasma concentration versus time curve when the concentration is extrapolated to zero using the slope of the β-phase of the model.
- Total AUC = $AUC_{0\text{-}48\ h}$ + Cp, last / (-β)
- $T_{1/2}$ is calculated as $\log_e 2/\lambda$, where λ is the regression slope in the terminal phase of the least absolute deviations regression model.
- CL is computed as the dose divided by total AUC.
- MRT is computed as total AUMC divided by the total AUC.
- Vss is computed as CL∗MRT.
- C_{max} is determined as the highest FVIII activity achieved post infusion.

In addition, estimates for total AUC and $AUC_{0\text{-}48\ h}$ are presented adjusted for dose (i.e., divided by dose per kg body weight) and reported in units of (IU x dL^{-1} x h) / (IU/kg).

Acceptable Pharmacokinetic Assessment

For the complete PK assessment to be deemed acceptable and evaluable, all of the following three criteria were to be fulfilled:

- Subject received the PK infusion of the IP Advate according to the specified dosing (i.e., 3000 IU) for both infusions.
- Plasma FVIII activity measurements are available for each of the following:
  - Both pre infusion and 30-minutes post infusion time points, and
  - At least two of the 6-, 9-, or 24-hours post infusion time points, and
  - At least two of the 28-, 32-, or 48-hours post infusion time points
- FVIII activity measurements generally decreases from the 3-hour (±10 minutes) post infusion time point until pre infusion values are approached.

If the third criterion was not met, the PK data was to be evaluated by the medical director.

Safety Analysis:

The occurrence of IP related AEs was documented and evaluated. Adverse events are tabulated by MedDRA preferred term for related and unrelated events.

Summary – Conclusions

Pharmacokinetic Results:

A total of 23 male subjects received two PK infusions of 3000 IU Advate using one 3000 IU potency vial followed by two 1500 IU potency vials or the alternate sequence. FVIII activity was determined using chromogenic and one-stage activated partial thromboplastin time (aPTT)-based assay.

The mean area under the plasma concentration versus time curve from 0 to 48 hours (AUC_{0-48h}) (primary pharmacokinetic endpoint) was 1158 IU·h/dL for the one 3000 IU infusion and 1264 IU·h/dL for the two 1500 IU infusions with a ratio of 0.94 and a difference in log of -0.09, measured by chromogenic assay, and 1129 IU·h/dL and 1226 IU·h/dL for the 3000 IU and 2 x 1500 IU infusions, respectively, with a ratio of 0.95 and a difference in log of -0.08, measured by one-stage aPTT-based assay. Paired t-test showed no statistical difference between the AUC_{0-48h} after administration of one 3000 IU vial and two 1500 IU vials (p=0.103 chromogenic, p=0.162 one-stage aPTT-based assay).

Additional PK parameters ($AUC_{0-\infty}$, IR, C_{max}, $T_{1/2}$, CL, MRT, and V_{ss}) were determined for the PP and ITT datasets. Although no formal comparisons were made, the mean values for these parameters were comparable for the one 3000 IU vial and two 1500 IU vials.

Safety Results:

All 23 subjects were additionally treated for prevention of bleeding and six subjects also for bleeding episodes.

Advate 3000 IU was shown to be safe and well tolerated in all 23 subjects treated, with no FVIII inhibitors recorded. Only one mild, transient adverse reaction occurred. No deaths or SAEs occurred and no abnormal hematology or clinical chemistry results were recorded that were not due to a pre existing condition.

Conclusion:

The PK evaluation of 3000 IU Advate using one 3000 IU potency vial or two 1500 IU potency vials demonstrated no difference in terms of $AUC_{0\text{-}48h}$ and other PK parameters. The safety assessments in this study demonstrated that Advate was safe and well tolerated.

Date of Report: 13 August 2010