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SHP656, a polysialylated recombinant factor VIII (PSA-rFVIII): First-in-human study evaluating safety, tolerability and pharmacokinetics in patients with severe haemophilia A

Andreas Tiede[1] [ID] | Geoffrey Allen[2] [ID] | Alexander Bauer[3] | Pratima Chowdary[4] [ID] | Peter Collins[5] | Brahm Goldstein[2] | Hongyu Jeanne Jiang[2] | Kathleen Köck[6] | István Takács[7] | Margarita Timofeeva[8] | Martin Wolfsegger[3] | Shouryadeep Srivastava[2]

[1]Hannover Medical School, Hannover, Germany

[2]Baxalta US Inc, a member of the Takeda group of companies, Cambridge, MA, USA

[3]Baxalta Innovations GmbH, a member of the Takeda group of companies, Vienna, Austria

[4]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK

[5]Institute of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK

[6]IQVIA, Overland Park, KS, USA

[7]Semmelweis University, Budapest, Hungary

[8]Federal State Budgetary Institution of Science "Kirov Scientific and Research Institute of Hematology and Blood Transfusion of Federal Medico-Biological Agency", Kirov, Russian Federation

Correspondence
Geoffrey Allen, Takeda Pharmaceutical Company Limited, 650 E. Kendall Street, Cambridge, MA 02142, USA.
Email: geoffrey.allen@takeda.com

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Abstract

Introduction: SHP656 is the first factor VIII (FVIII) product developed using polysialylation (PSA) technology, in which full-length recombinant (r) FVIII (anti-haemophilic factor [recombinant]) is conjugated with a 20 kDa PSA polymer.

Aim: To compare the safety, immunogenicity and pharmacokinetics of SHP656 vs the parent rFVIII (octocog alfa) after single infusions of 25-75 IU/kg in patients with severe haemophilia A (FVIII activity <1%).

Methods: Multinational, phase 1, prospective, open-label, two-period, fixed-sequence, dose-escalation trial (clinicaltrials.gov NCT02716194). Patients received single doses of rFVIII and then SHP656 sequentially at the same dose: 25 ± 3 IU/kg (Cohort 1), 50 ± 5 IU/kg (Cohort 2) and 75 ± 5 IU/kg (Cohort 3).

Results: Forty patients received rFVIII: 11 in Cohort 1, 16 in Cohort 2 and 13 in Cohort 3. Two patients withdrew before receiving SHP656, leaving 38 patients who completed the study and received both treatments. No treatment-related adverse events (AEs), serious AEs, deaths, study withdrawals, thrombotic events or allergic reactions were reported; and no significant treatment-related changes in laboratory parameters or vital signs. No patients developed FVIII inhibitors or antibodies to PSA. FVIII activity was significantly prolonged following SHP656 administration vs rFVIII with an approximately 1.5-fold extension in mean residence time ($P < .05$). Exposure increased proportional to the SHP656 dose over the 25-75 IU/kg dose range.

Conclusion: Polysialylation of rFVIII confers a half-life extension similar to that of approved extended half-life products that use either PEGylation or Fc fusion technology and was not associated with any treatment-related adverse events.

KEYWORDS
haemophilia A, pharmacokinetics, polysialic acid, recombinant FVIII, safety, tolerability

1 | INTRODUCTION

Haemophilia A is an inherited disorder characterized by a deficiency of functional factor VIII (FVIII) leading to uncontrolled bleeding.[1] Patients with severe haemophilia A (FVIII activity levels <1%) may experience frequent spontaneous bleeds into joints that can lead to serious arthropathy.[1] The goal of therapy for many patients is to avoid bleeding episodes and thereby preserve joints using regular (prophylactic) intravenous infusions of exogenous FVIII.[2] During prophylaxis, the time spent at a FVIII activity level of <1% was correlated with the annual bleeding rate.[3] Therefore, the goal of prophylaxis is to maintain FVIII activity levels greater than at least 1%.[4]

