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ORIGINAL RESEARCH

# Pharmacokinetic-Pharmacodynamic Comparison of Recombinant and Plasma-Derived von Willebrand Factor in Patients with von Willebrand Disease Type 3

Alexander Bauer[1], Sofia Friberg-Hietala[2], Giovanni Smania[2], Martin Wolfsegger[1]

[1]Statistical and Quantitative Sciences, Baxalta Innovations GmbH, a Takeda Company, Vienna, Austria; [2]Pharmetheus AB, Uppsala, Sweden

Correspondence: Alexander Bauer, Baxalta Innovations GmbH, a Takeda company, Donau-City-Straße 7, Vienna, A-1220, Austria, Tel +43 1 201002472997, Email alexander.bauer@takeda.com



**Background:** Recombinant von Willebrand factor (rVWF, vonicog alfa, Vonvendi/Veyvondi, Takeda Pharmaceuticals USA, Lexington, MA) and several plasma-derived VWF/factor VIII (pdVWF/FVIII) concentrates are available for treating bleeding episodes in patients with von Willebrand disease (VWD).

**Purpose:** To develop population pharmacokinetic (PK)/pharmacodynamic (PD) models that describe VWF:ristocetin cofactor (VWF:RCo) activity and its relationship with FVIII activity (FVIII:C) over time following intravenous administration of either rVWF or a pdVWF/FVIII concentrate (VWF:RCo/FVIII:C 2.4:1) in patients with VWD; to use the final PK/PD models for an in silico comparison of rVWF and pdVWF/FVIII.

**Methods:** The population PK model for rVWF was based on data from four clinical studies in which rVWF was administered to adult patients with VWD type 1, 2 or 3 (phase 1: NCT00816660; phase 3: NCT01410227 and NCT02283268) or severe hemophilia A (phase 1: EudraCT 2011–004314-42). The PK and PK/PD models for pdVWF/FVIII were based on data from the phase 1 study (NCT00816660) in patients with type 3 VWD who received either rVWF plus recombinant FVIII (rFVIII, octocog alfa, ADVATE®, Takeda Pharmaceuticals USA, Lexington, MA, USA) or pdVWF/FVIII.

**Results:** There was a marked difference in clearance following rVWF administration compared with pdVWF/FVIII in type 3 VWD, leading to a ~1.75 longer mean residence time (ie, persistence of VWF:RCo activity in the body) and half-life for rVWF versus pdVWF/FVIII. Simulations showed that following repeated administration of rVWF (50 IU/kg), a FVIII:C activity of >40 IU/dL can be maintained for the full 72 h dosing interval.

**Conclusion:** The slower elimination of VWF:RCo following rVWF administration results in a prolonged effect on FVIII turnover compared with pdVWF/FVIII administration.

**Keywords:** factor VIII, pharmacodynamics, pharmacokinetics, plasma-derived, recombinant, von Willebrand factor

## Introduction

Von Willebrand disease (VWD) is an inherited bleeding disorder characterized by qualitative or quantitative defects in von Willebrand factor (VWF), a large multimeric glycoprotein that mediates platelet adhesion and stabilizes factor VIII (FVIII) in the circulation.[1–4] Recombinant VWF (rVWF, vonicog alfa, Vonvendi® [USA, Japan, Australia] / VEYVONDI™ [EU, UK, Switzerland], Takeda Pharmaceuticals USA, Lexington, MA, USA) has demonstrated efficacy with a favorable safety profile when used for on-demand treatment of hemorrhage and the prevention and treatment of surgical bleeding in adults with VWD.[5–8] The efficacy and safety of prophylaxis with rVWF in patients with severe VWD has also been assessed in a phase 3, open-label, nonrandomized trial.[9] In that study, rVWF reduced the rate of treated, spontaneous bleeding events in patients previously receiving on-demand VWF therapy by 91.5%.[9] Several human plasma-derived VWF (pdVWF)/FVIII concentrates have been approved for the treatment of bleeding episodes in patients with VWD, and their efficacy, safety, and pharmacokinetic (PK) data are published.[10–12] Of these, Haemate P®/Humate-P® (pdFVIII/VWF complex [Human]; CSL Behring GmbH, Marburg,

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Germany: VWF: ristocetin cofactor [RCo]/ factor VIII activity [FVIII:C] 2.4:1) is a widely used pdVWF/FVIII concentrate for the treatment of VWD that is effective in the prevention and control of bleeding in patients with VWD.[12–14]

Intravenous administration of rVWF corrects VWF platelet binding activity (as measured by VWF:RCo), and increases FVIII:C to hemostatically effective levels within 6 hours (h) in most patients.[5,6,8] rVWF replaces VWF without necessarily requiring the coadministration of exogenous FVIII in most of the cases.[15] All currently licensed pdVWF products, except for Wilfactin®/Willfact® (LFB, France), contain FVIII, with a ratio of VWF:RCo/FVIII:C varying from 1.1 to 2.54.[16] As a result, the pdVWF from these products will stabilize both exogenously administered FVIII (if the product contains it), as well as the endogenous FVIII pool. This may result in FVIII accumulation, especially in patients undergoing surgery who have increased levels of FVIII:C postoperatively as part of the physiological response to the procedure.[17,18]

The objective of this work was to develop population PK/pharmacodynamic (PD) models that describe VWF:RCo activity and its relationship with FVIII:C over time following intravenous administration of either rVWF or pdVWF/FVIII (VWF:RCo/FVIII:C 2.4:1) in patients with VWD. Then, use the final PK/PD models for an in silico comparison of rVWF and pdVWF/FVIII. An improved understanding of the PK and PK/PD of these products should help with the individualized treatment of patients with VWD based on PK/PD-guided dosing strategies.

