



Design of a Real-World Observational Study in Previously Untreated and Minimally Treated Hemophilia A Patients: Protect-NOW

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Abstract

Keywords

- ▶ coagulation factor VIII
- ▶ hemophilia A
- ▶ inhibitors
- ▶ previously untreated patients
- ▶ real-world study

Background The efficacy, safety, and immunogenicity of each of Octapharma's factor VIII (FVIII) products, Nuwiq, octanate, and wilate, have been investigated in previously untreated patients (PUPs) with severe hemophilia A in prospective clinical trials. The aim of the Protect-NOW study is to evaluate the effectiveness, safety, and utilization patterns of Nuwiq, octanate, and wilate in PUPs and minimally treated patients (MTPs; <5 exposure days [EDs] to FVIII concentrates or other blood products containing FVIII) with severe hemophilia A in a real-world setting. Real-world data provide valuable information that complement data obtained from interventional clinical trials.

Methods Protect-NOW (ClinicalTrials.gov identifier: NCT03695978; ISRCTN identifier: 11492145) is a real-world study in PUPs and MTPs treated with either the human cell line-derived recombinant FVIII Nuwiq (simoctocog alfa) or a plasma-derived FVIII concentrate containing von Willebrand factor (octanate or wilate). It is a prospective and (partly) retrospective, observational, international, noncontrolled, noninterventional study. A total of 140 PUPs and MTPs with severe hemophilia A will be enrolled across around 50 specialized centers worldwide and followed for either 100 EDs or a maximum period of 3 years from ED1. The primary objectives are to assess effectiveness in the prevention and treatment of bleeding episodes and overall safety, including inhibitor development. The secondary objectives are to assess utilization patterns (including dosage and frequency of administration) and the effectiveness in surgical prophylaxis.

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Conclusions The Protect-NOW study will provide information on the treatment of PUPs and MTPs in routine clinical practice, which will help guide clinical decision making for treating these patients in the future.

Introduction

Severe congenital hemophilia A is a rare blood disorder characterized by a deficiency of coagulation factor VIII (FVIII) activity (<1% of normal), leaving patients at risk of frequent, prolonged, and recurrent bleeding.^{1–3} Severe hemophilia A is usually diagnosed soon after birth and requires lifelong therapy from an early age to prevent and control bleeding.^{3,4} FVIII replacement therapy using plasma-derived FVIII (pdFVIII) or recombinant FVIII (rFVIII) concentrates is a long-established approach to restore hemostasis in hemophilia A patients.^{3,5}

Early bleed prevention in young children is important to minimize the risk of severe and life-threatening bleeds, such as intracranial hemorrhage (ICH),⁶ and to protect patients from later joint damage, a major complication associated with hemophilia A.^{7,8} Unfortunately, approximately 25 to 40% of previously untreated patients (PUPs) with hemophilia A develop neutralizing antibodies (inhibitors) against FVIII.⁹ Inhibitors typically develop during the first 20 exposure days (EDs) to FVIII treatment, although a residual risk persists up to 75 EDs.^{10,11}

Nuwiq (simoctocog alfa) is a fourth-generation rFVIII produced in a human cell line without chemical modification or protein fusion. The efficacy and safety of Nuwiq for the prevention and treatment of bleeds has been demonstrated in prospective phase 3 trials in PUPs and previously treated patients (PTPs) with severe hemophilia A.^{12–14} In the NuProtect study, 17 of 105 (16.2%) PUPs treated with Nuwiq for up to 100 EDs developed high-titer inhibitors.¹⁴

Octanate and wilate are high-purity pdFVIII concentrates containing von Willebrand factor (VWF) with FVIII:VWF ratios of 0.4:1 and 1:1, respectively. Both octanate (Octapharma, data on file) and wilate have demonstrated efficacy and safety in patients with severe hemophilia A for the prevention and treatment of bleeds in prospective open-label studies.¹⁵ High-titer inhibitors developed in 4 of 51 (7.8%) PUPs who received octanate and 3 of 28 (10.7%) PUPs who received wilate.