Traditional FVIII products typically require infusions three times weekly or every other day[5]; newer preparations with extended half-lives may permit less frequent infusion and therefore benefit patients and caregivers. Manufacturers have investigated several mechanisms to extend FVIII activity half-life in vivo, including the use of Fc fusion protein[6,7] and PEGylation (PEG).[8-11] These approaches have resulted in approximately 1.4 to 1.5-fold extensions in half-life,[12] making twice-weekly prophylactic dosing a realistic option for many patients, as seen with ADYNOVATE® (rurioctocog alfa pegol; ADYNOVI™, Baxalta US Inc, a Takeda company)[10] and ELOCTATE® (Fc-rFVIII; Antihemophilic Factor [Recombinant], Fc Fusion Protein, Bioverativ Therapeutics).[7] However, there remains a need for a FVIII product with more convenient dosing (such as once weekly or less frequent), which could improve the adherence to treatment in this patient population.[13]

To address this need, we investigated another approach to the extension of FVIII half-life using polysialylation. Polysialic acids (PSAs) have been successfully utilized in other therapeutic areas to prolong half-life, improve stability and reduce renal excretion.[14,15] SHP656 (Baxalta US Inc, a Takeda company), formerly known as BAX 826, is the first FVIII product to be developed using polysialylation technology, in which full-length recombinant FVIII (rFVIII) (octocog alfa; anti-haemophilic factor [recombinant]; ADVATE®, Baxalta US Inc, a Takeda company) is conjugated with a 20 kDa PSA polymer, using polysialylation methods developed in conjunction with Xenetic Biosciences, Inc. In preclinical studies, the new compound achieved 2-3-fold greater extension of mean residence time (MRT) than the parent compound, rFVIII.[16]

Based on these promising pharmacokinetic (PK) characteristics, and evidence of a potentially improved immunogenicity profile of SHP656 compared to ADYNOVATE,[17] we conducted this first-in-human study evaluating the safety, tolerability and PKs of SHP656 in patients with severe haemophilia A.

2 | METHODS

This study was performed in accordance with Good Clinical Practice and ethical principles consistent with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT02716194). The study protocol, consent forms and all amendments were approved by all relevant ethics committees, and written informed consent was obtained from all patients prior to enrolment.

2.1 | Patient population

The study enrolled adult males (aged 18-65 years) with severe haemophilia (FVIII activity <1% at prior diagnosis or confirmed at screening). Patients were previously treated with FVIII concentrates for ≥150 exposure days; human immunodeficiency virus-negative, or with stable disease and CD4 + cell counts ≥200 cells/mm^3; and hepatitis C virus-negative, or positive with chronic stable disease as assessed by the investigator, and had Karnofsky Performance[18] scores ≥60. Potential patients were excluded if they had detectable FVIII inhibitors (titre ≥0.6 Bethesda units [BU] by Nijmegen-Bethesda assay[19] performed by a central laboratory at screening) or a history of FVIII inhibitors at any time with a titre ≥0.4 BU (Nijmegen-Bethesda assay) or ≥0.6 BU (Bethesda assay).[20] Exclusion criteria also included severe chronic renal (serum creatinine >2.0 mg/dL) or hepatic impairment (alanine aminotransferase ≥5 × the upper limit of normal or international normalized ratio >1.5) and the presence of any other inherited or acquired bleeding disorder.

2.2 | Study design

This was a multinational, phase 1, prospective, open-label, two-period, fixed-sequence, dose-escalation trial to evaluate the safety and PK of SHP656 compared with unmodified rFVIII in patients with severe haemophilia A (FVIII activity <1%). The study was conducted at 20 sites in the European Union and Russia. Patients underwent a 30-day screening period followed by a minimum 4-day washout, after which they were divided into three cohorts (Figure 1). Cohort 1 received a single dose of rFVIII (25 ± 3 IU/kg) followed by 3 days of PK sampling. Following a minimum 4-day washout, patients then received the same dose of SHP656 (25 ± 3 IU/kg) followed by a 7-day PK evaluation. SHP656 was administered to the first three patients with a minimum 24-hour staggered interval to allow in-hospital safety observation for 24 hours; subsequent infusions were dependent on confirmation of safety in these three patients. After data from Cohort 1 had been reviewed and approved by the funder's internal safety monitoring committee, this sequential dose comparison was repeated with single doses of rFVIII and then SHP656 at 50 ± 5 IU/kg in Cohort 2. After review of results from Cohort 2, Cohort 3 received 75 ± 5 IU/kg rFVIII and then SHP656. For all patients, safety assessments were performed at days −1 (admission), 1, 4, 8, 14 and at 6 weeks post-SHP656 infusion. Immunogenicity evaluations were carried out at screening, prior to infusion during each study period, on day 8 after SHP656 infusion, and at 6 weeks ± 4 days. Patients remained on their standard therapy during the screening and follow-up periods (Figure 1).