# Methods

## Patients and Data Collection

The population PK model for rVWF was based on four clinical studies in which rVWF was administered in adult patients with VWD type 1, 2 or 3 (phase 1: NCT00816660;[19] phase 3: NCT01410227[6] and NCT02283268)[7] or severe hemophilia A (phase 1: EudraCT 2011–004314-42) (Table 1 and Table 2). Patients who developed inhibitory antibodies to VWF or FVIII (titer ≥0.6 Bethesda units using the Bethesda assay) or were co-administered plasma-derived replacement therapy (treatment with pdVWF/FVIII in NCT00816660)[19] were excluded from the analysis. In addition, observations associated with a bleeding event were excluded. VWF:RCo and FVIII:C were measured before dosing and over various time points up to 120 h after intravenous rVWF infusion. Because patients in the phase 1 studies received concomitant exogenous FVIII concentrates, the population PK/PD model for rVWF was developed using data from the two phase 3 studies. FVIII activity was quantified by the one-stage clotting assay in all studies.

**Table 1** Clinical Studies Contributing Data to the Development of the Population PK/PD Models for rVWF and pdVWF/FVIII

| Study Number | Study Design | Study Population | rVWF Dosage Regimen | Patients with VWF:RCo Observations, n (m)[a,b] | Patients with FVIII Observations, n (m)[a] |
|---|---|---|---|---|---|
| Study 070701, NCT00816660[19] | Phase 1, randomized, single-blind, dose escalation | Severe types 1 and 3 VWD | rVWF:rFVIII at 2–50 IU/kg VWF:RCo | 29 (479) | - |
| Study 071001, NCT01410227[6] | Phase 3, multicenter, open-label, on-demand treatment | Severe types 1, 2A, 2N and 3 VWD | rVWF 50 IU/kg or 80 IU/kg VWF:RCo | 31 (694) | 30 (475) |
| Study 071101, NCT02283268[7] | Phase 3, open-label, uncontrolled, nonrandomized, surgery | Severe types 1, 2A, 2B, 2M, 3 VWD | Dose/frequency of rVWF dependent on type of surgery | 11 (241) | 11 (211) |
| Study 071104, EudraCT 2011–004314-42[c] | Phase 1, uncontrolled, nonrandomized, multicenter, proof of concept | Severe hemophilia A (FVIII activity <1%) | 50 IU/kg rFVIII alone, then in combination with 10 IU/kg rVWF, then in combination with 50 IU/kg rVWF | 10 (250) | - |

**Notes**: [a]n, number of patients; m, number of samples for the rVWF population PK/PD model. [b]Two patients were included in both study NCT00816660 and NCT01410227. These patients were counted once when summing up the total. [c]EudraCT 2011–004314-42 was registered on EudraCT but is not publicly available as it is a phase 1 study. **Abbreviations**: FVIII, factor VIII; PD, pharmacodynamic; PK, pharmacokinetic; rFVIII, recombinant FVIII; rVWF, recombinant von Willebrand factor; VWD, von Willebrand disease; VWF:RCo, von Willebrand factor:ristocetin cofactor.

**Table 2** rVWF Population PK and PK/PD Models: Patient Baseline Characteristics

| | VWF:RCo PK Model Population | FVIII PK/PD Model Population |
|---|---|---|
| No. of patients | 79 | 41 |
| No. of plasma samples | 1664 | 686 |
| rVWF dose range, IU/kg | 2–80 | 5–80 |
| LLOQ, IU/dL | 1 and 8[a] | 1 |
| **Continuous covariates, median (range)** | | |
| Age, years | 35 (18–70) | 36 (18–70) |
| Body weight, kg | 74 (43.8–145) | 72.5 (45–143) |
| Hematocrit, L/L | 0.417 (0.310–0.480) | 0.402 (0.31–0.48) |
| **Categorical variables, n (%)** | | |
| Sex | | |
| Male | 46 (58) | 20 (49) |
| Female | 33 (42) | 21 (51) |
| Race | | |
| White | 73 (92) | 38 (93) |
| Asian | 6 (8) | 3 (7) |
| Disease type | | |
| Type 1 VWD | 5 (6) | 3 (7) |
| Type 2 VWD[b] | 7 (9) | 7 (17) |
| Type 3 VWD | 57 (72) | 31 (76) |
| Severe hemophilia A[c] | 10 (13) | 0 (0) |

**Notes**: [a]The LLOQ for VWF:RCo was 1 IU/dL in study NCT00816660 and 8 IU/dL in studies NCT01410227, NCT02283268, and EudraCT2011-004314-42. [b]VWD type 2A (n=5), type 2B (n=1) and type 2M (n=1). [c]The cohort of patients with hemophilia A was retained for the development of the rVWF population PK model because, after accounting for individual endogenous VWF:RCo levels, no PK differences between the different VWD types and hemophilia A were observed (see PK Model for rVWF results section).
**Abbreviations**: FVIII, factor VIII; LLOQ, lower limit of quantification; PD, pharmacodynamic; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWD, von Willebrand disease; VWF:RCo, von Willebrand factor:ristocetin cofactor.

The population PK and PK/PD models of pdVWF/FVIII were based on data in patients with type 3 VWD from a single cohort (n=22) of a phase 1, dose escalation study (NCT00816660)[19] (Table 1 and Table 2). Patients received single doses of either rVWF and recombinant FVIII (rFVIII; octocog alfa, ADVATE®, 50 IU/kg VWF:RCo/38.5 IU/kg FVIII:C) or pdVWF/FVIII (Humate-P, 50 IU/kg VWF:RCo, VWF:RCo/FVIII:C 2.4:1) in a random, crossover cohort design. VWF:RCo and FVIII:C were measured over various time points up to 96 h following intravenous pdVWF/FVIII infusion.[19] Measurements following administration of rVWF and rFVIII were not included in the analysis. Measurements at screening and at the end of the study (30 days × 24 h from the last infusion) were also excluded due to uncertain dosing history at these times. The lower limit of quantification (LLOQ) for VWF:RCo and FVIII:C was 1 IU/dL for all included observations in study NCT00816660.

## Model Development

PK and PK/PD models were developed for rVWF (full details in the Supplementary Methods and Supplementary Table 1) and then used to develop models for pdVWF/FVIII. Model development and evaluation were performed in accordance with United States Food and Drug Administration and European Medicines Agency guidelines[20,21] and were based on

a prespecified statistical analysis plan. Population models were developed using nonlinear mixed-effects modeling as implemented in NONMEM software (NONMEM® version 7.3.0 or 7.4.0; ICON Development Solutions, Ellicott City, MD, USA).[22] Data assembly and graphical analyses were performed using R version 3.5.3.[23]

The final population PK and PK/PD models for the respective products were used to simulate VWF:RCo or FVIII activity–time profiles following repeated administration of rVWF and pdVWF/FVIII (VWF:RCo/FVIII:C 2.4:1). For this analysis, a typical patient with type 3 VWD was defined as having a body weight of 75 kg and a hematocrit level of 0.4 L/L based on the central tendency of the study population.