As hemophilia A is a rare disease, the numbers of patients, particularly PUPs, treated in clinical trials are low. The international, noninterventional study *PRactical Utilization of Octapharma FVIII Concentrates in Previously Untreated and Minimally Treated Hemophilia A Patients Entering Routine Clinical Treatment* (with Nuwiq, octanate or wilate) (Protect-NOW; NCT03695978 ISRCTN 11492145) was designed to collect real-world data on the effectiveness, safety, and utilization of the FVIII products Nuwiq, octanate, and wilate in PUPs and minimally treated patients (MTPs) with severe hemophilia A. The Protect-NOW study will provide evidence on the effectiveness and safety of FVIII

products in routine clinical practice, to complement the data obtained from clinical trials.

Methods and Analysis

Study Design

Protect-NOW is a prospective and (partly) retrospective, observational, international, noncontrolled, noninterventional study designed to assess the long-term effectiveness, safety, and utilization of Nuwiq, octanate, and wilate in PUPs and MTPs with severe hemophilia A treated in routine clinical practice (►Fig. 1). The treatment regimen is at the discretion of the treating physician. A patient completes the study upon reaching 100 EDs or 3 years after ED1. Patients who develop inhibitors and do not continue with FVIII prophylaxis may continue in the study for up to 3 years if they use an Octapharma FVIII concentrate for immune tolerance induction (ITI). ITI patients who achieve complete ITI success will be followed for a further 12 months on prophylaxis to assess the rate of inhibitor relapse. The study plans to document a total of 140 patients. Subgroup analyses have not been predefined. The study will be performed in approximately 50 countries where Nuwiq, octanate, or wilate is registered and used in real-life clinical practice.

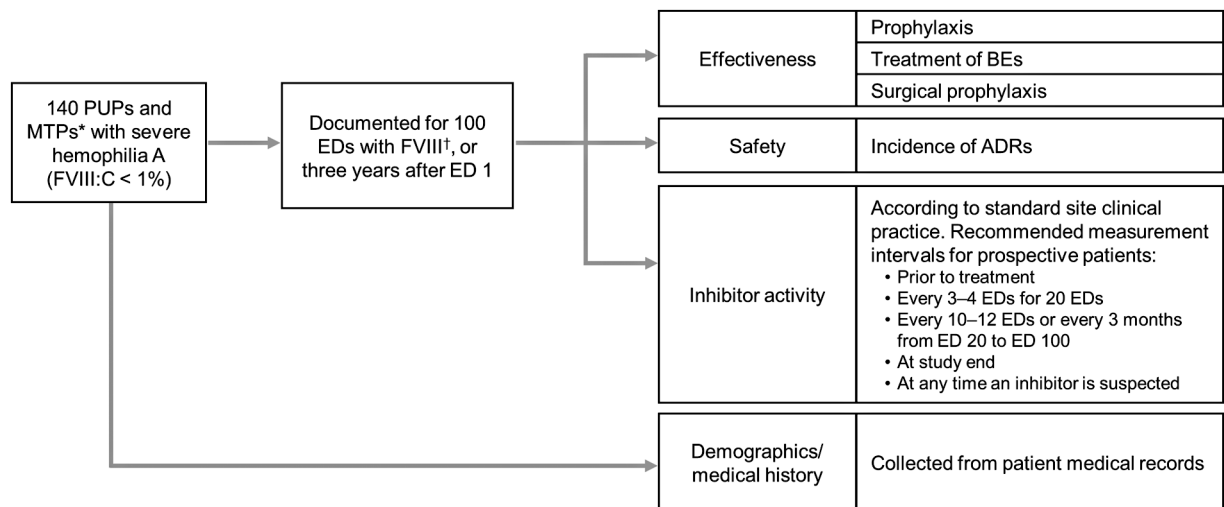
Study Objectives and Endpoints

The primary objectives of the study are to investigate the effectiveness and overall safety of Nuwiq, octanate, and wilate in routine clinical practice for the prevention and treatment of bleeding episodes (BEs) in PUPs and MTPs with severe hemophilia A (►Box 1). As secondary objectives, the study aims to investigate product utilization patterns, including dosage and treatment frequency, and to assess the effectiveness of the products in surgical prophylaxis.