2.3 | Objectives

The primary objective of the study was to assess the tolerability and safety of SHP656 after single infusions of 25 ± 3, 50 ± 5 or 75 ± 5 IU/kg. Clinical adverse events (AEs), immunogenicity, vital signs and clinical laboratory analyses were recorded up to 6 weeks ± 4 days after

Measure	Visit 1 Screening assessments	Visit 2				Visit 3				Visit 4 (Termination visit)
	Days -30 to -2	Day -1 (admission)	Day 1	Days 2-3	Day 4	Day 1	Days 2-8	Day 14	Day 23	6 weeks ± 4 days[a]
Treatment administration			rFVIII (25, 50, or 75 IU/Kg)[b]			SHP656 (25, 50, or 75 IU/Kg)				
PK assessment[c]	✓		✓	✓	✓	✓	✓			
Immunogenicity evaluation	✓		✓ (Predose)			✓ (Predose)	✓ (Day 8)			✓
AE evaluation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

FIGURE 1 Study design. [a]6 wk ± 4 d post-SHP656 infusion. [b]Followed by minimum 4-day (96-h) washout period (maximum 4 wk) prior to SHP656 infusion. [c]Blood samples for PK analysis were collected predose and up to 72 h following rFVIII administration and predose and up to 168 h following SHP656 administration. Blood samples for measurement of FVIII activity and FVIII antigen levels were collected at screening, during PK study visits, and at termination visit. Patients were to remain at the study site for 12-h postinfusion and return the following day for the 24-hour PK sampling. AE, adverse event; FVIII, factor VIII; PK, pharmacokinetic; rFVIII, recombinant human factor VIII

infusions. Secondary objectives included comparison of the PK profiles of SHP656 with those for equivalent doses of rFVIII and determination of the PK dose proportionality of SHP656. The influence of anti-PSA antibodies on the PK profile of SHP656 was also determined.

2.4 | Analytical methods

Blood samples were drawn for FVIII activity assessments and PK evaluation within 30 minutes prior to infusion, and postinfusion at 15 ± 5, 30 ± 5, 60 ± 5 minutes, 3 ± 0.5, 6 ± 0.5, 9 ± 0.5, 12 ± 0.5, 24 ± 4, 32 ± 4, 48 ± 4, 56 ± 4 and 72 ± 4 hours for both rFVIII and SHP656. Additional blood samples for determination of SHP656 levels were carried out at 96 ± 6, 120 ± 6, 144 ± 6 and 168 ± 6 hours.

Factor VIII activity levels were determined using both chromogenic assay (HemosIL ELECTRACHROME FVIII, Instrumentation Laboratory Company) and one-stage clotting assay (OSCA; ACL TOP 500, Instrumentation Laboratory Company) using FVIII-depleted plasma and activator reagent Pathromtin SL (Siemens). Immunogenicity assessments using enzyme-linked immunosorbent assay included inhibitory antibodies to FVIII (Nijmegen-Bethesda assay); immunoglobulin G (IgG)- and immunoglobulin M (IgM)-binding antibodies to FVIII and SHP656, IgG and IgM anti-PSA antibodies, total Ig anti-Chinese hamster ovary (CHO) antibodies and human anti-mouse antibodies (HAMA).

