Article published online: 2023-05-10

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

Johannes Oldenburg[1] Susan Halimeh[2] Georgina W. Hall[3] Robert Klamroth[4] Pascual Marco Vera[5] Martina Jansen[6] Mary Mathias[7]

[1] Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany
[2] Coagulation Centre Rhein-Ruhr, Duisburg, Germany
[3] Oxford Haemophilia and Thrombosis Comprehensive Care Centre, Oxford University Hospital NHS Foundation Trust, Children's Hospital Oxford, Oxford, United Kingdom
[4] Department of Haemophilia and Haemostasis, Vivantes Hospital Friedrichshain, Berlin, Germany
[5] Department of Haematology, University General Hospital of Alicante, Alicante, Spain
[6] Octapharma Pharmazeutika Produktionsges m.b.H., Vienna, Austria
[7] Haemophilia Comprehensive Care Centre, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, United Kingdom

Address for correspondence Johannes Oldenburg, MD, PhD, Institute of Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Venusberg-Campus 1, Building 43, 53127 Bonn, Germany (e-mail: Johannes.Oldenburg@ukbonn.de).

TH Open 2023;7:e110–e116.

Abstract

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.

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

received
January 3, 2023
accepted
March 24, 2023

DOI https://doi.org/10.1055/s-0043-1768464.
ISSN 2512-9465.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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 *PR*actical utilization of *O*ctapharma FVIII Concentrates in Previously Untreated and Minimally *T*reated Hemophilia A Patients *E*ntering Routine *C*linical *T*reatment (with *N*uwiq, *o*ctanate or *w*ilate) (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.

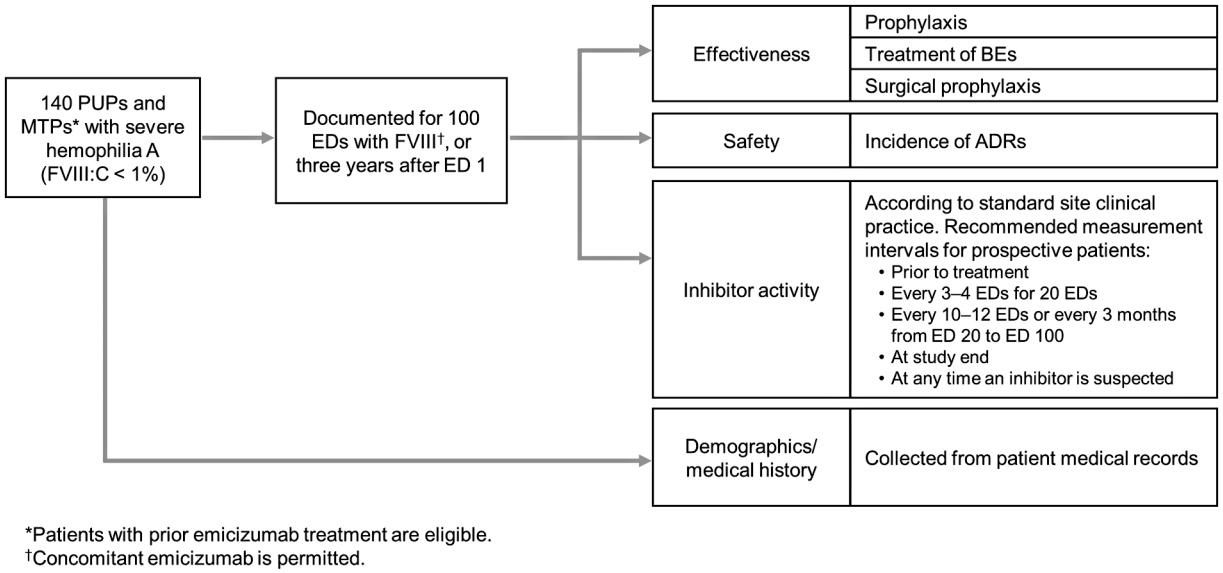

Fig. 1 Protect-NOW study design. ADRs, adverse drug reactions; BE, bleeding episode; ED, exposure day; FVIII, factor VIII; MTP, minimally treated patient; PUP, previously untreated patient.

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:

Primary
- Effectiveness in the prevention and treatment of bleeding episodes.
- Safety based on the incidence of ADRs, including inhibitor development.

