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Superior Prophylactic Effectiveness of a Recombinant FVIIIFc Over Standard Half-Life FVIII in Hemophilia A: A-SURE Study

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ABSTRACT

Objectives: The 24-month, prospective, non-interventional, European multicenter A-SURE study evaluated the real-world effectiveness of prophylaxis using an extended half-life recombinant factor VIII (FVIII) Fc fusion protein, efmoroctocog alfa (hereinafter rFVIIIFc), compared with prophylaxis using standard half-life (SHL) FVIII products in patients with hemophilia A.

Methods: Primary endpoints were annualized bleeding rate (ABR), annualized injection frequency, and annualized factor consumption. A comparative study design unique for an observational hemophilia study was implemented to reduce potential confounding in effectiveness estimates, wherein each patient prescribed rFVIIIFc was matched with one receiving SHL FVIII. Propensity scores were used for adjustment in statistical analyses.

Results: Outcomes for all primary endpoints were significantly better in the rFVIIIFc group ($n = 184$) compared with the SHL FVIII group ($n = 170$): mean ABR 1.5 versus 2.3 (difference of −0.8; $p = 0.0147$); mean annualized injection frequency 114.4 versus 169.2 (difference of −54.8; $p < 0.0001$); and mean annualized factor consumption 243 024.2 versus 288 718.6 International Units (difference of 45 694.5; $p = 0.0003$). rFVIIIFc was well tolerated, with no inhibitor development.

Conclusions: rFVIIIFc has superior prophylactic effectiveness versus SHL FVIII, providing higher bleed protection with fewer injections and lower factor consumption.

A complete list of the members of the A-SURE Study Group appears in the Supporting Information Table S8.

1 | Introduction

Hemophilia A causes impaired hemostasis and prolonged bleeding episodes, which can be life-threatening [1]. In severe hemophilia A (< 1% of normal factor VIII [FVIII] activity), frequent, spontaneous bleeding into joints and muscles may lead to hemophilic arthropathy [1, 2]. Patients with hemophilia A (PwHA) can experience impaired physical function and chronic pain due to progressive joint damage [3]. Reduced health-related quality of life is associated with an increased number of chronically affected (target) joints [4].

For a severe bleeding phenotype, current guidelines recommend long-term prophylaxis with hemostasis products to prevent bleeding and maintain joint health [1]. Early initiation is recommended in children, prior to the onset of joint disease [1]. However, prophylaxis with standard half-life (SHL) FVIII products is associated with frequent injections to maintain measurable trough levels and, despite treatment, patients can still experience bleeds [5, 6], joint damage [7], and reduced health-related quality of life [8].

Efmoroctocog alfa, a recombinant FVIII Fc fusion protein (referred herein as rFVIIIFc), is an extended half-life (EHL) FVIII product approved for treatment and prophylaxis in patients of all ages with hemophilia A [9]. It has a half-life of ~19 h, compared with 11–12 h for SHL FVIII products [10], which, based on population-pharmacokinetic simulation data, allows for longer intervals between injections, while maintaining higher FVIII trough levels without increasing overall factor consumption [11]. The recommended dosing regimen for rFVIIIFc prophylaxis is 50 International Units (IU)/kg every 3–5 days; dose adjustment ranging 25–65 IU/kg based on patient response [9]. This enables a lower injection frequency than for SHL FVIII products [12], allowing for increased treatment flexibility and individualization [11].

Clinical trials in previously treated patients of all ages with severe hemophilia A (A-LONG, NCT01181128, and Kids A-LONG, NCT01458106) have shown that rFVIIIFc can treat and prevent bleeds, while being generally well tolerated with no inhibitor development [13, 14]. These results were confirmed in an extension study, ASPIRE (NCT01454739), describing data over 4.5 and 3.5 years, for A-LONG and Kids A-LONG patients, respectively [15].

