PK-guided personalized prophylaxis with Nuwiq® (human-cl rhFVIII) in adults with severe haemophilia A

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Introduction: Nuwiq® (human-cl rhFVIII) is a 4th generation recombinant human FVIII, without chemical modification or protein fusion, produced in a human cell-line. Aims/Methods: This study (NuPreviq) was a prospective, open-label, multicentre, phase IIIb study of the efficacy and safety of personalized prophylaxis with Nuwiq® in 66 previously treated adults with severe haemophilia A. NuPreviq had three phases: (i) a 72-h pharmacokinetic (PK) phase; (ii) a 1–3 month standard prophylaxis phase; and (iii) a 6-month personalized prophylaxis phase. The personalized prophylaxis regimen was based on individual PK modelling for each patient according to whether their PK profile most closely fitted a two- or one-compartment model (NuPreviq approach). In cases of uncertainty, a noncompartment model was applied. Results: The median dosing interval during personalized prophylaxis was 3.5 days, with 57% of patients on ≤2 weekly dosing. Mean annualized bleeding rates during personalized prophylaxis were 1.45 (median [interquartile range, IQR]: 0 [0, 1.9]) for all bleeds, 0.79 (median [IQR]: 0 [0, 0]) for spontaneous bleeds, and 0.91 (median [IQR]: 0 [0, 0]) for joint bleeds. During personalized prophylaxis, 83.1% of patients were spontaneous bleed-free. Compared with standard prophylaxis, median weekly prophylaxis dose was reduced by 7.2% from 100.0 to 92.8 IU kg⁻¹ during the last 2 months of personalized prophylaxis. There were no FVIII inhibitors or treatment-related serious or severe adverse events. Conclusion: PK-guided personalized prophylaxis with Nuwiq® provided bleeding protection and enabled the dosing interval to be extended to twice weekly or less in many patients and an overall dose reduction.

Keywords: haemophilia A, human-cl rhFVIII, Nuwiq®, personalized prophylaxis, pharmacokinetics, recombinant FVIII

Introduction

Replacement therapy with human plasma-derived FVIII or recombinant FVIII (rFVIII), prophylactically or on-demand, is the mainstay therapy for correcting the deficiency in coagulation FVIII in patients with haemophilia A [1,2]. Prophylaxis is the gold standard treatment for maintaining haemostasis and preserving joint function in children with severe haemophilia A [1,3–5]. There is strong evidence for the benefits of prophylaxis vs. on-demand treatment in adults with severe haemophilia A [1,3,6–10] and that patients who discontinue early prophylaxis as young adults experience a deterioration in joint status [11]. The World Health Organization, the National Hemophilia Foundation, and the World Federation of Hemophilia recommend lifelong prophylaxis [12–14]. In general, the minimum goal is to protect from recurrent bleeding events that ultimately lead to disability. Ideally, every bleed should be prevented and the patient
should be enabled to participate in all normal activities in life.

Due to interindividual differences in FVIII pharmacokinetic (PK) responses, a ‘one size fits all’ approach to prophylaxis is not ideal, as it potentially leads to over-treatment in some individuals and under-treatment in others, and a generic plan fails to take into account a patient’s lifestyle and personal preferences [15]. As haemophilia A patients with FVIII coagulant activity (FVIII:C) >1% experience fewer spontaneous bleeds and consequential damage, currently the main aim of prophylaxis is to keep the FVIII plasma level >1% [15].

Standard prophylaxis typically requires three FVIII infusions per week in a strict regimen due to the mean half-life of approximately 12 h for most currently available FVIII concentrates. However, PK responses to FVIII infusion vary widely between patients due to factors such as age, weight and clinical phenotype [15,16]. The concept of personalized, patient-tailored prophylaxis, whereby dose and dosing frequency is individualized based on PK data, is of growing interest and has the potential to further optimize patient care and enable fewer infusions [10,15,17–19]. Scientifically matching the dosing regimen to the PK of each patient can ensure that all patients achieve a predetermined FVIII trough level and protection from bleeding.

Nuwiq® (human-cl rhFVIII, simoctocog alfa; Octapharma AG, Switzerland) is a 4th generation rFVIII protein, without chemical modification or protein fusion, which is produced in a human cell-line [20–23]. Nuwiq® has been shown to be effective in the prevention and treatment of bleeds in clinical trials including both paediatric and adult previously treated patients (PTPs) with severe haemophilia A [24–27]. In these studies, patients received ‘standard’ prophylaxis with Nuwiq®.