2.5 | Pharmacokinetic analysis

PK parameters were calculated by standard non-compartmental methods using Phoenix® WinNonlin® 6.4 (Pharsight Corp.) and preinfusion-corrected data. Predose values greater than the lower limit of quantification, regardless of their magnitude, indicated unexpected endogenous and/or exogenous FVIII activity that had to be

accounted for in the PK analysis.[21] Corresponding adjustments were applied on a case-by-case basis taking all available data into account. For profiles with apparent endogenous FVIII activity at baseline, postdose activity levels were adjusted by subtracting the baseline level from all postdose FVIII activity levels.[22] For those without an apparent endogenous background at baseline, a proportional adjustment[23] was used postdose to account for residual FVIII activity from a previous infusion. FVIII activity data collected after the occurrence of a bleeding episode during a PK assessment period were excluded from the PK parameter analysis and were not included in mean PK parameter plots. PK parameters of the affected period were also excluded for statistical analysis.

Actual sampling times, doses and the duration of the infusion were used for the calculation of PK parameters, including the area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinity ($AUC_{0-\infty}$), AUC up to the last quantifiable concentration (AUC_{0-last}), AUC from time 0-72 hours (AUC_{0-72h}) for rFVIII and SHP656, and AUC from time 0-168 hours for SHP656 only. Terminal half-life ($t_{1/2}$), MRT, maximum plasma concentration (C_{max}), incremental recovery at C_{max} (IR), clearance (CL), volume of distribution at steady state (V_{ss}) and minimum time to reach C_{max} (T_{max}) were determined. The dose proportionality of SHP656 over the administered dose range was assessed using a power law model.

2.6 | Statistical analyses

A sample size of 30 patients was considered sufficient to allow assessment of the tolerability and the safety of SHP656 and to determine the PK profile.[24] Statistical analyses were performed using SAS® Version 9.4 (SAS Institute, Inc).

As recommended by Brett et al,[25] PK parameters $AUC_{0-\infty}$, AUC_{0-72h}, C_{max}, $t_{1/2}$, MRT and CL were log-transformed prior to statistical evaluation. PK parameters were analysed by cohort for treatment

Parameter	Cohort 1 rFVIII/SHP656 25 IU/kg (n = 11)	Cohort 2 rFVIII/SHP656 50 IU/kg (n = 16)	Cohort 3 rFVIII/SHP656 75 IU/kg (n = 13)
Race, n (%)			
White	10 (90.9)	16 (100)	13 (100)
Other	1 (9.1)	0	0
Ethnicity, n (%)			
Hispanic or Latino	1 (9.1)	0	1 (7.7)
Not Hispanic or Latino	10 (90.9)	16 (100)	12 (92.3)
Age, y, mean ± SD (min-max)	36.0 ± 10.6 (20-59)	34.6 ± 9.9 (19-55)	35.5 ± 11.9 (18-63)
Weight, kg, mean ± SD (min-max)	84.6 ± 13.8 (70-118)	86.9 ± 18.3 (59-139)	79.5 ± 12.5 (66-110)
Height, cm, mean ± SD (min-max)	176 ± 6.2 (168-190)	177 ± 8.9 (155-194)	175 ± 5.2 (163-182)
BMI, kg/m^2, mean ± SD (min-max)	27.5 ± 5.5 (20-41)	27.6 ± 5.4 (21-41)	26.0 ± 3.7 (22-33)

Abbreviations: BMI, body mass index; max, maximum; min, minimum; rFVIII, recombinant factor VIII; SD, standard deviation.

comparison using a linear mixed-effects model with treatment as a fixed effect and patient as a random effect. Least-squares (LS) means with corresponding 95% confidence intervals (CIs) for the two treatments were determined. The differences in LS means between SHP656 and rFVIII and the corresponding 95% CIs were also determined. Back transformation provided the ratios of the geometric means and corresponding CIs for the treatment comparisons (SHP656 vs rFVIII).

The dose proportionality of the PK parameters $AUC_{0-\infty}$, AUC_{0-last} and C_{max} for SHP656, over the administered dose range, was explored using the following power law model: log (parameter) = a + b * log (dose). The power law model parameters were estimated using an LS regression method and the 90% CIs were constructed. The increase in PK parameter values in response to a doubling of the dose was estimated with corresponding two-sided 90% CIs.[26]