# Results

## Population Characteristics

A total of 1664 VWF:RCo samples from 79 patients treated with rVWF in the four clinical studies were available for the PK analysis. Patients treated with rVWF in the two phase 3 VWD studies (n=41) provided 686 FVIII samples for the PK/PD analysis (Table 1). Data from seven patients with antibodies to VWF or FVIII were excluded from the analyses (n=4 binding antibodies to VWF; n=1 inhibitory antibodies to FVIII; n=2 binding antibodies to FVIII IgG). Four VWF:RCo and FVIII:C observations associated with a bleeding event and 308 VWF:RCo and FVIII:C observations collected after the coadministration of plasma-derived therapy were also excluded. The VWF:RCo and FVIII:C analysis populations were heterogenous with respect to demographics and clinical characteristics (Table 2).

A total of 281 samples were available for VWF:RCo and FVIII:C following administration of pdVWF/FVIII to 20 patients. Two patients were excluded from the analysis: one patient had no PK/PD measurements following administration of pdVWF/FVIII and one patient dropped out prior to receiving the pdVWF/FVIII dose. Details of patient baseline characteristics of the pdVWF/FVIII analysis population are shown in Table 3.

**Table 3** pdVWF/FVIII Population PK and PD Models: Patient Baseline Characteristics

| | **VWF:RCo PK Model Population** | **FVIII PK/PD Model Population** |
|---|---|---|
| No. of patients | 20 | 20 |
| No. of samples | 281 | 281 |
| No. of samples >LLOQ | 232 | 281 |
| No. of samples <LLOQ | 49 | 0 |
| **Continuous covariates, median (range)** | **VWF:RCo PK and FVIII PD** | |
| Age, years | 30 (18–60) | |
| Body weight, kg | 66.3 (43.8–132) | |
| Hematocrit, L/L | 0.406 (0.334–0.483) | |
| **Categorical variables, n (%)** | | |
| Sex | | |
| Male | 9 (45) | |
| Female | 11 (55) | |
| Race | | |
| White | 20 (100) | |
| Disease type | | |
| Type 3 VWD | 20 (100) | |

**Abbreviations**: FVIII, factor VIII; LLOQ, lower limit of quantification; PD, pharmacodynamic; pdVWF/FVIII, plasma-derived von Willebrand factor/FVIII; PK, pharmacokinetic; VWD, von Willebrand disease; VWF:RCo, von Willebrand factor:ristocetin cofactor.

## PK Model for rVWF

One- and two-compartment disposition models were evaluated for VWF:RCo PK, accounting for endogenous background in VWF:RCo. The final model was a two-compartment model, parametrized in terms of clearance, intercompartmental clearance, central volume of distribution, and volume of distribution for the peripheral compartment. Parameters were allometrically scaled to body weight. As expected, the volume of the central compartment (anticipated to represent blood volume) decreased with increasing hematocrit. Once the individual endogenous VWF:RCo levels were accounted for, no PK differences were observed between the different VWD types and hemophilia A (Supplementary Results).

## PK/PD Model for rVWF

The population PK/PD model was an indirect response model in which VWF:RCo inhibited FVIII elimination, accounting for the delayed FVIII response in relation to rVWF levels (Supplementary Figures 1 and 2). Model evaluation demonstrated that there was good agreement between individual model predictions and observations of VWF:RCo and FVIII:C data after rVWF doses (Figure 1).

The simulated VWF:RCo and FVIII activities following a single rVWF dose of 50 IU/kg and following repeated administration every 72 h, stratified by VWD type, are shown in Figure 2A and B. Summary measures of FVIII exposure were computed from the simulated profiles in terms of area under the activity–time curve during the dosing interval ($AUC_{72}$) and maximum activity ($C_{max}$) after a single dose and at steady state, and their relationship with VWF:RCo clearance is shown in Figure 2C and D. The simulations at steady state indicated that the median FVIII:C in patients with type 3 VWD was between 40 and 100 IU/dL, and that at least 80% and 97.5% of the treated population would achieve maximal FVIII plasma levels below 150 and 250 IU/dL, respectively.

## PK Model for pdVWF/FVIII

The starting point for the population PK model of pdVWF/FVIII was the PK model developed for rVWF; detailed results of the PK modeling for pdVWF/FVIII are provided in the Supplementary Results. Goodness-of-fit plots demonstrated that the model for pdVWF/FVIII adequately predicted the observed VWF:RCo (Figure 3A), and FVIII:C (Figure 3B), respectively. Subsequently, there is no indication of a marked model misspecification in these plots.

The primary PK parameter estimates for the pdVWF/FVIII model are presented alongside estimates for the rVWF model in Table 4. There was a marked difference in clearance between the rVWF model and pdVWF/FVIII model (2.10 dL/h vs 4.14 dL/h, respectively), which led to a 1.76 longer mean residence time (MRT, which represents the persistence