Post hoc analyses of these trials demonstrated improvements in pain and joint health in rFVIIIFc-treated PwHA [16, 17], along with reductions in weekly injections and annualized bleeding rate (ABR), compared with pre-trial SHL FVIII treatment [18]. Population-pharmacokinetic simulations using these data [11] and real-world case series [19] also indicated that rFVIIIFc can provide higher bleed protection, lower injection frequency, and lower factor consumption than SHL recombinant FVIII (rFVIII). There is, however, a lack of prospective clinical data demonstrating whether all three outcomes can be met simultaneously rather than higher bleed protection resulting from maintained injection frequency or factor consumption. Furthermore, it is unclear whether treaters would prioritize convenience (through lower injection frequency) or cost savings (through lower factor consumption) over bleed protection if all three outcomes cannot be improved at once. To promote optimal patient care, there is a need for real-world evidence to examine whether all three endpoints could be improved with rFVIIIFc compared with SHL rFVIII prophylaxis, and how rFVIIIFc is used in clinical practice.

The A-SURE study (NCT02976753) was performed to evaluate the comparative real-world effectiveness of rFVIIIFc prophylaxis compared with a matched treatment group on SHL FVIII. The EHL of rFVIIIFc may offer flexibility to personalize prophylactic regimens to meet individual patient needs, including lower injection frequency, reduced factor consumption, and increased bleed protection and/or physical activity [11]. Therefore, to provide a comprehensive understanding of the outcomes, the study had three primary endpoints: ABR, injection frequency, and factor consumption. Matching treatment groups at enrollment and propensity scores based on patients' baseline characteristics facilitated effective comparisons by reducing potential between-group differences. Each patient prescribed rFVIIIFc was matched with a patient on SHL FVIII therapy.

2 | Methods

The design for the A-SURE study (ClinicalTrials.gov identifier: NCT02976753) has been published previously [20]. Key points are summarized below. The study protocol was approved by institutional review boards and/or ethics committees at participating institutions [20]. Subjects, or their guardians, provided written informed consent prior to participation in the study; if appropriate, adolescent/pediatric subjects also provided assent. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice [21].

2.1 | Study Design

This was a 24-month, prospective, non-interventional, European multicenter study to evaluate the effectiveness of prophylaxis with rFVIIIFc compared with SHL FVIII products in PwHA in a real-world setting (Figure 1). Patients were enrolled from December 2016 to April 2019, with follow-up until November 2021. Patients were prescribed factor prophylaxis according to usual clinical practice (not determined by the study protocol). Switching between factor products was allowed. To reduce potential differences in patient characteristics between groups, patients were matched, as described in Methods S1.

2.2 | Study Treatment

The evaluated treatments were rFVIIIFc and SHL FVIII products, including both plasma-derived and recombinant products.

2.3 | Study Population

Patients from hemophilia centers across Europe were invited to participate during their routine clinic visits. Inclusion criteria