The mean (standard deviation, SD) half-life using the one-stage assay in registration studies in PTPs was 17.1 (11.2) h in adults and adolescents, 11.9 (5.4) h in children aged 2–5 years and 13.1 (2.6) h in children aged 6 to ≤12 years [25,28]. Based on the half-life of Nuwiq® and considerable interpatient variability in FVIII half-life observed with Nuwiq® and across products [25,28–32], a personalized prophylaxis study applying individually appropriate two-, one- or non-compartmental PK methods (NuPreviq approach) was initiated to evaluate the opportunity for extended dosing intervals during PK-guided personalized prophylaxis in adult PTPs with severe haemophilia A.

Patients and methods

Study design and patients

This study (NuPreviq, NCT01863758) was a prospective, open-label, multicentre phase IIIb study investigating the efficacy and safety of individually tailored prophylaxis with Nuwiq® in adult (≥18 years) PTPs with severe haemophilia A (FVIII:C <1%) and at least 150 exposure days (EDs) to previous FVIII concentrates. Patients were enrolled at 20 centres in eight countries (Austria, Bulgaria, Germany, Hungary, Poland, Romania, Slovakia, and the UK). All patients were immunocompetent (CD4+ count >200 μL⁻¹). Patients with severe liver or kidney disease or with present or past FVIII inhibitor activity were excluded. The study was conducted in compliance with Good Clinical Practice, the Declaration of Helsinki and national laws. Each patient provided a freely given written consent before commencing the study.

The study consisted of three phases: (i) a 72-h, PK evaluation phase; (ii) a 1–3 month standard prophylaxis treatment phase; and (iii) a 6-month PK-guided personalized prophylaxis phase (Fig. 1).

For the PK evaluation, patients received a single dose of Nuwiq® at a labelled dose of 60 ± 5 IU kg⁻¹ after a ≥96 h washout period. Blood samples were taken before infusion and at 0.5, 1, 3, 6, 9, 24, 30, 48 and 72 h after the end of infusion and plasma FVIII:C measured with the one-stage assay at a central laboratory (LabCorp, Englewood, CO, USA). The central laboratory also measured the FVIII concentration in the Nuwiq® vials used for PK infusions to calculate the actual dose that patients received.

Calculations of PK parameters (Accovion GmbH, Marburg, Germany) were made by applying two-, one- or noncompartmental PK methods (as individually appropriate) to plasma levels obtained, based on actual time points and actual potency of Nuwiq®. The choice of two-, or one-compartment model was made based on visual inspection, the Akaike information criterion [33], goodness-of-fit statistics (adjusted R²) and the coefficient of variation of PK parameters; a noncompartment model was chosen in cases of uncertainty.

Dosing during prophylaxis is described in Fig. 1. Dosing for the treatment of breakthrough bleeds depended on bleed severity, and dosing for surgical prophylaxis depended on surgery type.

Outcome measures

Annualized bleeding rates (ABRs), dosing intervals and FVIII consumption during prophylaxis were calculated. Inhibitor activity (Bethesda assay, Nijmegen modification [34]) was measured at the initial PK assessment prior to infusion and at study completion using trough level samples (LabCorp, Englewood, CO, USA). Adverse events were monitored throughout the study. Additional outcome measures included the efficacy in the treatment of breakthrough bleeds and during surgical prophylaxis. Assessment of clinical efficacy in the treatment of bleeds was rated on an
objective four-point scale as follows: Excellent = abrupt pain relief and/or unequivocal improvement in objective signs of bleeding within approximately 8 h after a single infusion; Good = definite pain relief and/or improvement in signs of bleeding within approximately 8–12 h after an infusion requiring up to two infusions for complete resolution; Moderate = probable or slight beneficial effect within approximately 12 h after the first infusion requiring more than two infusions for complete resolution; None = no improvement within 12 h, or worsening of symptoms, requiring more than two infusions for complete resolution. Efficacy during surgical prophylaxis was assessed at the end of surgery by the surgeon and the haematologist using objective criteria based on actual intra-operative blood loss compared with predicted blood loss and post-operative blood loss.