3 | RESULTS

3.1 | Patient characteristics

Forty-four subjects were enrolled, of which two failed screening and two withdrew before administration of the study drug. Forty patients received rFVIII; 11 in Cohort 1 (25 ± 3 IU/kg), 16 in Cohort 2 (50 ± 5 IU/kg) and 13 in Cohort 3 (75 ± 5 IU/kg). Of these, two further patients withdrew before receiving SHP656, leaving 38 patients who completed the study (10, 15 and 13 in Cohorts 1, 2 and 3, respectively). All 40 patients who received rFVIII were included

in the safety analysis, and 39 were included in the PK analyses. The demographic and clinical characteristics of the patients are summarized in Table 1. Thirty-nine (97.5%) patients were white, the mean (±standard deviation [SD]) age of the 40 patients who received rFVIII was 35.3 (±10.5) years, and the mean body mass index (BMI) was 27.1 (±4.9). Mean age, height and BMI did not differ among the three cohorts, but patients in Cohort 3 had slightly lower body weights than those in Cohorts 1 and 2 (Table 1).

3.2 | Safety and tolerability

No serious AEs, thrombotic events or allergic reactions were reported following rFVIII or SHP656 administration, and no treatment-related AEs occurred at any point during the study. A total of 58 non-serious AEs occurred during the study; all events were resolved or resolving at study completion. No significant treatment-related changes in either clinical laboratory values or vital signs were recorded.

3.3 | Immunogenicity

Five patients had positive antibodies at screening; anti-SHP656 IgG (n = 1), anti-SHP656 IgM and anti-PSA IgM (n = 1), and anti-PSA IgM (n = 3). New anti-FVIII and anti-PSA FVIII IgG antibodies were detected in two of these patients after initiation of SHP656 dosing. Both had low (1:40-1:80) unconfirmed titres for these antibodies at screening, and it was considered unlikely that they represented de
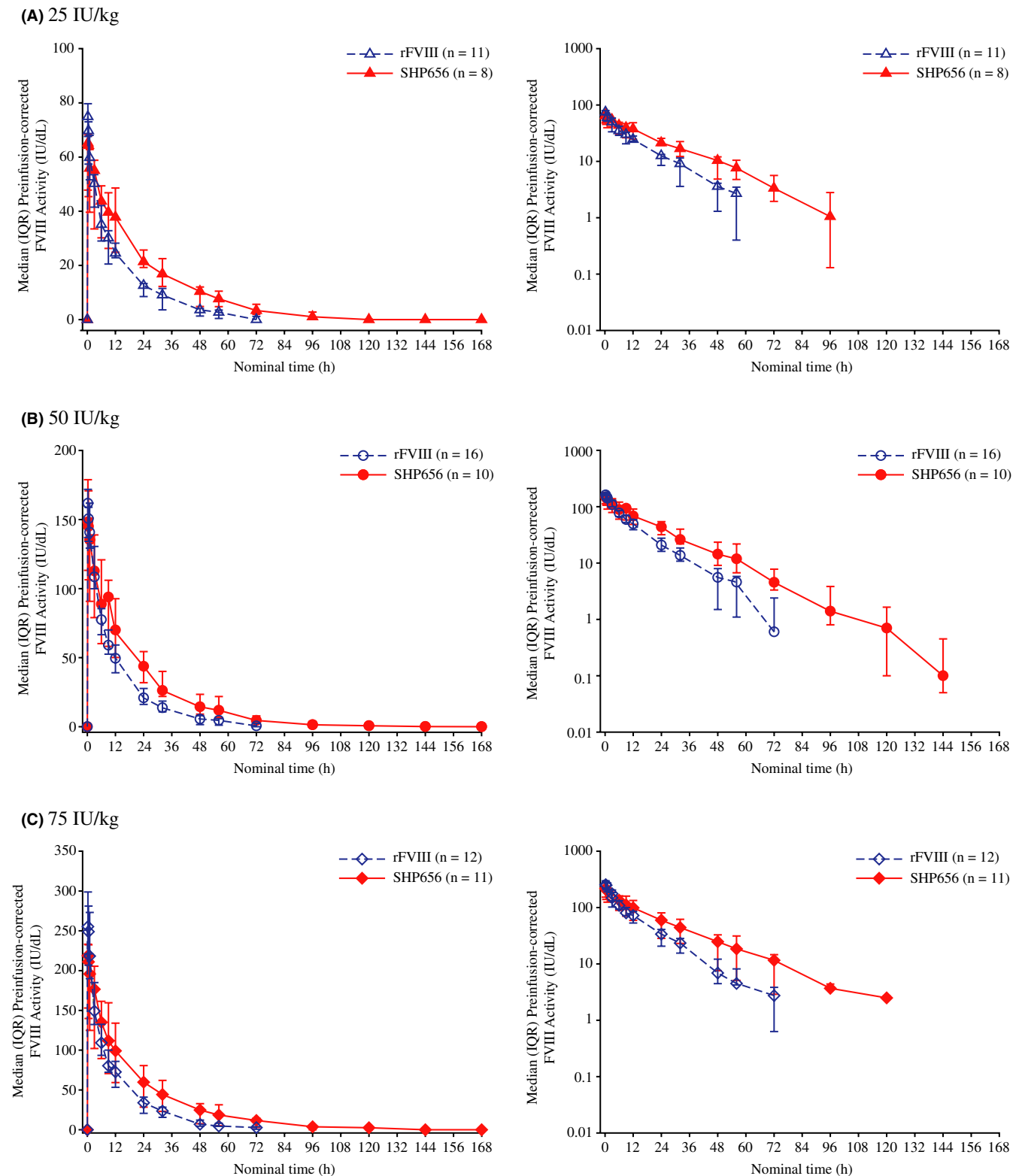
FIGURE 2 Median (IQR) preinfusion-corrected plasma FVIII activity (linear and semi-logarithmic scales) following infusion of rFVIII and SHP656 at (A) 25, (B) 50 and (C) 75 IU/kg. IQR, inter-quartile range; FVIII, factor VIII; rFVIII, recombinant factor VIII