Secondary
- 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: • 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 - 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 $\geq$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

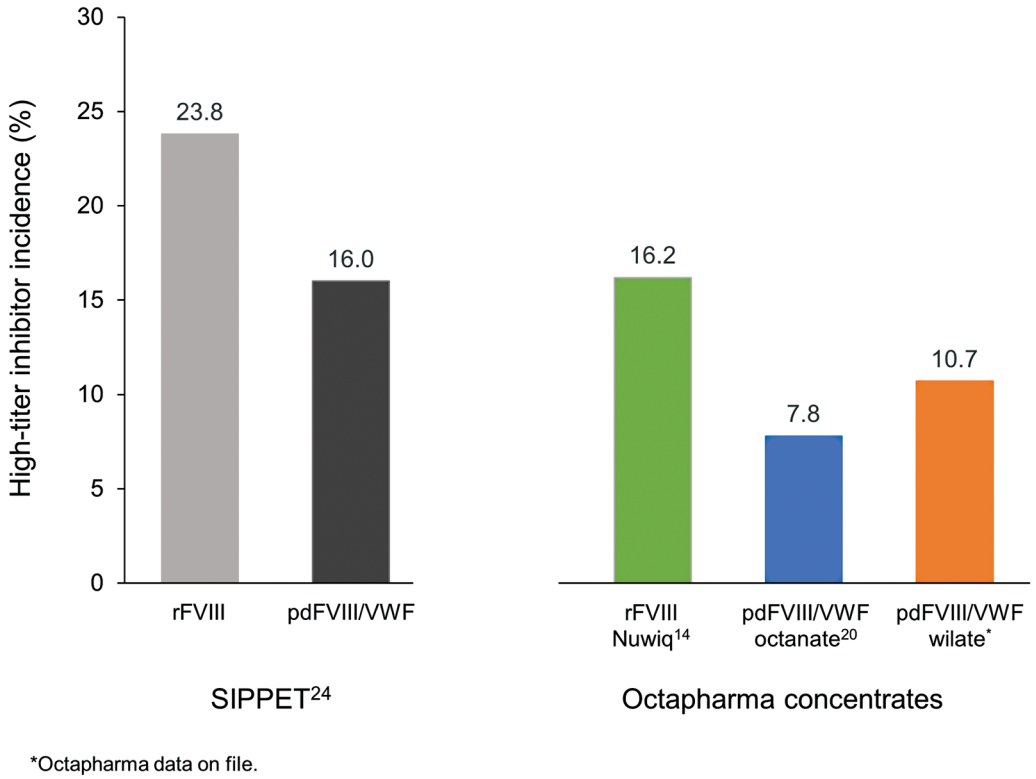

Fig. 2 Absolute incidences of high-titer inhibitors in the SIPPET study for rFVIII and pdFVIII/VWF, and in separate studies with Octapharma concentrates. pdFVIII: plasma-derived factor VIII; rFVIII: recombinant factor VIII.

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 nonnull *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.

Funding

The Protect-NOW study is funded by Octapharma AG, Lachen, Switzerland. Medical writing assistance was provided by nspm ltd (Meggen, Switzerland) and funded by Octapharma AG.

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.

Susan Halimeh reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Baxalta (now Shire), Bayer, Biotest, CSL Behring, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, and Swedish Orphan Biovitrum, participation on advisory boards for Bayer, Biotest, Chugai, CSL Behring, Novo Nordisk, and Octapharma, and research grants from Baxalta (now Shire), Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Swedish Orphan Biovitrum.

Georgina W. Hall reports consulting fees, payment, or honoraria for lectures and support for attending meetings and/or travel from Octapharma.

Robert Klamroth reports consulting fees and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, BioMarin, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, Swedish Orphan Biovitrum, and Takeda.

Pascual Marco Vera reports payment or honoraria for lectures from Bayer, Octapharma, and Takeda, support for attending meetings and/or travel from Bayer, Octapharma, and Roche, and participation on advisory boards for Bayer and Takeda.

Mary Mathias reports an honorarium for a lecture and support for attending a virtual conference from Octapharma, and is Steering Committee Member for the MOTIVATE study (funded by Octapharma). She is a principal investigator for the following studies: MOTIVATE, Protect-NOW (sponsored by Octapharma), HAVEN 6 (sponsored by Roche), XTEND-1 and XTEND-ed (sponsored by Sanofi), and Explorer 7 and 10 (sponsored by Novo Nordisk).

Martina Jansen is a full-time employee of Octapharma Pharmazeutika Produktionsges. m.b.H., Vienna, Austria.

Acknowledgments

The authors also thank in advance the investigators, trial personnel, patients, and caregivers for their participation in the Protect-NOW study. Medical writing assistance was provided by nspm ltd (Meggen, Switzerland) and funded by Octapharma AG.