Statistics

Statistical analyses were descriptive and were performed by Accovion GmbH (Marburg, Germany).

Results

Patients

A total of 66 patients were enrolled and entered all three phases. Two patients discontinued from the study prematurely during the personalized prophylaxis phase: one patient completed the study, in error, earlier than planned after 91 EDs (263 days) and one patient was lost to follow-up after 73 EDs (172 days), as the patient moved to another country. Neither of the patients experienced any bleeds. Mean (SD) treatment duration was 2.7 (0.6) months for standard prophylaxis and 6.2 (0.5) months for personalized prophylaxis.

Patient demographics and baseline characteristics are shown in Table 1. Mean (SD) age at baseline was 33.6 (9.9) years and the total Haemophilia Joint Health Score (HJHS) at baseline was 37.4 (25.3). The majority of patients (62%, 41/66) received only on-demand treatment in the 6 months prior to the study (HJHS: 45.6 (23.7)), and 38% (25/66) received prophylaxis (mainly irregular) (HJHS: 27.8 (30.3)). Prior mean (SD) ABRs were 38.9 (27.5), 45.6 (23.7) and 27.8 (30.3) for all patients, prior on-demand and prophylaxis patients, respectively, during which the weekly doses were 34.3 (28.6), 21.1 (8.7) and 56.6 (36.19) IU kg\(^{-1}\), respectively.

All 66 patients were included in the PK and safety analyses. One patient was excluded from the efficacy and dose/dose regimen analyses as this patient had 79 bleeds during the study and was a major outlier. This patient already had a high prestudy bleeding frequency (prior ABR of 94) despite prophylaxis.

Dose and dosing interval based on initial PK evaluation

In the initial PK evaluation (N = 66), the FVIII PK profile was best described by a two-compartment PK model for 36 (54.5%) patients and by a one-compartment model for 23 (34.8%) patients. For the remaining seven patients (10.6%), a noncompartment model was used as neither a two- nor a one-compartment
model appeared to be appropriate. There was considerable variation in half-life between patients, with a range of 6.2–31.9 h (Fig. 2). Mean (SD) half-lives were 15.1 (4.7) hours overall, 16.2 (5.3) hours for the two-compartment model, 14.3 (3.1) hours for the one-compartment group, and 12.2 (3.9) hours for the non-compartment group.

Dosing intervals during personalized prophylaxis with Nuwiq® for the 65 patients included in the efficacy analyses are summarized in Table 2. The median dosing interval during personalized prophylaxis was 3.5 days, with 57% of patients on ≤2 weekly dosing. The recommended dosing interval was followed for 96.7% (3572/3695) of actual dosing intervals. The median dosing interval was 3.5 days in the two- and one-compartment model groups and 2.5 days in the noncompartment group (Table 3). The percentage of patients on twice weekly or less frequent dosing was 51% (18/35) in the two-compartment group, 74% (17/23) in the one-compartment group and 29% (2/7) in the noncompartment group (Table 3).

During the last 2 months of personalized prophylaxis, the median weekly prophylaxis dose was reduced by 7.2% to 92.8 IU kg⁻¹ compared with 100.0 IU kg⁻¹ during standard prophylaxis (Table 4). In patients dosed ≤2 weekly, median (IQR) weekly dose during the last 2 months of personalized prophylaxis was 85.0 (73.6, 102.0) IU kg⁻¹ compared with 99.0 (91.0, 114.2) IU kg⁻¹ in patients dosed >2 weekly. The lowest possible median dose that could have been given in the last two months of personalized prophylaxis, based on FVIII:C trough level >1.5% at 2 months and the absence of spontaneous bleeds at 4 months, was 78.3 IU kg⁻¹ in patients with available trough measurements from samples taken within the sampling time window (N = 19). This would have corresponded to a 24% reduction in median dose compared with the first recommended regimen during personalized prophylaxis (102.6 IU) in these 19 patients.

Mean (SD) FVIII trough levels after 2, 4 and 6 months of personalized prophylaxis were 3.4% (4.0) [N = 19], 4.2% (7.0) [N = 24] and 2.7% (2.4) [N = 20], respectively, in patients with available measurements from samples taken within the sampling time window.