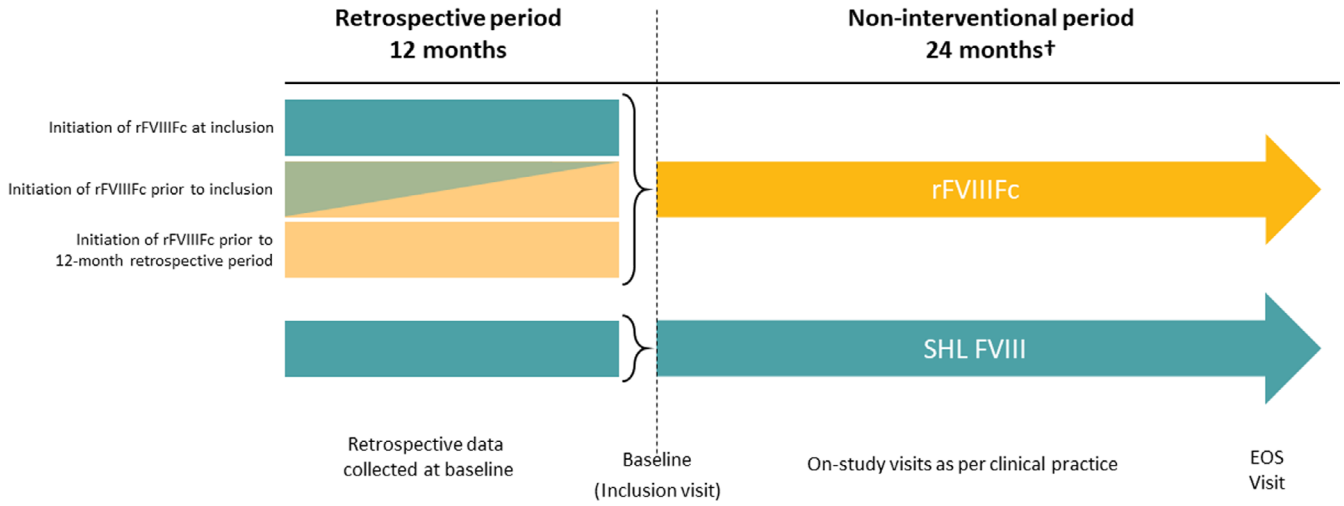

FIGURE 1 | A-SURE non-interventional study design. †Switches in prophylaxis were allowed during this period. EOS, end of study; FVIII, factor VIII; rFVIIIFc, recombinant factor VIII Fc fusion protein; SHL, standard half-life.

were male patients with a confirmed diagnosis of hemophilia A receiving prophylaxis with a factor product within 12 months before enrollment. At least 12 months documented pre-study treatment data (prophylaxis prescriptions and bleeding episode details) were required. Patients were prescribed prophylaxis with rFVIIIFc or SHL FVIII at enrollment. All patients, or their legal representatives, provided informed consent.

Patients with FVIII inhibitors at their most recent testing (Nijmegen modified Bethesda assay; inhibitor titer $\geq$0.6 Bethesda units/mL) were excluded, as was anyone receiving prior treatment with a commercially available EHL product other than rFVIIIFc or an investigational medicinal product in any other clinical study in the 12 months before enrollment.

Each patient prescribed rFVIIIFc was matched at the local site level based on age and previous SHL FVIII dose at enrollment with a patient on SHL FVIII therapy (Methods S1).

2.4 | Objectives

The primary study objective was to evaluate the effectiveness of rFVIIIFc compared with SHL FVIII products in the prophylaxis of PwHA over a 24-month prospective period.

The secondary objectives were to evaluate the effectiveness of rFVIIIFc on the bleeding rate, injection frequency, and factor consumption over a 24-month prospective period compared with SHL FVIII product(s) assessed retrospectively for patients initiating rFVIIIFc at inclusion; and to evaluate the effectiveness of rFVIIIFc on patient-reported outcomes (PROs) and health economic parameters compared with SHL FVIII over a 24-month prospective period.

2.5 | Endpoints

The primary endpoints were ABR, annualized injection frequency, assessed by prescription, and annualized factor consumption (IU). Secondary endpoints supporting the primary objective were annualized joint bleeding rate (AjBR) and annualized target joint bleeding rate (AtjBR). Additional secondary endpoints included primary endpoint changes during the 24-month prospective period, compared with the 12-month retrospective period (for patients initiating rFVIIIFc at inclusion), as well as PROs and health economic parameters (further details in Methods S2). Safety outcomes were also captured.

2.6 | Data Collection

Demographic factors and relevant medical history (including comorbidities, hemophilia history, blood type, and inhibitor history) were recorded at baseline. Prophylactic factor product prescription/dispensation and bleeding history during the previous 12 months was also collected.

Subsequently, the prescribed dose and injection frequency of prophylactic factor treatment, the product used, as well as the amount and date of dispensed factor product were recorded prospectively. Where, due to local regulations, it was not possible to retrieve consumption data from dispensed product information, total factor consumption was calculated based on medical records and/or physician estimates. Any changes of prophylactic factor prescription were recorded, alongside the clinical justification for the change.

Bleeding episodes (overall, and for joints/target joints) were collected through a patient diary. ABR, AjBR, and AtjBR were determined based on bleeding episodes assessed by local practice.

Serious adverse events (SAEs) from the first dose to the end of study (any SAEs; SAEs related to rFVIIIFc; SAEs leading to permanent discontinuation of rFVIIIFc; fatal SAEs) and non-SAEs leading to permanent discontinuation of rFVIIIFc were captured; SAEs occurring during the 12-month retrospective period were captured at baseline. Data were not collected for the

SHL FVIII products. Results from inhibitor-level testing were recorded during routine visits.

