# An Open-Label Study of the Safety and Efficacy of ReFacto AF in Previously Untreated Patients in Usual Care Settings

Published: 26-04-2011
Last updated: 27-04-2024

The primary objective is to evaluate the safety of ReFacto AF in previously untreated patients (no prior exposure to factor products or any blood products) of less than 6 years of age.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Coagulopathies and bleeding diatheses (excl thrombocytopenic) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON39506

**Source**
ToetsingOnline

**Brief title**
B1831006

### Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

**Synonym**
factor VIII deficiency, Hemophilia A

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Pfizer

**Source(s) of monetary or material Support:** Pfizer

## Intervention

**Keyword:** Hemophilia A, ReFacto AF, untreated patients

## Outcome measures

### Primary outcome

The primary safety outcome measure will be the proportion of subjects who develop clinically significant FVIII inhibitors during the course of the study. Clinically significant inhibitors are defined as a central laboratory confirmed positive inhibitor (* 0.6 BU using the Nijmegen modification of the Bethesda assay present at 2 consecutive blood draws within a 4-week interval) and the occurrence of one or more of the following clinical observations: decreased FVIII recovery, need for alternative hemostatic products, increase in number of breakthrough bleeds while on preventive or prophylactic treatment, or more than one report of Less Than Expected Therapeutic Effect (LETE) in the absence of confounding factors. Mandatory laboratory assessments to screen for FVIII inhibitor will be performed at the 10-15 ED, and 50 ED visits. Laboratory assessments for inhibitors are strongly recommended, but are at the discretion of the investigator at the subsequent 6-Month Interval visits through the Final Visit. It is recommended that the investigator obtain serial follow-up inhibitor testing for any subject with a FVIII inhibitor result * 0.6 BU until the result is < 0.6 BU or the subject reaches the Final Visit. After the Final Visit, it is recommended that the investigator continue to follow subjects with ongoing inhibitors until the inhibitor resolves or stabilizes. A central laboratory Nijmegen modification of the Bethesda assay will confirm

local positive inhibitor assays. Factor VIII ELISA antibody testing will also be performed by the central laboratory to correlate with positive inhibitor test results.

The efficacy endpoints include annualized bleeding rates (ABRs) in patients receiving treatment with Refacto AF, the responses to the first on-demand treatment with Refacto AF for all new bleeds (4-point scale of assessment) as assessed by the parent/legal representative, the number of Refacto AF infusions to treat each new bleed, the number of breakthrough (spontaneous/non-traumatic) bleeds within 48 hours of a preventive/prophylaxis dose of Refacto AF, the average infusion dose and total factor consumption, and the incidence of less-than-expected therapeutic effect (LETE). All subjective assessments will be provided by the parent/legal representative.

**Secondary outcome**

Secondary safety outcome measures are the incidence of SAEs and nonserious AEs. Subject withdrawal for safety reasons will be at the discretion of the investigator and treating physicians.

# Study description

**Background summary**

Hemophilia A is an X-linked recessive disease in which clotting factor VIII (FVIII) is deficient or inactive. Patients with a low level of FVIII have an increased tendency to bleed. When the levels of FVIII are very low (<1% of normal), frequent spontaneous bleeding episodes may occur. Infusing patients with a concentrated formulation of the missing FVIII protein can control the bleeding. Until the late 1980s such concentrates were produced exclusively from human plasma. However, several side effects were seen with these plasma-derived products, such as the transmission of viral diseases, especially human

immunodeficiency virus (HIV). Rapidly evolving recombinant DNA technology has enabled the development of several recombinant coagulation products, including ReFacto. Moroctocog alfa (AF-CC) with the trade name ReFacto AF represents the next generation of ReFacto that improves theoretical viral safety following several enhancements, including the removal of albumin from the ReFacto manufacturing process.
Newborns, infants and very young children with severe hemophilia A typically require FVIII replacement treatments early in life for various bleeding events, preventive infusions, or prophylaxis. Historically, it is well-known that young children, especially those naïve to FVIII, are at greater risk for developing neutralizing antibodies (inhibitors) and may have altered responses to replacement therapy than older subjects with hemophilia A. While factors such as clinical severity, genetic mutations, exposure intensity, and inherent immunoresponse heterogeneity may be risk factors for such safety issues, it is also important to ensure that these are not specifically related to different FVIII replacement products. Since the clinical trials that support approval of hemophilia treatments are based on limited numbers of subjects, including children, it is important to continue to characterize product safety in the pediatric patient population. Thus, previously untreated patients (PUPs) represent a group of interest as they are at higher risk for inhibitor development and may have altered response to therapy. Previous studies of ReFacto AF suggest that subjects less than 12 years of age with hemophilia A may respond differently to FVIII therapy compared to older subjects with this disorder. One potential explanation for altered response may be the presence of sub-clinical inhibitory antibodies, a phenomenon seen with replacement infusions of therapeutic proteins. Biotechnology-derived proteins, such as recombinant clotting factor concentrates, may induce humoral immune responses (antibodies) in patients exposed to these products because the immune system may recognize these proteins as non-self-immunogens. In order to expand the safety profile for pediatric patients obtained through the clinical safety and efficacy trials used for regulatory approval of these products, additional safety studies are conducted so as to have the opportunity to obtain additional data on such humoral immune responses or other adverse events that may not be fully appreciated until larger numbers of pediatric patients are exposed. Moreover, risk factors for such responses may be host specific, product specific, or related to route or duration of exposure. A series of recently completed clinical trials have confirmed that the risk of developing neutralizing antibodies (inhibitors) to moroctocog alfa (AF-CC) is comparable to that observed with its predecessor product ReFacto and is no greater than that seen with other recombinant FVIII products. To fulfill an EMEA requirement for postauthorization safety surveillance and risk management and to ensure that ReFacto AF has an acceptable rate of inhibitor development, this study will also monitor development of clinically significant and laboratory-confirmed inhibitors in a population of patients with hemophilia A, that after consultation with their physician, choose to be treated with ReFacto AF independent of this study. Patients will be monitored in the usual care setting while following treatment practice recommendations of their prescribing