**Prevention of bleeds**

During personalized prophylaxis (6.2 months), 73.8% (48/65) of patients had no bleeds and 83.1% (54/65) had no spontaneous bleeds. In the preceding standard

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**Table 1.** Baseline demographic and clinical characteristics.

| Parameter                          | All patients (N = 66) |
|------------------------------------|-----------------------|
| Age (years)                        | 33.6 (9.89)           |
| Height (cm)                        | 177.6 (8.23)          |
| Weight (kg)                        | 80.5 (19.91)          |
| Body mass index (kg m⁻²)           | 25.4 (5.35)           |
| Race, N (%)                        |                       |
| White                              | 65 (98.5)             |
| Black or African American          | 1 (1.5)               |
| Prior FVIII treatment*, N (%)       |                       |
| pdFVIII                            | 49 (74.2)             |
| rFVIII                             | 10 (15.2)             |
| pdFVIII and rFVIII                 | 7 (10.6)              |
| Prior ABR*                         | 38.9 (27.59)          |
| Prior on-demand only treatment (N = 41) | 45.6 (23.71) |
| Prior prophylaxis† treatment (N = 25) | 27.8 (30.33)         |
| Prior weekly FVIII consumption (IU kg⁻¹)*| 34.3 (28.64)|
| Prior on-demand only treatment (N = 39) | 21.1 (8.78) |
| Prior prophylaxis† treatment (N = 23) | 56.6 (36.19) |

ABR, annualized bleeding rate; IU, international units; pdFVIII, plasma-derived FVIII; rFVIII, recombinant FVIII.

Data are expressed as mean (SD) unless otherwise indicated.

*Based on 6 months prior to screening.

†Patients who received at least one dose of (regular or irregular) prophylactic treatment.

‡Data were missing for four patients.

§Data were missing for two patients.

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Fig. 2. Terminal half-lives for Nuwiq® by PK model group. CP, compartment; PK, pharmacokinetic; SD, standard deviation.

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Table 2. Dosing intervals during personalized prophylaxis with Nuwiq<sup>®</sup>.

| Dosing interval, (days) | Frequency (%) | N = 65 | N = 65 |
|------------------------|---------------|--------|--------|
| 2.0                    | 3 (4.6)       | 2 (3.1) |
| 2.3<sup>†</sup>        | 17 (26.2)     | 21 (32.3) |
| 2.5                    | 2 (3.1)       | 0 (0) |
| 3.0                    | 6 (9.2)       | 5 (7.7) |
| 3.5                    | 17 (26.2)     | 21 (32.3) |
| 4.0                    | 14 (21.5)     | 12 (18.5) |
| 4.5                    | 3 (4.6)       | 1 (1.5) |
| Median                 | 3.5           | 3.5    |

<sup>†</sup>Starting treatment scheme in personalized prophylaxis phase.
<sup>‡</sup>Final treatment scheme in personalized prophylaxis phase.
<sup>§</sup>Three times per week.

Table 3. Dosing intervals during personalized prophylaxis with Nuwiq<sup>®</sup> (last planned dosing scheme) by PK model group.

| Dosing interval (Days) | Frequency (%) | All patients N = 65 | 2-CP model N = 35 | 1-CP model N = 23 | Non-CP model N = 7 |
|------------------------|---------------|---------------------|-------------------|------------------|-------------------|
| 2.0                    | 2 (3.1)       | 1 (2.9)             | 1 (4.3)           | 0                |
| 2.3<sup>†</sup>        | 21 (32.3)     | 13 (37.1)           | 3 (13.0)          | 5 (71.4)         |
| 3.0                    | 5 (7.7)       | 5 (8.6)             | 2 (8.7)           | 0                |
| 3.5                    | 21 (32.3)     | 13 (37.1)           | 7 (30.4)          | 1 (14.3)         |
| 4.0                    | 12 (18.5)     | 4 (11.4)            | 8 (34.8)          | 0                |
| 4.5                    | 1 (1.5)       | 0                   | 1 (4.3)           | 0                |
| 5.0                    | 3 (4.6)       | 1 (2.9)             | 1 (4.3)           | 1 (14.3)         |
| Median                 | 3.5           | 3.5                 | 3.5               | 2.3<sup>†</sup>  |

<sup>†</sup>The numerator for the percentage calculation is the number of patients in the group.
<sup>§</sup>Three times per week.