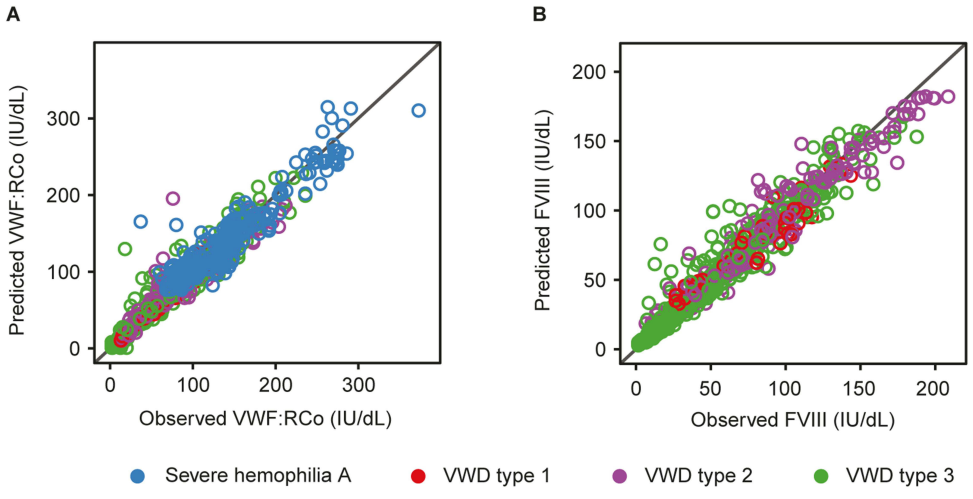
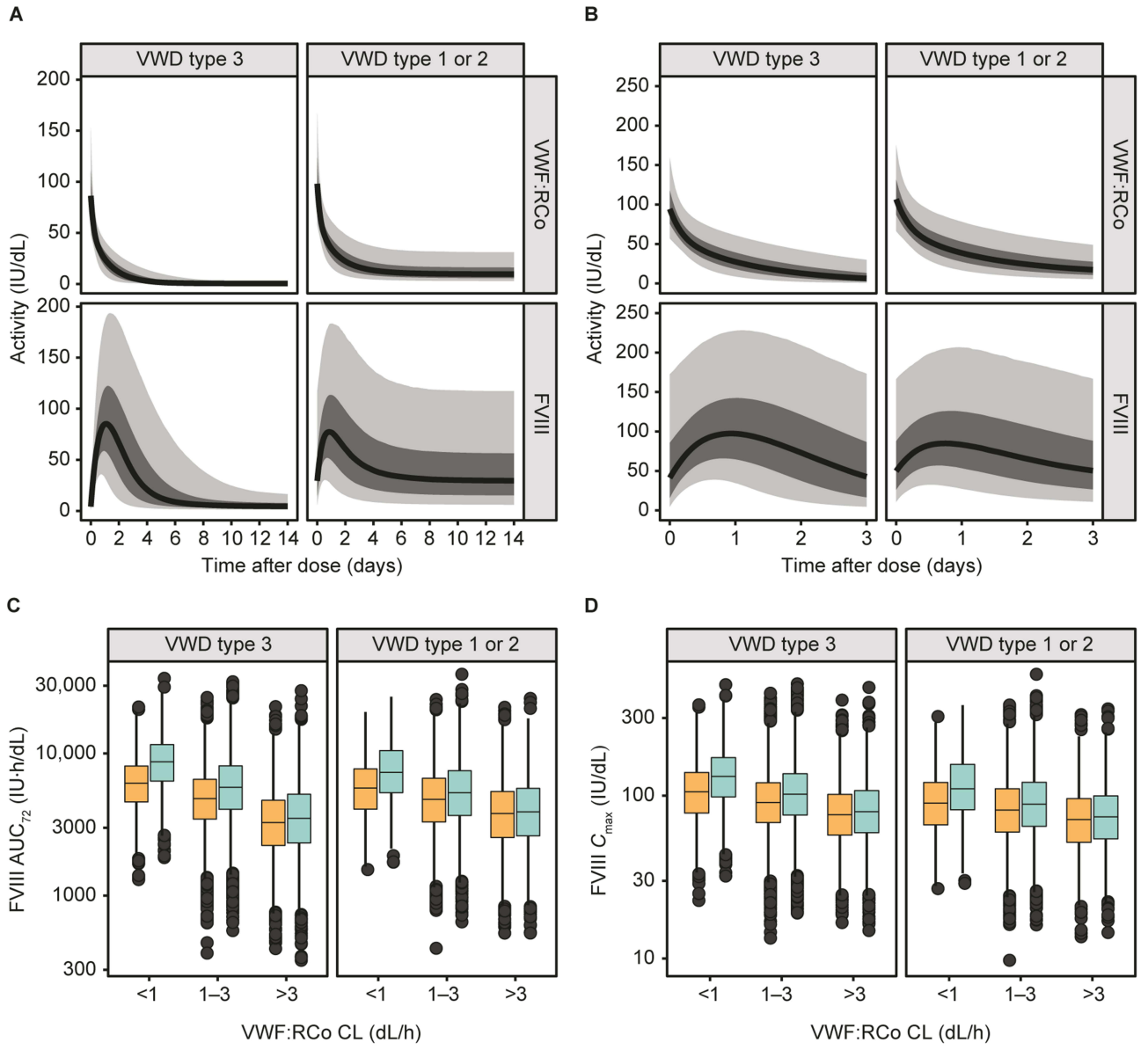



**Figure 1** Goodness-of-fit plots for the final population PK and PK/PD models of rVWF. Observed versus individual predictions are shown for (**A**) VWF:RCo and (**B**) FVIII:C data, colored by disease type. The diagonal line depicts the line of identity.

**Abbreviations**: FVIII, factor VIII; FVIII:C, FVIII activity; PD, pharmacodynamic; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor; VWD, von Willebrand disease.




| | VWD type 3 | | | VWD type 1 or 2 | | |
|---|---|---|---|---|---|---|
| VWF:RCo CL, dL/h | <1 | 1–3 | >3 | <1 | 1–3 | >3 |
| Number of simulated profiles | 1545 | 23,246 | 6209 | 400 | 7206 | 2394 |
| Median $AUC_{72}$ (95% PI), IU·h/dL | | | | | | |
| Single dose | 6182 (2604–13,374) | 4811 (1728–11,413) | 3266 (1049–8955) | 5715 (2194–14,347) | 4754 (1618–12,194) | 3781 (1204–10,309) |
| Steady state | 8738 (3391–19,512) | 5780 (1867–14,879) | 3494 (1076–10,123) | 7360 (2542–17,588) | 5296 (1713–13,820) | 3880 (1226–10,698) |
| Median $C_{max}$(95% PI), IU/dL | | | | | | |
| Single dose | 105 (45–226) | 91 (39–201) | 76 (33–173) | 90 (38–214) | 82 (33–189) | 71 (28–167) |
| Steady state | 131 (56–279) | 102 (42–230) | 80 (34–183) | 110 (45–261) | 89 (35–211) | 74 (30–172) |

**Figure 2** PK/PD model simulations of VWF:RCo and FVIII:C activity following rVWF dosing by VWD type. Simulated VWF:RCo and FVIII activity–time profiles following (**A**) a single rVWF dose of 50 IU/kg and (**B**) at steady state after dosing every 72 h. The solid line depicts the median simulated profile, and the dark and light shaded areas represent the 60% and 95% PIs, respectively. The distribution of (**C**) simulated FVIII $AUC_{72}$ and (**D**) $C_{max}$ after a single dose (orange) and at steady state (turquoise) for different ranges of VWF:RCo clearance (the y-axis is displayed in a logarithmic scale); summary statistics for $AUC_{72}$ and $C_{max}$ are reported in the table.