novo antibody formation in response to SHP656. No patients developed antibodies to CHO or HAMA.

Given the low number of patients who had positive antibody results, the assessment of interactions with PK parameters was limited to three patients in Cohort 3 who were positive for anti-PSA antibodies at screening. In these three patients, mean (SD) MRT after administration of SHP656 was shorter compared with those who were anti-PSA antibody negative (20.0 [3.8] vs 26.8 [6.3] hours, respectively).

TABLE 2 Geometric mean of FVIII PK parameters for rFVIII and SHP656

Parameter	Cohort 1 25 IU/kg Geometric mean (95% CI)			Cohort 2 50 IU/kg Geometric mean (95% CI)			Cohort 3 75 IU/kg Geometric mean (95% CI)		
	SHP656 (n = 8)	rFVIII (n = 11)	Ratio SHP:rFVIII[a] (95% CI)	SHP656 (n = 10)	rFVIII (n = 16)	Ratio SHP:rFVIII[a] (95% CI)	SHP656 (n = 11)	rFVIII (n = 12)	Ratio SHP:rFVIII[a] (95% CI)
$AUC_{0-\infty}$, IU*h/dL	1155 (813, 1642)	819 (598, 1121)	1.41 (0.99, 2.01)	2717 (2233, 3307)	1747 (1480, 2061)	1.56 (1.28, 1.89)	3743 (2850, 4917)	2693 (2067, 3509)	1.39 (1.06, 1.82)
AUC_{0-72}, IU*h/dL	1087 (776, 1521)	803 (595, 1084)	1.35 (0.96, 1.91)	2587 (2134, 3137)	1717 (1460, 2018)	1.51 (1.24, 1.83)	3513 (2714, 4548)	2638 (2053, 3388)	1.33 (1.03, 1.72)
C_{max}, IU/dL	59.6 (52.2, 68.2)	72.0 (64.2, 80.7)	0.83 (0.69, 0.99)	142.2 (122.5, 165.0)	159.5 (141.1, 180.3)	0.89 (0.75, 1.06)	190.6 (164.6, 220.7)	258.7 (225.0, 297.4)	0.74 (0.60, 0.90)
$t_{\frac{1}{2}}$, h	15.4 (12.1, 19.5)	11.2 (8.92, 14.1)	1.37 (1.19, 1.58)	14.7 (12.1, 17.8)	11.2 (9.5, 13.3)	1.31 (1.09, 1.57)	16.7 (14.1, 19.9)	12.1 (10.2, 14.4)	1.39 (1.25, 1.53)
MRT, h	22.6 (17.8, 28.6)	15.2 (12.1, 19.1)	1.48 (1.28, 1.72)	22.1 (18.9, 25.8)	14.6 (12.6, 16.8)	1.52 (1.36, 1.69)	24.0 (20.2, 28.6)	15.4 (12.9, 18.3)	1.56 (1.47, 1.66)
CL, dL/kg*h	0.022 (0.015, 0.031)	0.031 (0.022, 0.043)	0.71 (0.50, 1.01)	0.019 (0.015, 0.023)	0.029 (0.024, 0.034)	0.65 (0.54, 0.79)	0.020 (0.0154, 0.0279)	0.028 (0.021, 0.036)	0.73 (0.55, 0.97)