Data collection for additional secondary endpoints is detailed in Methods S2.

2.7 | Statistical Methods

A sample size of 150 patients per treatment was estimated to have a power of approximately 85% to reject the null hypothesis of no difference between treatment groups for ABR and annualized injection frequency at the 5% significance level. To allow for dropouts, patient switch, and potential difficulties in finding a matched control, 175 patients were needed per treatment (350 in total) [20].

To minimize potential confounding factors influencing the effectiveness estimates, in addition to matching, propensity scores based on patients' baseline characteristics were estimated via logistic regression. Method S3 outlines the propensity score quality assessment and the baseline covariates considered for inclusion in the propensity score model.

To compare the treatment effectiveness of rFVIIIFc versus SHL FVIII on the primary endpoints, a generalized mixed linear model, stratified on the propensity score quintiles, and additionally adjusted for age, and ABR during the 12-month retrospective period, was used. The model-based mean (95% confidence interval [CI]) and differences between rFVIIIFc and SHL FVIII (95% CI) were presented. A negative binomial distribution was considered for analysis of ABR estimates but, due to poor model fit, was deemed inappropriate and rejected as the primary analysis model (Methods S4).

The primary and secondary endpoints supporting the primary objective were presented descriptively, with the mean (standard deviation [SD]) and median (interquartile range [IQR]) presented for ABR, annualized injection frequency, annualized factor consumption, AjBR, and AtjBR. For the descriptive analysis, all annualized rates were defined as the number of bleeding events, injections, or the total amount of factor dispensed or consumed during the specific treatment period divided by the duration of the specific treatment period in days, multiplied by 365 [22]. The methodology for additional secondary endpoint analysis is detailed in Methods S2.

A bleeding episode was defined as requiring factor treatment based on assessment by local practice. Injection frequency was derived from the prescribed dosing frequency and treatment period duration. Factor consumption was primarily assessed by the dispensed factor product or calculated by the investigator based on medical records and/or physician's estimate.

Safety data were analyzed descriptively.

2.8 | Role of the Funding Source

Sobi was involved in the study design, data collection, data analysis, data interpretation, and development of the manuscript. All authors prepared the manuscript with assistance from a medical writer funded by Sobi. All authors had access to the study data, reviewed and approved the manuscript, vouched for the accuracy and completeness of the data, and had final responsibility for the decision to submit the manuscript for publication.

3 | Results

Of 361 patients initially enrolled, 356 were eligible for inclusion in the analysis population—186 in the rFVIIIFc group and 170 in the SHL FVIII group (Figure 2). Prophylactic treatment prescribed in the 12 months prior to inclusion is summarized in Table S1.

The median (IQR) follow-up duration for the primary endpoint analysis was 21.4 (19.4; 24.3) and 21.0 (18.6; 24.6) months in the rFVIIIFc and SHL FVIII groups, respectively (Table S2).

3.1 | Baseline Characteristics

Baseline characteristics (Tables 1 and S3) were similar and well balanced between treatment groups, except for significant imbalances in inhibitor history ($p = 0.0323$), present in 10.2% and 18.8% of those in the rFVIIIFc and SHL FVIII groups, respectively, and patient blood type ($p = 0.0466$). These were nonsignificant after adjustment for the propensity score (Table S4). Blood group data were unknown for 107 PwHA (rFVIIIFc, 49; SHL FVIII, 58); these values were treated as a separate category in the propensity score model.

3.2 | Primary Endpoints: ABR, Annualized Injection Frequency, and Annualized Factor Consumption

During the 24-month prospective study period, all three primary endpoint outcomes were significantly better in the rFVIIIFc group compared with the SHL FVIII group (Table 2). Results from the descriptive analysis are presented in Table 3.