Table 4. Weekly dose of Nuwiq<sup>®</sup> for prophylaxis.

| Treatment period | All patients N = 65 | 2-CP model N = 35 | 1-CP model N = 23 | Non-CP model N = 7 |
|------------------|---------------------|-------------------|------------------|-------------------|
| Standard prophylaxis | 100.0 (91.8, 107.8) | 101.0 (91.8, 108.9) | 97.1 (91.3, 110.1) | 99.0 (89.4, 106.2) |
| Personalized prophylaxis | 95.0 (82.7, 108.9) | 95.0 (85.6, 108.5) | 93.1 (74.3, 104.6) | 111.4 (77.9, 113.9) |
| Months 1 to 4<sup>*</sup> | 97.5 (83.9, 111.0) | 95.9 (85.4, 110.3) | 97.8 (74.6, 111.1) | 109.8 (77.1, 124.8) |
| Months 5 and 6<sup>‡</sup> | 92.8 (79.7, 107.0) | 97.5 (82.8, 104.5) | 85.4 (73.0, 124.4) | 100.5 (79.8, 116.2) |

<sup>CP</sup>, compartment; PK, pharmacokinetic.
<sup>†</sup>The numerator for the percentage calculation is the number of patients in the group.
<sup>§</sup>Three times per week.

and in patients who received ≥2 doses per week (N = 28) were 0 (0, 0) for all bleeds and for spontaneous bleeds.

Treatment of breakthrough bleeds

During the study, 95 breakthrough bleeds (46 during standard prophylaxis and 49 during personalized prophylaxis) occurred in 23 of 65 patients and all were treated with at least one dose of Nuwiq<sup>®</sup>. The median (range) total dose used for the treatment of a bleed was 38.9 (11–617) IU kg<sup>–1</sup> (mean (SD): 63.9 (81.1) IU kg<sup>–1</sup>). The median number of infusions was 1.0 (range 1–18) (mean (SD) 1.7 (2.2)). For 88.4% of bleeds, one or two infusions were sufficient to treat the bleed. Efficacy ratings for the 95 bleeds were excellent or good for 86 bleeds (90.5%), moderate for eight bleeds (8.4%) and none for one bleed (1.1%). All bleeds with a moderate efficacy rating were moderate-to-major in severity. The bleed with the efficacy rating of none was a moderate-to-major traumatic bleed in the left ankle during standard prophylaxis. The patient received eight infusions of Nuwiq<sup>®</sup> (four of 33.3 IU kg<sup>–1</sup>) followed by four of 44.4 IU kg<sup>–1</sup> over six EDs and the bleed resolved without additional treatment. Efficacy ratings for the 49 bleeds during personalized prophylaxis were excellent or good for 45 bleeds (91.8%) and moderate for four bleeds (8.2%).

Surgical prophylaxis

Three patients underwent three major surgical procedures: an appendectomy (3956.5 IU kg<sup>–1</sup>, 76 infusions); a plate osteosynthesis (1425 IU kg<sup>–1</sup>, 43 infusions); and a tenotomy (900.7 IU kg<sup>–1</sup>, 36 infusions). Overall efficacy was rated as excellent for two of the surgeries (plate osteosynthesis and tenotomy) and good for the appendectomy. No intra-operative infusions were required.

Safety

A total of 6612 infusions of Nuwiq<sup>®</sup> were administered to 66 patients. During standard prophylaxis (2.7 months), patients received a mean (SD) of 34.0 (8.2) infusions and a total dose of 1157.6 (307.7)
IU kg$^{-1}$. During the personalized prophylaxis phase (6.2 months), patients received a mean (SD) of 58.8 (15.0) infusions and a total dose of 2574.4 (631.1) IU kg$^{-1}$.

One patient (1.5%) experienced malaise and dizziness after one infusion during standard prophylaxis that were considered treatment related; both events were nonserious and resolved. There were no unexpected or serious adverse drug reactions, no clinically significant abnormalities in laboratory parameters and no cases of thromboembolism. No FVIII inhibitors were detected in any patient at any time during the study.