**Abbreviations**: $AUC_{72}$, area under the activity–time curve during the dosing interval; CL, clearance; $C_{max}$, maximum activity; FVIII, factor VIII; FVIII:C, FVIII activity; PI, prediction interval; PD, pharmacodynamic; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor; VWD, von Willebrand disease.

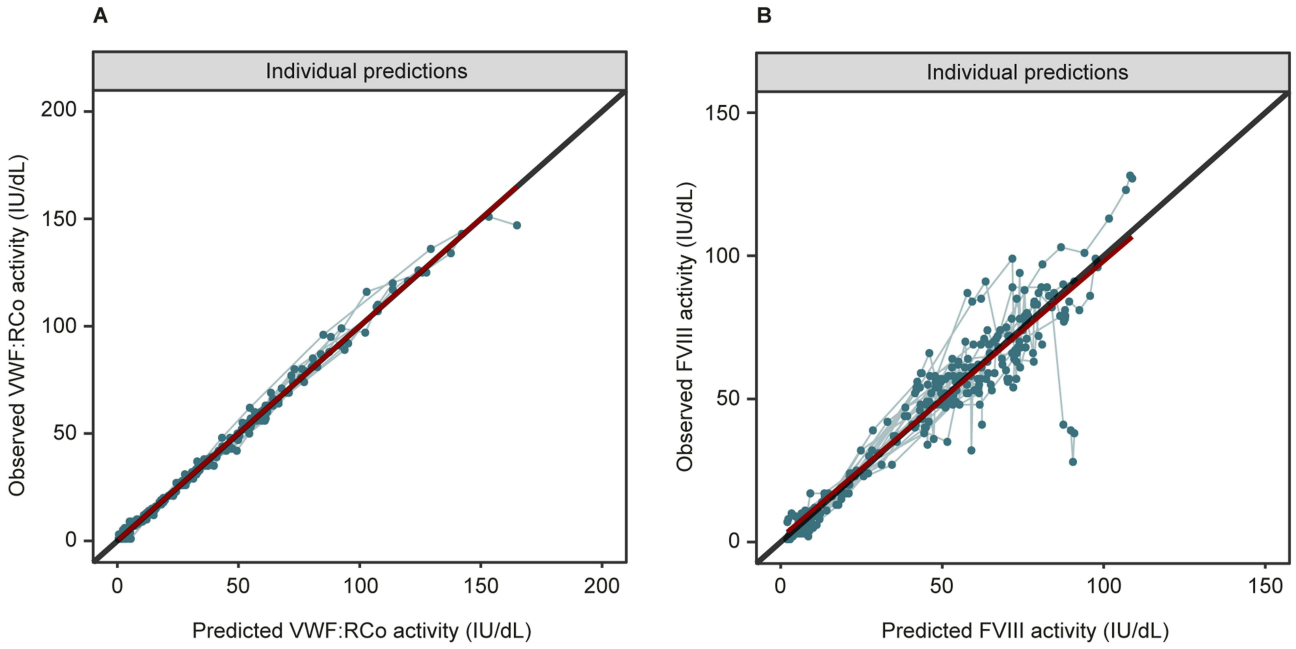



**Figure 3** Goodness-of-fit plots for the final population PK and PK/PD models for pdVWF/FVIII. Observed versus individual predictions for (**A**) VWF:RCo and (**B**) FVIII:C data. Individual data points are indicated by dots and the points for each individual are connected with a line. The black diagonal line depicts the line of identity. The red smooth (gam) lines are close to this line indicating that no bias is present. Values below the limit of quantification are not included in the plots.
**Abbreviations**: FVIII, factor VIII; FVIII:C, FVIII activity; PD, pharmacodynamic; pdVWF/FVIII, plasma-derived von Willebrand factor/FVIII; PK, pharmacokinetic; VWF:RCo, von Willebrand factor:ristocetin cofactor.

of VWF:RCo activity in the body) and 1.74 times longer half-life ($t_{½}$) for rVWF than for pdVWF/FVIII. The VWF:RCo $AUC_{0\text{-inf}}$ was estimated to be 1.97 times greater following rVWF administration than after pdVWF/FVIII.

The estimated interindividual variability (IIV) in VWF:RCo clearance following pdVWF/FVIII administration was 23.5% versus 40.1% following rVWF administration. There was considerable uncertainty in the estimated IIV for the pdVWF/FVIII model, with a relative standard error of 38.3% versus 9.9% for the rVWF model.

## PK/PD Model for pdVWF/FVIII

The starting point for the population PK/PD model of pdVWF/FVIII was the indirect response model developed for rVWF; additional details are provided in the Supplementary Results. Parameter estimates of the final PK/PD model are shown in Table 4. Estimated maximum inhibition ($I_{max}$) values were similar in both the rVWF and pdVWF/FVIII models, but activity level at half maximum inhibition ($IC_{50}$) was lower in the pdVWF/FVIII model than in the rVWF model (0.0577 IU/dL vs 0.0658 IU/dL). A volume of distribution term for FVIII (FVIII V) was added to account for the distribution of the pdFVIII dose. The FVIII V was estimated to be 32.9 dL, which is in line with a previous report (32.8 dL).[24]

## PK and PK/PD Model Simulations

PK/PD model simulations of the typical VWF:RCo and FVIII:C profiles following repeated administration of rVWF 50 IU/kg or pdVWF/FVIII 50 IU/kg every 72 h are shown in Figure 4A. There was a modest accumulation of VWF:RCo and FVIII:C with both treatments. The simulations suggest that a FVIII:C above 40 IU/dL can be maintained for the full 72 h dosing interval for a typical patient at this dose of rVWF, in line with recommendations from the European Medicines Agency.[25]