To evaluate factors potentially associated with inhibitor development and eradication, optional sub-studies (►Table 1) include *F8* gene mutation analysis, detection of anti-FVIII nonneutralizing antibodies, epitope mapping, and product-specific batch selection for wilate and octanate (in patients with inhibitors who undergo ITI).

Patient Eligibility and Recruitment

To be eligible for the study, patients must fulfil all of the inclusion criteria and none of the exclusion criteria (►Table 2). Participants must either have had no previous treatment with FVIII products (PUPs) or fewer than five EDs to FVIII concentrates or other blood products containing FVIII (MTPs). PUPs and MTPs with prior and/or concomitant emicizumab treatment are also eligible for the study, if 100 EDs can be reached within the maximum individual study duration of 3 years.



*Patients with prior emicizumab treatment are eligible.
 †Concomitant emicizumab is permitted.

Fig. 1 Protect-NOW study design. ADRs, adverse drug reactions; BE, bleeding episode; ED, exposure day; FVIII, factor VIII; MTP, minimally treated patient; PUP, previously untreated patient.

Box 1 Protect-NOW study objectives

Protect-NOW study objectives	
➤ To investigate, in PUPs and MTPs with severe hemophilia A treated in routine clinical practice with Nuwiq, octanate, and wilate:	
<i>Primary</i>	
➤ Effectiveness in the prevention and treatment of bleeding episodes.	
➤ Safety based on the incidence of ADRs, including inhibitor development.	
<i>Secondary</i>	
➤ FVIII utilization patterns, including dosage and treatment frequency.	
➤ Effectiveness in surgical prophylaxis.	

Abbreviations: ADRs, adverse drug reactions; MTP, minimally treated patient; PUP, previously untreated patient.

Table 1 Optional sub-studies

Analysis	Objective	Laboratory sites
F8 gene mutation analysis	To determine the F8 gene mutation present and to investigate whether specific mutations have an influence on clinical outcomes	University Clinic Bonn, Bonn, Germany
Measurement of anti-FVIII nonneutralizing antibodies	To determine the incidence of anti-FVIII antibodies that do not inhibit FVIII function (nonneutralizing)	University Clinic Bonn, Bonn, Germany
Mapping of FVIII epitopes	To identify the FVIII domains acting as epitopes to anti-FVIII antibodies and to investigate the relationship between epitopes and clinical outcomes	University Clinic Bonn, Bonn, Germany
Product-specific batch selection analysis for patients receiving ITI with octanate or wilate	To determine the effect of batch selection on ITI outcomes in patients receiving octanate or wilate	Hemophilia Centre Rhein Main (HZRM), Mörfelden-Walldorf, Germany

Abbreviations: FVIII, factor VIII; ITI, immune tolerance induction.

Data Collection and Primary Analyses

Analyses will be performed on available data collected from routine clinical practice. Treating physicians will collect the following: demographics and medical history before the start of treatment; and changes in weight, comorbidities that may significantly impact blood coagulation/immune

reaction, and relevant concomitant medications at routine visits. If home treatment is used, patient diaries will be used to collect any relevant information.

To analyze FVIII treatment patterns, the reason for treatment (prophylaxis/on-demand/surgical prophylaxis/ITI), dose (FVIII IU/kg body weight per infusion, date and time