### Discussion

The NuPreviq study evaluated the efficacy and safety of a patient-tailored personalized prophylaxis approach with Nuwiq$^\circledR$, a 4th generation rFVIII protein produced in a human cell-line and without modification or protein fusion, in adult PTPs with severe haemophilia A. The personalized prophylaxis regimen was based on individual PK modelling for each patient according to whether their PK profile most closely fitted a two-, one- or noncompartment PK model (NuPreviq approach).

The mean ABR for all bleeds during 6-months of personalized prophylaxis was 1.45 (median 0), which compares with a mean ABR of 2.28 (median 0.9) observed in a study of standard prophylaxis with Nuwiq$^\circledR$ in adult PTPs [24]. These results compare favourably with studies with other FVIII products [10,19,35,36] although differences in study designs and patient populations limit direct comparisons between different studies. An ABR of 2.9 (median 1.6) observed in a study evaluating recombinant FVIII-Fc fusion protein (rFVIII-Fc) in an individualized prophylactic regimen in which 67% of patients had ≤2 infusions per week [19], a mean ABR of 1.9 (median 2.0) for PK-tailored prophylaxis with a full-length rFVIII derived from Chinese hamster ovary (CHO) cells [10], a mean ABR of 3.7 (median 1.9) with twice weekly prophylaxis with pegylated full-length rFVIII derived from CHO cells [35], and a mean ABR of 3.27 (median 0) with twice weekly single-chain rFVIII derived from CHO cells [36]. In addition, 73.8% of patients remained bleed-free (83.1% free of spontaneous bleeds) during personalized prophylaxis with Nuwiq$^\circledR$ in the NuPreviq study. This compares with 45% of patients in the rFVIII-Fc study [19], 39.6% of patients treated with full-length pegylated rFVIII [35], and 43% of patients treated with single-chain rFVIII [36], in studies of a similar duration, and 26.5% of patients treated with full-length rFVIII in a 1-year study [10].

Personalized prophylaxis with Nuwiq$^\circledR$ enabled the majority of patients (57%) to increase the dosing interval from three times weekly or every other day during standard prophylaxis to twice weekly or less frequently during personalized prophylaxis. The median dosing interval in the personalized prophylaxis phase was extended to 3.5 days with a decrease in

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Table 5. ABRs during personalized prophylaxis with Nuwiq$^\circledR$.

| Type of bleed          | ABR, mean (SD), median (IQR) [min, max] |
|------------------------|----------------------------------------|
|                        | All patients N = 65 | 2-CP model N = 35 | 1-CP model N = 23 | Non-CP model N = 7 |
| -----------------------|---------------------|-------------------|-------------------|-------------------|
| Standard prophylaxis*  |                     |                   |                   |                   |
| All bleeds             | 3.16 (7.64)         | 4.40 (9.35)       | 1.86 (5.12)       | 1.26 (3.33)       |
|                        | 0 (0, 0) [0, 34.2]  | 0 (0, 4.74) [0, 34.2] | 0 (0, 0) [0, 23.6] | 0 (0, 0) [0, 8.8] |
| Personalized prophylaxis |                   |                   |                   |                   |
| All bleeds             |                     |                   |                   |                   |
| Months 1 to 6          | 1.45 (3.51)         | 1.40 (3.48)       | 1.55 (4.02)       | 1.42 (1.91)       |
|                        | 0 (0, 1.90) [0, 17.5] | 0 (0, 1.97) [0, 17.5] | 0 (0, 0) [0, 15.4] | 0 (0, 3.97) [0, 4.1] |
| Months 1 to 4†         | 1.24 (3.49)         | 1.11 (3.62)       | 1.17 (3.59)       | 2.08 (2.80)       |
|                        | 0 (0, 0) [0, 17.3]  | 0 (0, 0) [0, 17.3] | 0 (0, 0) [0, 15.0] | 0 (0, 5.66) [0, 6.1] |
| Months 5 and 6‡        | 1.81 (4.68)         | 1.92 (4.33)       | 2.20 (5.78)       | 0                 |
|                        | 0 (0, 0) [0, 26.5]  | 0 (0, 0) [0, 18.0] | 0 (0, 0) [0, 26.5] | 0                 |
| Dose frequency ≤2/week§ | 1.32 (3.16)         | 1.53 (2.71)       | 1.02 (3.73)       | 1.99 (2.81)       |
|                        | 0 (0, 0) [0, 15.4]  | 0 (0, 2.01) [0, 9.6] | 0 (0, 0) [0, 15.4] | 1.99 (3.97) [0, 4.0] |
| Dose frequency >2/week¶ | 1.56 (4.00)         | 1.15 (4.24)       | 3.03 (4.78)       | 1.20 (1.81)       |
|                        | 0 (0, 0.95) [0, 17.5] | 0 (0, 0) [0, 17.5] | 1.61 (3.93) [0, 12.2] | 0 (0, 1.90) [0, 4.1] |
| Spontaneous bleeds     | 0.79 (2.31)         | 0.77 (2.49)       | 0.61 (2.17)       | 1.42 (1.91)       |
|                        | 0 (0, 0) [0, 11.7]  | 0 (0, 0) [0, 11.7] | 0 (0, 0) [0, 10.2] | 0 (0, 3.97) [0, 4.1] |
| Traumatic bleeds       | 0.64 (1.91)         | 0.57 (1.15)       | 0.93 (2.90)       | 0                 |
|                        | 0 (0, 0) [0, 13.5]  | 0 (0, 0) [0, 4.2]  | 0 (0, 0) [0, 13.5] | 0                 |
| Joint bleeds           | 0.91 (2.40)         | 0.78 (2.11)       | 0.95 (2.30)       | 1.42 (1.91)       |
|                        | 0 (0, 0) [0, 12.2]  | 0 (0, 0) [0, 7.8]  | 0 (0, 0) [0, 12.2] | 0 (0, 3.97) [0, 4.1] |