Abbreviatiuons: AUC_{0-72h}, area under the plasma concentration-time curve from time 0-72 h; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; CL, clearance; C_{max}, maximum plasma concentration; FVIII, factor VIII; MRT, mean residence time; PK, pharmacokinetic; rFVIII, recombinant factor VIII; $t_{\frac{1}{2}}$, terminal half-life.

[a]A two-sided 95% CI for the ratio not containing the value 1 is equivalent to rejecting the null hypothesis of no difference against the two-sided alternative at the 5% level of statistical significance.

3.4 | Pharmacokinetics

PK data were evaluable for 39 patients, of which 38 received both treatments. There is generally a good agreement between OSCA and chromogenic assay results for human plasma FVIII and rFVIII. However, for SHP656, preliminary in vitro and in vivo investigations suggested that OSCA resulted in under-estimation of FVIII activity compared with the chromogenic assay (unpublished data). Therefore, all PK parameters presented in this paper were calculated using the chromogenic assay.

Dose-related increases in preinfusion-corrected FVIII activity were observed for both rFVIII and SHP656 (Figure 2). Median preinfusion-corrected FVIII activity rose sharply to a maximum shortly after administration of rFVIII and SHP656, and then declined exponentially, with a more rapid decline observed for rFVIII, as expected T_{max} corresponded with the first sampling time points (Figure 2).

Median observed FVIII activity following SHP656 infusion remained >1% for ≥96 hours in all cohorts, and for 120 hours in the 75 IU/kg cohort. Consistent with these observations, geometric mean $AUC_{0-\infty}$ and AUC_{0-72} were higher for SHP656 than rFVIII, as were $t_{\frac{1}{2}}$ and MRT while C_{max} and CL were lower (Table 2). The extension of MRT with SHP656 compared with rFVIII was approximately 1.5-fold for all dose cohorts. These differences were also statistically significant (at the 5% level) in all three cohorts indicated by an exploratory comparison based on the ratio of geometric means and corresponding two-sided 95% CIs. As estimated from the power law model, $AUC_{0-\infty}$, AUC_{0-last} and C_{max} increased proportional to the dose of SHP656 over the 25-75 IU/kg range evaluated. The estimated increases per doubling of dose were 1.98 (90% CI: 1.55-2.53) for $AUC_{0-\infty}$, 2.01 (90% CI: 1.56-2.59) for AUC_{0-last} and 2.06 (90% CI: 1.78-2.37) for C_{max}. Geometric mean estimates for V_{ss}, presented here for completeness, were 0.43 dL/kg [geometric coefficient of variation (CV) 21%] for rFVIII and 0.46 dL/kg (CV 34%) for SHP656 for all cohorts combined. Corresponding estimates for IR were 3.2 IU/dL:IU/kg (CV 18%) and 2.6 IU/dL:IU/kg (CV 29%) for FVIII and SHP656, respectively.

4 | DISCUSSION

In this single-dose study, there were no treatment-related AEs, serious AEs, deaths, study withdrawals, thrombotic events or allergic reactions, and no significant treatment-related changes in laboratory parameters or vital signs associated with SHP656. No patients developed de novo FVIII inhibitors or antibodies to PSA during the study. FVIII activity was significantly prolonged following SHP656 administration compared with rFVIII, with an approximately 1.5-fold extension based on MRT and 1.3- to 1.4-fold extension based on $t_{\frac{1}{2}}$. Exposure also appeared to increase proportional to the dose of SHP656 over the 25-75 IU/kg range.