The mean (95% CI) ABR was 1.5 (1.0; 1.9) for the rFVIIIFc group and 2.3 (1.8; 2.8) for the SHL FVIII group, with a significant difference between treatments (95% CI) of −0.8 (−1.5; −0.2): $p = 0.0147$. Treatment with rFVIIIFc resulted in a lower mean (95% CI) annualized injection frequency of 114.4 (100.6; 128.2) compared with SHL FVIII, 169.2 (155.2; 183.2). A significant difference was seen between treatments (95% CI) of −54.8 (−64.6; −45.0): $p < 0.0001$. The mean (95% CI) annualized factor consumption (IU) was significantly lower with rFVIIIFc treatment (243 024.2 [210 077.8; 275 870.5]) compared with SHL FVIII treatment (288 718.6 [255 261.0; 322 176.3]). The resulting difference between treatments (95% CI) was −45694.5 (−70414.6; −20974.3): $p = 0.0003$.

3.3 | Secondary Endpoints Supporting the Primary Objective: AjBR and AtjBR Rate

AjBR was significantly lower in the rFVIIIFc group than the SHL FVIII group during the 24-month prospective study period

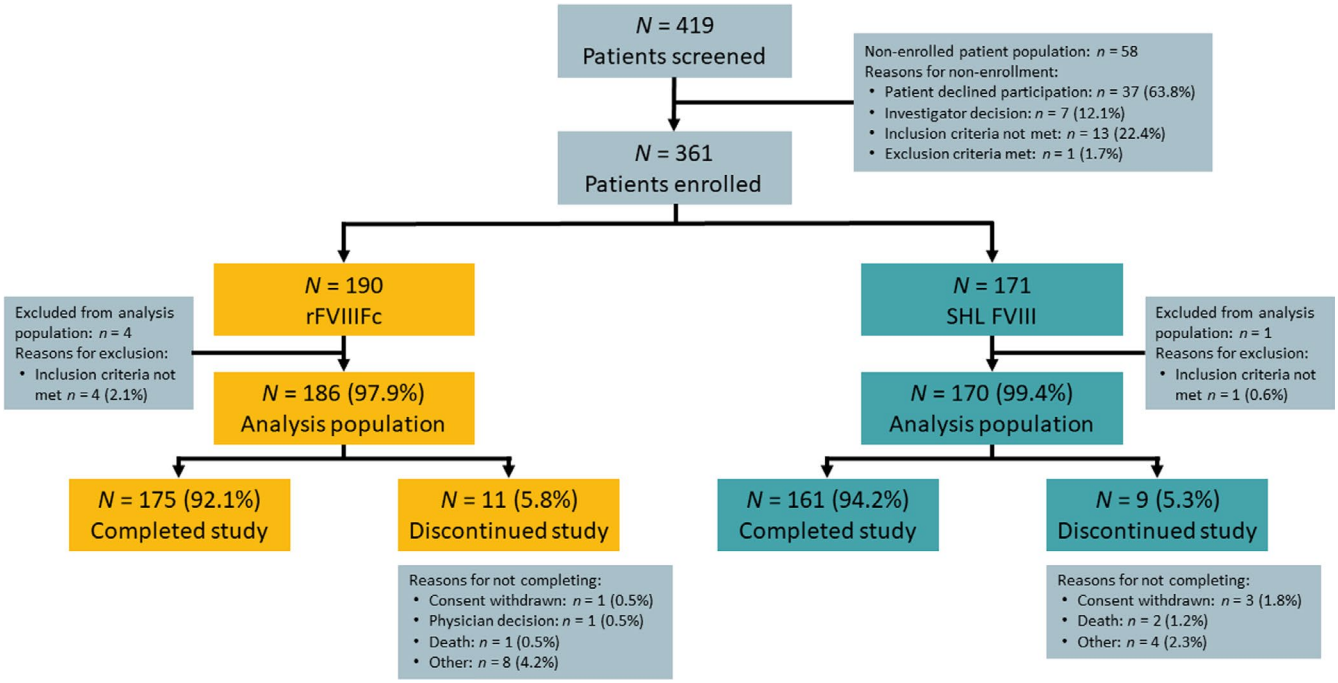

FIGURE 2 | Patient disposition flow chart. FVIII, factor VIII; rFVIIIFc, recombinant factor VIII Fc fusion protein; SHL, standard half-life.