ABR, annualized bleeding rate; CP, compartment; IQR, interquartile range; SD, standard deviation.
*ABR during the standard prophylaxis phase prior to the personalized prophylaxis phase.
†One patient was excluded from the analysis (lost to follow-up after 2.9 months of personalized prophylaxis).
‡N = 37 (2-CP [N = 18], 1-CP [N = 17], N-CP [N = 2]).
§N = 28 (2-CP [N = 17], 1-CP [N = 6], N-CP [N = 5]).
NUWIQ® PK-GUIDED PERSONALIZED PROPHYLAXIS

FVIII consumption, which is similar to findings in other trials evaluating individualized prophylaxis with modified rFVIII [19,35,36]. The high FVIII trough levels of 3.4%, 4.2% and 2.7% after 2, 4 and 6 months, respectively, of Nuwiq® treatment, together with the low bleeding rates, support the accuracy of individual PK modelling using the NuPreviq approach to guide prophylaxis and optimize therapy. Moreover, the study confirmed that there is considerable interpatient variation in FVIII half-life with Nuwiq®, which ranged from 6.2 to 31.9 h (mean 15.1 h) and is common across rFVIII products [29,30,32], and provides a strong rationale for the PK-guided personalized prophylaxis. The consistently low bleeding rates during personalized prophylaxis using the NuPreviq approach, irrespective of PK-model group or dosing frequency (≤2 weekly or >2 weekly), supports its use to determine individual dosing regimens for personalized prophylaxis. In the NuPreviq study, blood samples were taken at 10 time points up to 72 h after infusion. However, data indicate that six sampling time points could be used to determine a personalized prophylaxis regimen using the NuPreviq approach [37].

Efficacy was rated as excellent or good for the majority (91.8%) of the bleeds during personalized prophylaxis. Three patients underwent major surgeries, for which efficacy was rated excellent or good. There were no product-related serious or severe adverse events. No FVIII inhibitors were detected in any patient at any time during the study, consistent with other studies of Nuwiq® in PTPs. A study evaluating the immunogenicity of Nuwiq® in 100 previously untreated paediatric patients, who are at the highest risk of inhibitor formation, is ongoing [38].

In conclusion, this study indicates that personalized prophylaxis with Nuwiq®, applying individually appropriate two-, one- or noncompartmental PK models (NuPreviq approach), provided bleeding protection with 73.8% of patients bleed-free and 83.1% spontaneous bleed-free, which to our knowledge are the highest bleed-free percentages published for personalized prophylaxis. In addition, dosing interval was extended to twice weekly infusions or less in 57% of patients and the dose was decreased compared with standard prophylaxis.

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Author contributions

All authors provided input, reviewed and approved the manuscript.

Disclosures

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