Table 2 Patient eligibility criteria

Inclusion criteria	Exclusion criteria
Male and female patients of any age and ethnicity with a diagnosis of severe hemophilia A (FVIII:C < 1%)	Diagnosis of any coagulation disorder other than hemophilia A
Decision to prescribe Octapharma's FVIII concentrate before enrolment into the study	Concomitant treatment with any systemic immunosuppressive drug
Either: <ul style="list-style-type: none"> • No previous treatment with FVIII concentrates or other blood products containing FVIII (PUPs) OR • Less than 5 EDs to FVIII concentrates or other blood products containing FVIII (MTPs) if <ul style="list-style-type: none"> - First ED occurred after January 1, 2015, AND - They did not develop an inhibitor at any time point, OR - They developed an inhibitor during treatment with an Octapharma FVIII concentrate and continued treatment with the same Octapharma FVIII concentrate 	Participation in an interventional clinical trial during the time period evaluated
Signed and dated informed consent form provided by the participant or participants' parent(s)/legal guardians(s)	Participation in another Octapharma noninterventional study
Note: Patients with prior emicizumab treatment are eligible	

Abbreviations: ED, exposure day; FVIII, factor VIII; MTP, minimally treated patient; PUP, previously untreated patient.

of administration), FVIII concentrate, and FVIII batch number will be recorded for each FVIII injection. The number of EDs and overall FVIII consumption will be calculated from this information.

The effectiveness of prophylaxis will be assessed based on the annualized bleeding rate (ABR) of all BEs. If a BE occurs during the study, treating physicians will record the type of BE (spontaneous/traumatic/postoperative/other), date and time the BE first occurred or was noticed, date the BE ended, BE site, severity of BE (minor/moderate/major), FVIII consumption for treatment of the BE, and clinical assessment of BE treatment effectiveness.

The effectiveness of surgical prophylaxis is assessed by the treating physician according to a four-point scale. For each surgery, physicians are recommended to document available data, including surgery type (planned or emergency), location, severity (minor or major), dose(s) of FVIII given pre-, intra- or postoperatively, estimated and actual perioperative and postoperative blood loss, and relevant concomitantly administered medications.

Development of FVIII inhibitors is diagnosed based on clinical observations and FVIII inhibitor testing in the local laboratory by the Nijmegen-modified Bethesda assay (negative: <0.6 Bethesda units [BU]/mL and threshold used per local laboratory standard, if different). In case of a positive inhibitor result, as per routine practice, a second separately drawn sample is recommended to be retested. The following inhibitor testing schedule is recommended: before first FVIII treatment; every 3–4 EDs until ED 20; every 10–12 EDs or every 3 months from ED 20–100; and at study completion. Inhibitors will be classified as low-titer if <5 BU/mL and high-titer if ≥ 5 BU/mL. Inhibitors that fall below <0.6 BU/mL within 6 months without an increase in FVIII dose or frequency will be regarded as transient.

Safety

The long-term safety of Nuwiq, octanate, and wilate will be evaluated based on the incidence of adverse drug reactions (ADRs). FVIII inhibitor development and hypersensitivity reactions are ADRs of particular interest. Serious ADRs and other significant safety findings will be reported to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) if required. All suspected ADRs and other safety information (any drug abuse, misuse, or overdose, medication errors, interactions with other medicinal products/devices, and occupational exposure associated with FVIII) will be documented and reported.

Statistical Methods

The data will be analyzed using descriptive statistical methods. There will be no formal comparisons between the treatments. Up to three interim analyses may be conducted during the study. No formal sample size calculations were performed, and the sample size of 140 patients was chosen based on feasibility.

Ethics and Dissemination

The study is conducted in accordance with the ethical principles in the Declaration of Helsinki and in compliance with Good Pharmacoepidemiology Practice and regulatory requirements applicable centrally and in each of the study countries. All relevant documents were submitted to the IRBs/IECs and to the regulatory bodies (if applicable) and were approved before the start of the study. Any amendments to the protocol will be reviewed by the IRBs/IECs before implementation, except for changes necessary to eliminate an immediate hazard to participants.

All participants' parent(s)/legal guardian(s) provide written consent before entering the study. Patients may withdraw from the study at any time. Treating physicians ensure that the

patient's confidentiality is maintained. Results are planned to be presented at scientific meetings, published in a peer-reviewed journal, and summarized in a report that will be submitted to the relevant stakeholders.