Polysialylation prolonged the $t_{\frac{1}{2}}$ of FVIII activity to a similar degree to that shown for marketed extended half-life products utilizing either PEG (rurioctocog alfa pegol; ADYNOVATE®,

ADYNOVI™); or Fc fusion protein technology (Fc-rFVIII; ELOCTATE [Antihemophilic Factor [Recombinant], Fc Fusion Protein]).[12] The results for MRT, which adequately measures the overall persistence of the drug in the body,[27] indicated an approximately 1.5-fold prolonged FVIII activity with SHP656 compared with rFVIII across all dose levels. The differences in MRT were statistically significant (at the 5% level) in all three cohorts. Supplemental analyses indicated that a SHP656 dose of 75 IU/kg administered every 5 days may maintain a FVIII activity trough level of 1% for the majority of patients. When dosed once weekly, substantially higher doses than those used in routine prophylaxis (ie 20-80 IU/kg[4]) are expected to be necessary.

It has been hypothesized that clearance of modified rFVIII variants is largely regulated by interaction with von Willebrand factor (VWF), and longer-acting FVIII variants may require modifications that exclude association with endogenous VWF.[28] The in vitro and in vivo data had suggested that, besides other possible mechanisms, the prolonged half-life of PSA-rFVIII could be attributed to two possibly intertwined mechanisms: reduced binding to scavenger receptors (ie LRP1) and a largely VWF interaction-independent circulation time.[17] The improved PK behaviour of PSA-rFVIII compared with rFVIII in preclinical animal models appears to be translated to humans given the observed half-life extending effect of rFVIII polysialylation. In this study, while polysialylation prolonged the half-life of FVIII activity, it was to a similar degree to that shown for marketed extended half-life products. A small number of patients had pre-existing PSA antibodies at screening. In the highest dose cohort (75 IU/kg), there were three such individuals, and mean FVIII activity was lower in these patients compared with those without anti-PSA antibodies.

The safety profile of SHP656 in this study of 40 patients, with no treatment-related AEs or significant laboratory findings or vital signs, appears to be at least equivalent to the profiles of rFVIII or marketed extended half-life FVIII compounds. In the pivotal study of PEG-rFVIII, six out of 137 (4.4%) patients reported seven AEs that were considered possibly related to the product, all of which were non-serious and consistent with the known safety profile of the parent compound rFVIII.[10] Similarly, only 10 out of 164 (6.1%) patients in the phase 3 study of Fc-rFVIII experienced AEs related to the investigational product; none was serious.[7] While the de novo antibody formation in response to SHP656 was not a concern in this study, a multiple-dose study with a longer follow-up would be required to better understand the immunogenicity profile of SHP656.

5 | CONCLUSION

The results from this single-dose study indicate that polysialylation of rFVIII confers a half-life extension similar to that of approved extended half-life products that use either PEG or Fc fusion technology and was not associated with any treatment-emergent adverse events.

AUTHOR CONTRIBUTIONS

Geoffrey Allen, Brahm Goldstein, Martin Wolfsegger and Shouryadeep Srivastava contributed to the study conception and design. Andreas Tiede, Pratima Chowdary, Peter Collins, István Takács and Margarita Timofeeva were study investigators and participated in the study conduct and acquisition of data. Andreas Tiede, Alexander Bauer, Geoffrey Allen, Brahm Goldstein, Kathleen Köck, Hongyu Jeanne Jiang, Martin Wolfsegger and Shouryadeep Srivastava contributed to data analysis and review. All authors critically reviewed progressive drafts of the manuscript and approved the final version. All authors had access to the relevant data for the manuscript.

ORCID

Andreas Tiede (iD) https://orcid.org/0000-0002-3600-8536
Geoffrey Allen (iD) https://orcid.org/0000-0003-4351-1014
Pratima Chowdary (iD) https://orcid.org/0000-0002-6690-8586

*Now part of Takeda.

DATA AVAILABILITY STATEMENT

The data sets, including the redacted study protocol, redacted statistical analysis plan and individual participants data supporting the results reported in this article, will be available 3 months after the submission of a request, to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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