Additional simulations with an irregular dosing interval of 72 h and 96 h are shown in Figure 4B, reflecting how prophylactic rVWF treatment of patients with VWD could be administered in clinical practice. FVIII activity–time profiles for rVWF followed a similar trend as that for regular dosing (interval of 72 h), and as expected, only trough levels in the 96 h interval were below 40 IU/dL (unlike in hemophilia A,[26] FVIII trough levels are not well established in

**Table 4** Parameter Estimates of the Population PK (VWF:RCo) and PK/PD (FVIII) Models

| Parameter | rVWF Model | | pdVWF/FVIII Model | |
|---|---|---|---|---|
| | Point Estimate | RSE (%)[a] | Point Estimate | RSE (%) |
| **VWF:RCo PK model** | | | | |
| CL, dL/h | 2.10 | 8.10 | 4.14 | 12.7 |
| $V_c$, dL | 43.5 | 4.98 | 47.0 | 16.7 |
| Q, dL/h | 2.29 | 12.2 | 4.47 | 12.3 |
| $V_p$, dL | 15.8 | 4.47 | 19.3 | 3.12 |
| $E_{VWF}$, VWD type 3, IU/dL | 0.500 | (FIX) | 0.500 | (FIX) |
| WT effect on CL and Q | 0.750 | (FIX) | 0.750 | (FIX) |
| WT effect on $V_c$ and $V_p$ | 1.00 | (FIX) | 1.00 | (FIX) |
| Hematocrit effect on $V_c$ | −0.334 | 37.5 | −0.334 | (FIX) |
| IIV CL, CV[b] | 0.401 | 9.88 | 0.235 | 38.3 |
| IIV $V_c$, CV[b] | 0.292 | 10.7 | 0.373 | 51.7 |
| Proportional RUV, CV[b] | 0.138 | 1.26 | 0.0479 | 14.1 |
| Additive RUV, IU/dL[b] | 2.80 | 2.08 | 1.48 | 12.4 |
| **FVIII PK/PD model** | | | | |
| Baseline FVIII, IU/dL[c,d] | 0.500 | – | 0.500 | (FIX) |
| $k_{out}$, $h^{-1}$ [c] | 15.9 | – | 15.9 | (FIX) |
| $I_{max}$ | 0.998 | – | 0.994 | 0.0378 |
| $IC_{50}$, IU/dL | 0.0658 | – | 0.0577 | 20.4 |
| Hematocrit effect on baseline FVIII | −0.571 | – | −0.571 | (FIX) |
| FVIII V, dL | – | – | 32.9 | 1.65 |
| IIV baseline FVIII, CV | 0.296 | – | 0.215 | 44.4 |
| IIV $IC_{50}$, CV | 0.588 | – | 0.542 | 29.4 |
| Proportional RUV, CV | 0.190 | – | 0.172 | 2.50 |
| Additive RUV, IU/dL | 1.55 | – | 2.91 | 15.5 |

**Notes**: [a]The precision in parameter estimates for the rVWF PK/PD model was estimated using a bootstrap method, which showed that the population estimates of the final model were within the 2.5th to 97.5th percentile obtained from the bootstrap analysis (data not shown). [b]RSE reported on the approximate standard deviation scale. [c]Parameter was fixed in the pdVWF/FVIII model. [d]The estimated baseline FVIII:C represents the theoretical baseline FVIII:C assuming that no VWF is affecting $k_{out}$.

**Abbreviations**: CL, clearance; CV, coefficient of variation; $E_{VWF}$, endogenous von Willebrand factor; FVIII, factor VIII; FVIII:C, FVIII activity; $IC_{50}$, activity level at half maximum inhibition; IIV, interindividual variability; $I_{max}$, maximum inhibition; $k_{out}$, first-order removal; PD, pharmacodynamic; pdVWF/FVIII, plasma-derived von Willebrand factor/FVIII; PK, pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; RUV, residual unexplained variability; rVWF, recombinant von Willebrand factor; $V_c$, central volume of distribution; $V_p$, peripheral volume of distribution; FVIII V, volume of distribution for FVIII; VWD, von Willebrand disease; VWF:RCo, von Willebrand factor:ristocetin cofactor; WT, weight.