Patient and Public Involvement

There has been no patient or public involvement in the design of the Protect-NOW study. Study results will be distributed to participants via the investigators who will receive the study report.

Study Status

The first patient was enrolled in January 2018 and, as of the end of March 2023, 59 patients have been recruited at 18 centers in Belarus, Canada, France, Germany, Hungary, Italy, Lithuania, Spain, and the United Kingdom, with further sites and countries to be initiated.

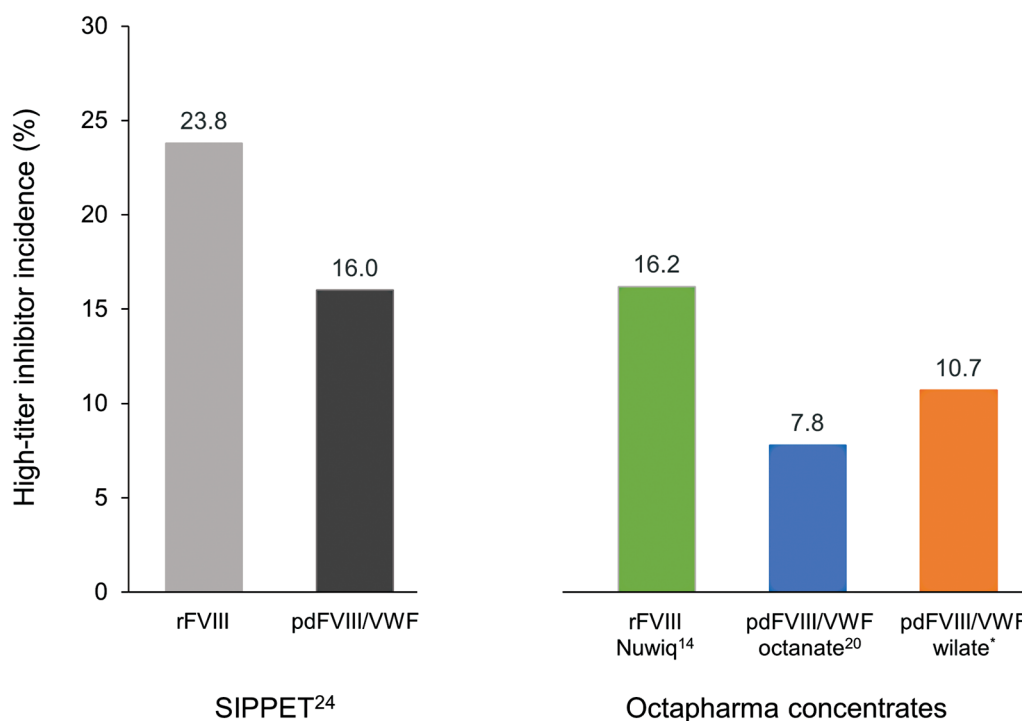
Discussion

Patients with severe hemophilia A often require therapeutic intervention from an early age, either to treat a bleed or to initiate prophylaxis.^{16,17} Young children commonly experience soft tissue/intramuscular hematomas and oral/nasal bleeds, and are at higher risk for ICH, a life-threatening bleed associated with a high rate of mortality in hemophilia patients.^{16,18} Furthermore, bleeding into the joints early in life—even subclinical bleeding that may go unnoticed—has been shown to negatively impact long-term joint health.^{7,8} Prevention of bleeding with FVIII prophylaxis has been

shown to both significantly reduce the risk of ICH and to improve joint health outcomes in children with severe hemophilia A.^{6–8} These observations have led to widespread recommendation to begin prophylaxis as early as possible in children with severe hemophilia A.³