References

1 Coppola A, Di Capua M, Di Minno MN, et al. Treatment of hemophilia: a review of current advances and ongoing issues. J Blood Med 2010;1:183–195

2 Franchini M. The modern treatment of haemophilia: a narrative review. Blood Transfus 2013;11(02):178–182
3 Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 2020; 26:1–158
4 Kulkarni R, Soucie JM. Pediatric hemophilia: a review. Semin Thromb Hemost 2011;37(07):737–744
5 Ljung RCR. Prevention and management of bleeding episodes in children with hemophilia. Paediatr Drugs 2018;20(05):455–464
6 Andersson NG, Auerswald G, Barnes C, et al. Intracranial haemorrhage in children and adolescents with severe haemophilia A or B - the impact of prophylactic treatment. Br J Haematol 2017;179 (02):298–307
7 Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med 2007;357(06):535–544
8 Warren BB, Thornhill D, Stein J, et al. Young adult outcomes of childhood prophylaxis for severe hemophilia A: results of the Joint Outcome Continuation Study. Blood Adv 2020;4(11):2451–2459
9 Carcao M, Escuriola-Ettingshausen C, Santagostino E, et al; Future of Immunotolerance Treatment Group. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. Haemophilia 2019;25(04):676–684
10 van den Berg HM, Fischer K, Carcao M, et al; PedNet Study Group. Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A. Blood 2019;134 (03):317–320
11 Goudemand J, Peyvandi F, Lacroix-Desmazes S. Key insights to understand the immunogenicity of FVIII products. Thromb Haemost 2016;116(Suppl 1):S2–S9
12 Klukowska A, Szczepański T, Vdovin V, Knaub S, Jansen M, Liesner R. Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq®) in children with severe haemophilia A: efficacy, safety and pharmacokinetics. Haemophilia 2016;22(02):232–239
13 Klukowska A, Szczepański T, Vdovin V, et al. Long-term tolerability, immunogenicity and efficacy of Nuwiq® (human-cl rhFVIII) in children with severe haemophilia A. Haemophilia 2018;24(04): 595–603
14 Liesner RJ, Abraham A, Altisent C, et al. Simoctocog alfa (Nuwiq) in previously untreated patients with severe haemophilia A: final results of the NuProtect study. Thromb Haemost 2021;121(11): 1400–1408
15 Klukowska A, Komrska V, Vdovin V, et al. octanate®: over 20 years of clinical experience in overcoming challenges in haemophilia A treatment. Ther Adv Hematol 2020;11:2040620720914692
16 Kulkarni R, Presley RJ, Lusher JM, et al. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. Haemophilia 2017;23(02):207–214
17 Nijdam A, Altisent C, Carcao MD, et al; PedNet and CANAL study groups. Bleeding before prophylaxis in severe hemophilia: paradigm shift over two decades. Haematologica 2015;100(03): e84–e86
18 Witmer C, Presley R, Kulkarni R, Soucie JM, Manno CS, Raffini L. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. Br J Haematol 2011;152(02):211–216
19 Neufeld EJ, Liesner RJ. Efficacy of simoctocog alfa in previously untreated patients with severe haemophilia A: final Results from the NuProtect study. Res Pract Thromb Haemost 2021;5 (Suppl 2):447
20 Klukowska A, Komrska V, Vdovin V, et al. Low incidence of factor VIII inhibitors in previously untreated patients with severe haemophilia A treated with octanate® : final report from a prospective study. Haemophilia 2018;24(02):221–228
21 Carcao M, Mancuso ME, Young G, Jiménez-Yuste V. Key questions in the new hemophilia era: update on concomitant use of FVIII and emicizumab in hemophilia A patients with inhibitors. Expert Rev Hematol 2021;14(02):143–148
22 Pipe SW. Delivering on the promise of gene therapy for haemophilia. Haemophilia 2021;27(Suppl 3):114–121
23 Garagiola I, Palla R, Peyvandi F. Risk factors for inhibitor development in severe hemophilia A. Thromb Res 2018;168:20–27
24 Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med 2016;374(21):2054–2064
25 Rosendaal FR, Palla R, Garagiola I, Mannucci PM, Peyvandi F; SIPPET Study Group. Genetic risk stratification to reduce inhibitor development in the early treatment of hemophilia A: a SIPPET analysis. Blood 2017;130(15):1757–1759
26 Liesner R, Versteden J, Lowndes S, Belyanskaya L, Oldenburg J, Pavlova A. Immunogenicity of two plasma-derived FVIII products and simoctocog alfa in previously untreated patients according to *F8* mutation type. Blood 2018;132:1204
27 Le Quellec S. Clinical evidence and safety profile of emicizumab for the management of children with hemophilia A. Drug Des Devel Ther 2020;14:469–481
28 Aledort L, Mannucci PM, Schramm W, Tarantino M. Factor VIII replacement is still the standard of care in haemophilia A. Blood Transfus 2019;17(06):479–486