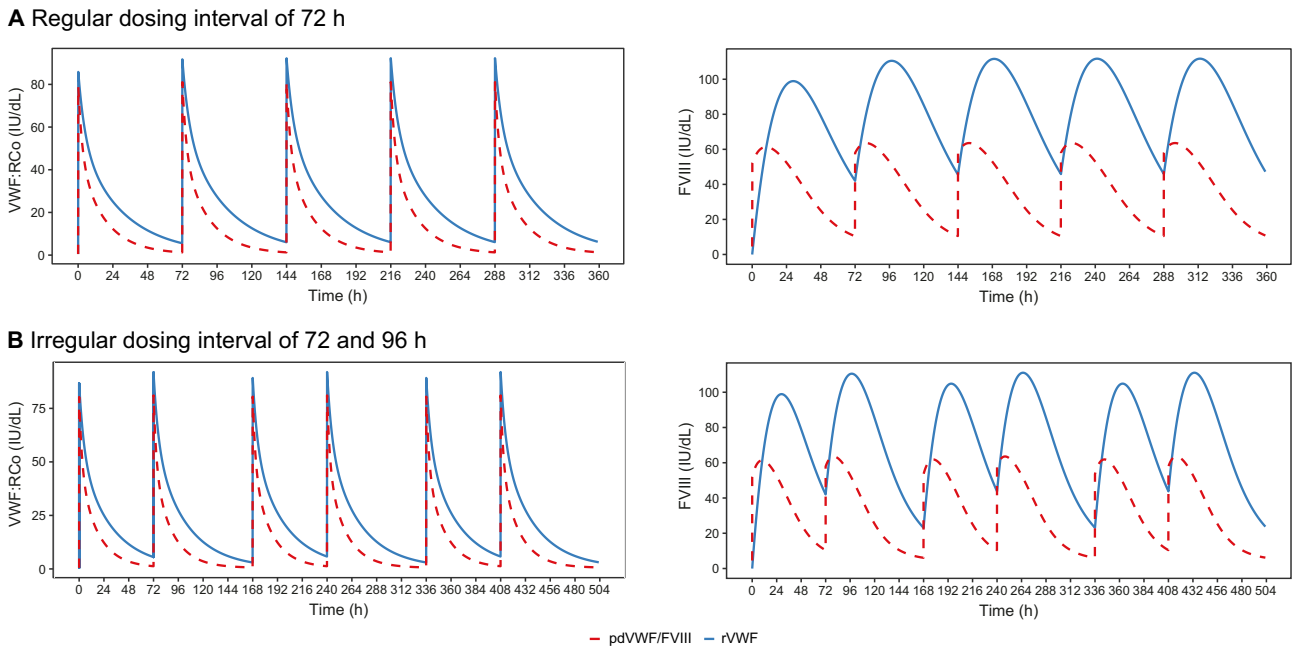



**Figure 4** PK/PD model simulations of VWF:RCo and FVIII activity following repeated administration of rVWF 50 IU/kg (blue line) or pdVWF/FVIII 50 IU/kg (VWF:RCo/FVIII:C 2.4:1, red dashed line) at (**A**) regular and (**B**) irregular dosing intervals in a 75 kg individual with a hematocrit of 0.4 L/L.
**Abbreviations**: FVIII, factor VIII; PD, pharmacodynamic; pdVWF/FVIII, plasma-derived von Willebrand factor/FVIII; PK, pharmacokinetic; rVWF, recombinant von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor.

VWD). The ratio of the elimination FVIII $t_{½}$ for rVWF treatment to the FVIII $t_{½}$ for pdVWF/FVIII ranged from 2.4 to 3.8 during a dosing interval of 72 h, demonstrating a marked difference in the impact on FVIII:C between the two products (Figure 5A and B).

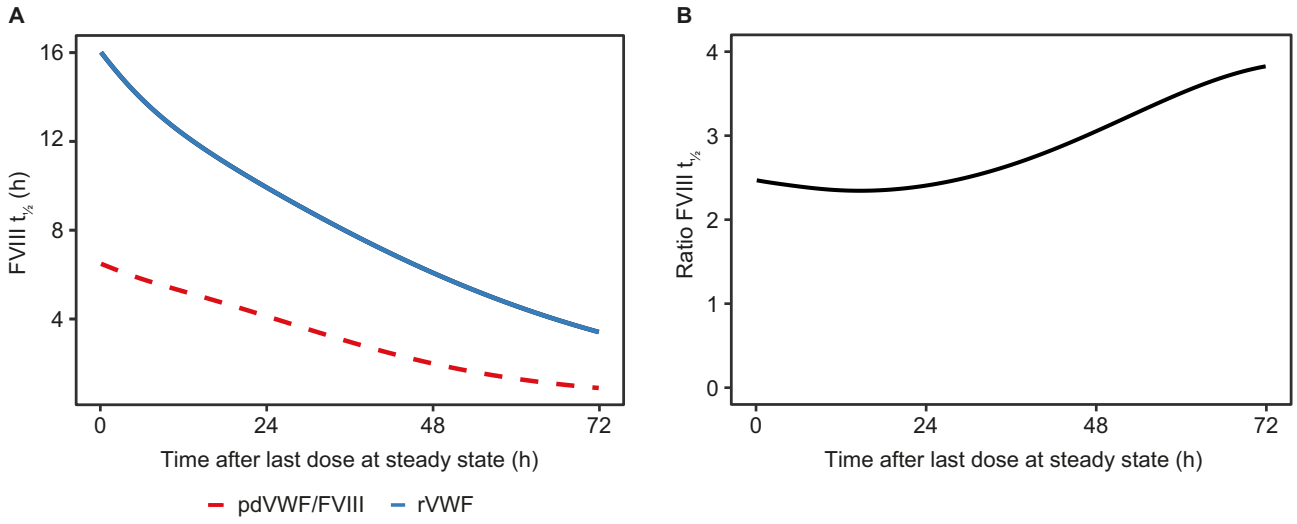



**Figure 5** Model predicted (**A**) FVIII $t_{½}$ and (**B**) ratio of FVIII $t_{½}$ for rVWF to FVIII $t_{½}$ for pdVWF/FVIII during a dosing interval at steady state following repeated administration of rVWF 50 IU/kg (blue line in A) or pdVWF/FVIII 50 IU/kg (VWF:RCo/FVIII:C 2.4:1; red dashed line in A) every 72 h to a 75 kg individual with a hematocrit of 0.4 L/L.
**Abbreviations**: FVIII, factor VIII; FVIII:C, FVIII activity; pdVWF/FVIII, plasma-derived von Willebrand factor/FVIII; rVWF, recombinant von Willebrand factor; $t_{½}$, half-life; VWF, von Willebrand factor; VWF:RCo, von Willebrand factor:ristocetin cofactor.

## Discussion

A personalized approach to the management of VWD has several benefits, as previously discussed.[27,28] A population PK/PD model in which individual PK data can be more easily considered when making dosage recommendations in VWD is important to facilitate this approach. The population PK and PK/PD models for rVWF developed in this study predict VWF:RCo and FVIII activity over time in patients with severe VWD type 1, 2 and 3 treated with rVWF. Patients with VWD type 3 have a total or near-total absence of VWF in the circulation, while patients with severe VWD types 1 and 2 have reduced VWF in the circulation.[1,29] The population PK and PK/PD models developed for rVWF were refined to fit pdVWF/FVIII (VWF:RCo/FVIII:C 2.4:1) data for a similar VWD type 3 patient population. The population PK for VWF:RCo following a single dose of rVWF or pdVWF/FVIII was adequately described by a two-compartment disposition model with first-order elimination from the central compartment (Supplementary Figure 1). This type of modeling is often used in PK analyses to represent the distribution of a drug in the body occurring between two compartments: a central compartment (commonly representing blood and well-perfused organs), and a peripheral compartment (commonly representing poorly perfused tissues).[30] Our findings demonstrated a slower clearance of VWF:RCo following rVWF compared with pdVWF/FVIII as indicated by longer MRT and $t_{½}$ values and a larger VWF:RCo $AUC_{0\text{-inf}}$ with rVWF; this results in a prolonged effect on FVIII turnover with rVWF compared with pdVWF/FVIII.