Clinical trial experience has demonstrated the efficacy and safety of Nuwiq, octanate, and wilate in PUPs for the prevention and treatment of bleeds and for hemostatic coverage during surgery. In a study of 108 PUPs, the efficacy of BE treatment with Nuwiq was “excellent” or “good” in 92.9% (747 of 804) of rated BEs; the efficacy of Nuwiq for surgical prophylaxis was “excellent” or “good” in 94.7% (18 of 19) of rated surgeries.¹⁹ In 50 PUPs receiving continuous prophylaxis with Nuwiq for at least 24 weeks, the median ABR was 0 for spontaneous bleeds and 0 for joint bleeds.¹⁹ In a study of 51 PUPs, the hemostatic efficacy of octanate, irrespective of the reason for administration was “excellent” in 99.6% of infusions (4,700 of 4,717 infusions), and 95.5% of bleeds resolved with 1 or 2 days of treatment.²⁰ The efficacy of all 201 infusions of octanate administered for 23 surgical procedures was rated as “excellent.”²⁰ In a study of 28 PUPs receiving wilate, efficacy was rated as “excellent” or “good” in all 885 infusions administered for prophylaxis, and 99.1% of 1,271 infusions administered for treatment of bleeds (Octapharma, data on file). The majority of bleeds (595; 75%) required 1 day of treatment. Five PUPs underwent nine surgical procedures, with the efficacy of all infusions rated as “excellent” or “good” (Octapharma, data on file).

The assessment of inhibitor development is an important aspect of the Protect-NOW study. The presence of high-titer



*Octapharma data on file.

Fig. 2 Absolute incidences of high-titer inhibitors in the SIPPET study for rFVIII and pdFVIII/VWF, and in separate studies with Octapharma concentrates. pdFVIII: plasma-derived factor VIII; rFVIII: recombinant factor VIII.

inhibitors renders FVIII replacement therapy ineffective and patients need to rely on bypassing agents, which are less effective for the control of bleeding in hemophilia A patients.²¹ Furthermore, patients with inhibitors may be excluded from clinical trials with new therapies for hemophilia A, such as gene therapy.²²

The risk of inhibitor development is influenced by several patient- and treatment-related factors, including F8 genotype and the type of FVIII product used.^{11,23} A large, randomized, controlled trial reported a higher incidence of high-titer inhibitor development in PUPs treated with hamster cell line-derived rFVIII products (23.8%) compared with pdFVIII/VWF products (16.0%) (►Fig. 2).²⁴ A posthoc analysis of the study demonstrated that amongst patients with non-null F8 gene mutations, 18.2% of patients treated with rFVIII products from hamster cell lines developed high-titer inhibitors, whereas none of the patients treated with pdFVIII developed inhibitors.²⁵

In prospective clinical studies, 16.2% of PUPs receiving Nuwiq developed high-titer inhibitors, while 7.8 and 10.7% (Octapharma, data on file) of PUPs treated with the plasma-derived concentrates octanate and wilate, respectively, developed high-titer inhibitors (►Fig. 2).^{14,20} No PUPs with a nonnull F8 gene mutation developed an inhibitor in clinical trials with Nuwiq, octanate, or wilate.^{14,20,26} These data suggest that Nuwiq, which is produced in a human cell line, has an immunogenicity profile more similar to pdFVIII than to rFVIII products produced in hamster cell lines.

With the availability of the nonfactor therapy emicizumab, PUPs with severe hemophilia A may be treated with emicizumab prophylaxis.²⁷ However, patients on emicizumab prophylaxis may still rely on FVIII for the treatment of breakthrough bleeds and management of surgery, and it remains to be seen whether this delayed FVIII exposure could put patients at higher risk of FVIII inhibitor development later in life.^{27,28} Patients who have previously used emicizumab, or who are treated with emicizumab and FVIII, are eligible for enrolment in the Protect-NOW study.

The limitations of the study include the absence of a control arm, the potential for missing data, and heterogeneity of the study population. However, real-world data from noninterventional studies add to the body of data on a particular treatment, and complement the data obtained from clinical trials. This is particularly relevant in rare diseases, such as hemophilia A, where the number of patients included in clinical trials is limited. The Protect-NOW study will provide information on the treatment of PUPs and MTPs in routine clinical practice, which will help guide clinical decision making for treating these patients in the future.

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Conflict of Interest

Johannes Oldenburg has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board, and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda.

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