physician. All male patients < 6 years of age with severe hemophilia A (FVIII:C <1%) based on clinical records, including newborns will be eligible to enroll.

## Study objective

The primary objective is to evaluate the safety of ReFacto AF in previously untreated patients (no prior exposure to factor products or any blood products) of less than 6 years of age.

## Study design

This nonrandomized, prospective, open-label, study will be conducted in major hemophilia treatment centers in Europe and other countries. The study will capture clinical and laboratory observations based on EMEA guidance for evaluating recombinant FVIII replacement product safety. For the purpose of this protocol, a previously untreated patient participating in this study will be referred to as a Subject. This study will enroll subjects who have not received any factor products or blood products for their hemophilia A. The subjects will be treated with intravenous infusions of ReFacto AF at a dose and frequency prescribed by the subjects* treating physician. Factor consumption, infusion days, treatment regimen, factor dose, purpose of infusion, type of bleed, location of bleed, and response of bleed to treatment, will be ascertained using an infusion log maintained by a parent/legal representative. The parent/legal representative will also complete a 4-point rating scale for efficacy of infusions. All subjects will be followed for at least 50 exposure days (EDs) and participation may conclude after the subjects have achieved 100 EDs, or have participated in the study for approximately 26 months, whichever occurs first.

## Intervention

An infusion diary should be maintained for the infusions of ReFacto AF. Furthermore the subjects will be questionned by the investigator for detection of adverse events and will be examined. Blood will be withdrawn, they will receive ReFacto AF and 30 minutes later a second blood sample will be withdrawn. A physical examination will be conducted and the vital functions will be determined.

## Study burden and risks

In comparison with the standard of care the patient will visit the hospital more often and blood will be withdrawn more often. Directly before and 30 minutes after dosing blood will be withdrawn to measure the factor VIII activity in plasma (FVIII:C). These blood samples will be taken via an venapunction in the arm contralateral to the infusion arm.

The risks are not different from the standard of care.

## Contacts

**Public**
Pfizer

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Collegeville 19426
US
**Scientific**
Pfizer

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US

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Children (2-11 years)

### Inclusion criteria

1) Male subjects <6 years of age with severe hemophilia A (FVIII:C <1%) based on clinical records, including newborns.;2) No prior exposure to factor products or any blood products.

### Exclusion criteria

1) Presence of any bleeding disorder in addition to hemophilia A.;2) Treatment with any investigational agent or device within the past 30 days.;3) Any condition(s) that compromises the ability to collect study-related observations, or that poses a contraindication to study

participation (these conditions include, but are not limited to, inadequate medical history to assure study eligibility; and expectation of poor adherence to study requirements).

# Study design

## Design

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|---|---|
| Study phase: | 4 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 08-01-2014 |
| Enrollment: | 2 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | ReFacto AF |
| Generic name: | moroctocog alfa (AF-CC) |
| Registration: | Yes - NL intended use |

# Ethics review

Approved WMO

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| Date: | 26-04-2011 |
| Application type: | First submission |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |

Approved WMO

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|---|---|
| Date: | 25-04-2013 |
| Application type: | First submission |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 04-02-2014 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |
| Approved WMO Date: | 26-07-2016 |
| Application type: | Amendment |
| Review commission: | IRB Nijmegen: Independent Review Board Nijmegen (Wijchen) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2008-008436-93-NL |
| ClinicalTrials.gov | NCT00950170 |
| CCMO | NL29918.072.11 |

# Study results

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| Date completed: | 02-11-2016 |

Actual enrolment: 1

**Summary results**
Trial is onging in other countries