Several published studies have investigated the population PK of pdVWF.[17,24,31] However, these studies did not quantify the PK/PD relationship in a formal model. The current model-based analysis is in good agreement with the findings of an exploratory noncompartmental analysis,[32] which was based on the observed VWF:RCo exposure data from patients with severe VWD who were administered rVWF in phase 1 (NCT00816660)[19] and phase 3 on-demand (NCT01410227)[6] studies. That exploratory noncompartmental analysis also showed longer MRT and $t_{½}$ values and a larger $AUC_{0\text{-inf}}$ for rVWF versus pdVWF/FVIII with respect to VWF:RCo.[32] A longer $t_{½}$ and larger $AUC_{0\text{-inf}}$ of VWF:RCo following rVWF could potentially allow for lower doses and fewer infusions. In a recent multicenter, retrospective study conducted in France in patients with VWD who underwent surgery, a low number of infusions and low doses of rVWF (median [range] total dose: major surgery, 108 [22–340] rVWF IU/kg; minor surgery 37 [12–288] rVWF IU/kg) provided effective prevention of bleeding in major and minor surgeries.[33] Our results also suggest that rVWF can be administered without FVIII in most patients receiving surgery. In some cases where the FVIII:C level is <40 IU/dL, it may be necessary to administer a rFVIII product to achieve a hemostatic plasma level of FVIII:C.[5,8]

The present results suggest a greater stabilization of endogenous FVIII due to slower elimination of VWF:RCo following rVWF administration compared with pdVWF/FVIII. This is in line with VWF acting as a chaperone for FVIII and protecting it from rapid clearance.[1] The longer FVIII $t_{½}$ following rVWF administration compared with pdVWF/FVIII might relate to differences in the VWF multimer profile of the two products. rVWF has a nonproteolytically degraded VWF multimer structure at administration and includes the most hemostatically active ultra-large multimers, which are not present in pdVWF/FVIII concentrates due to exposure to ADAMTS13 during manufacture.[34] pdVWF products contain a number of plasma-derived extraneous proteins, some including human albumin, that might lower their specific activity.[34]

Because patients with type 3 VWD have a total or near-total absence of VWF, they are at an increased risk of bleeding, which can be life-threatening or lead to long-term complications.[1,29] International management guidelines for VWD conditionally recommend long-term prophylaxis in patients with VWD and a history of severe and frequent bleeds.[29] We investigated VWF:RCo and FVIII:C profiles relevant to a prophylactic dosing regimen (ie, every 72 or 96 h). Simulations showed that following repeated administration of rVWF 50 IU/kg, FVIII:C >40 IU/dL can be maintained for the full 72 h between dosing, consistent with recommendations from the EMA.[25] Also based on the simulations in our study, a dosing schedule with an interval of 72 or 72/96 h could be a suitable option for prophylaxis in line with previous studies that demonstrate the potential for prophylaxis to help reduce bleed rates.[35–38]

Several studies have demonstrated that repeated dosing of pdVWF/FVIII concentrates with a VWF:RCo/FVIII:C ratio of >1, results in less FVIII accumulation if VWF concentrate dosing is based only on VWF levels.[39,40] However, FVIII accumulation has been observed after perioperative treatment with pdVWF/FVIII complex (human,

VWF:RCo/FVIII:C 2.4:1).[41] In this work, simulations of the VWF:RCo and FVIII:C profiles following repeated administration of rVWF 50 IU/kg or pdVWF/FVIII 50 IU/kg (2.4:1 VWF/FVIII ratio) with either regular or irregular dosing intervals did not indicate marked FVIII accumulation. The aim of the simulations was to mimic VWF prophylaxis treatment regimens of approximately twice-weekly administration. More frequent dosing, such as during surgery, might increase the risk of factor VIII accumulation.[42]

A study limitation was that the PK/PD comparison of rVWF and pdVWF/FVIII was based on a single pdVWF/FVIII (Humate-P, VWF:RCo/FVIII:C 2.4:1), so the study findings may not be applicable to other pdVWF concentrates with FVIII or to Wilfactin/Willfact (LFB, Les Ulis, France), which contains very little FVIII.[43] In addition, an in silico analysis of PK and PK/PD cannot fully reproduce in vivo interactions and due to the small number of patients in the current study, a formal covariate analysis was not possible for the pdVWF/FVIII PK model. However, given the mechanistic plausibility of the covariates identified for the rVWF model (body weight and hematocrit), these were applied also for the pdVWF/FVIII model.

## Conclusion

The population PK and PK/PD models reported herein allowed for the in silico comparison of rVWF and pdVWF/FVIII with respect to the relationship between VWF:RCo and FVIII:C following administration of either product. The slower elimination of VWF:RCo following rVWF administration results in a prolonged effect on FVIII turnover compared with pdVWF/FVIII. The improved understanding of the PK and PK/PD of these products should help with the individualized treatment of patients with VWD based on PK/PD-guided dosing strategies.

## Abbreviations

$AUC_{72}$, area under the activity–time curve during the dosing interval; $C_{max}$, maximum activity; FVIII, factor VIII; FVIII:C, FVIII activity; FVIII V, volume of distribution for FVIII; $IC_{50}$, activity level at half maximum inhibition; $I_{max}$, maximum inhibition; IIV, interindividual variability; LLOQ, lower limit of quantification; MRT, mean residence time; PD, pharmacodynamic; pdFVIII, plasma-derived FVIII; pdVWF, plasma-derived VWF; PK, pharmacokinetic; RCo, ristocetin cofactor; rFVIII, recombinant FVIII; rVWF, recombinant VWF; $t_{½}$, half-life; VWD, von Willebrand disease; VWF, von Willebrand factor.

## Data Sharing Statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization. Requests should be sent to the corresponding author, Alexander Bauer.

## Ethics Approval and Informed Consent

All trials contributing data for the research reported herein were approved by the respective institutional review boards or independent ethics committees at all participating sites (Supplementary Table 2), and patients provided written informed consent. The trials were conducted in accordance with the Declaration of Helsinki.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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