(Table S5), with a difference between treatments (95% CI) of −0.6 (−1.2; −0.1): $p = 0.0206$.

Very few target joints were reported during the 12-month retrospective period (rFVIIIFc 7.5%, SHL FVIII 7.6%; Table 1); the AtjBR during the prospective follow-up are presented in Table S5. Almost all target joints were resolved during the 24-month observation period: rFVIIIFc, 91.7% (11/12 [data missing for one patient]) and SHL FVIII, 85.7% (12/14).

3.4 | Additional Secondary Endpoints

Analyses of changes in the three primary endpoints during the 24-month prospective period compared with the 12-month retrospective period for patients who initiated rFVIIIFc at inclusion ($N = 27$) were consistent with the main analysis. The mean (SD) reduction in ABR of −0.8 (5.2) and annualized factor consumption (IU) of −38 116 (102 283) did not reach statistical significance ($p = 0.4354$ and $p = 0.2001$, respectively). A significant change was noted for annualized injection frequency ($p < 0.0001$) (Table S6). The analyzed subgroup was small ($N = 27$), due to low numbers of patients switching at enrollment, which was a confounding factor for the demonstration of significant change. Sensitivity analyses comparing changes during the 12-month retrospective period of treatment and, separately, for the first and second years of follow-up demonstrated that these results were consistent with the main analysis.

For the PROs analyzed, differences between treatment groups over time were inconclusive due to limited respondent numbers (data not shown). For the health economic parameters assessed, no significant differences were found in annualized inpatient hospitalization rates and annualized outpatient visit rates during the 24-month prospective period between treatment groups (data not shown). Results were inconclusive for missed planned activity and productivity due to hemophilia during the same period due to low observation numbers (data not shown).

3.5 | Safety

Thirty-five SAEs occurred in 25 patients (11.9%) during treatment with rFVIIIFc, none of which were assessed by the investigator as treatment-related. These included three SAEs ("central venous catheter removal," "device-related thrombosis," and "deep vein thrombosis") reported as medically important (according to the investigator's assessment regarding causality) in one patient and three clinically significant SAEs ("arthritis bacterial," "atrioventricular block," and "arthropathy"), each in one patient. The medically important SAEs occurred in the presence of an indwelling central venous catheter and inflammatory changes in the surrounding tissues and both events resolved upon repeated replacement of the affected central venous catheter and treatment with enoxaparine. The event "deep vein thrombosis" was associated with the event "device-related thrombosis." No SAEs related to rFVIIIFc were reported. There was one (0.5%) fatal SAE due to biliary metastatic cancer (also the one [0.5%] SAE leading to rFVIIIFc discontinuation). All SAEs except for the fatal case resolved or recovered. The single (0.5%) reported non-serious AE was "muscle hemorrhage" in the right forearm that resolved and was not considered related to rFVIIIFc (Table 4).

The safety data obtained in this study were consistent with the known safety profiles of rFVIIIFc and SHL FVIII, with no new safety concerns identified.

No inhibitor development was detected during treatment with rFVIIIFc (Table S7). In the SHL FVIII group, inhibitor relapse

TABLE 1 | Baseline characteristics.

	rFVIIIFc (*N* = 186)	SHL FVIII (*N* = 170)	*p*[a]
Median (IQR) age, years	24.0 (12.0; 41.0)	25.5 (12.0; 41.0)	0.5712
Age category, *n* (%), years			
< 8	20 (10.8)	22 (12.9)	
8– < 12	24 (12.9)	19 (11.2)	
12– < 18	29 (15.6)	20 (11.8)	
18– < 65	103 (55.4)	101 (59.4)	
≥ 65	10 (5.4)	8 (4.7)	
Median (IQR) body weight, kg[b]	69.0 (54.0; 81.0)	70.0 (48.5; 80.0)	0.5568
Blood group, *n* (%)			0.0466
O[c]	56 (40.9)	61 (54.5)	
A[c]	59 (43.1)	30 (26.8)	
B[c]	17 (12.4)	18 (16.1)	
AB[c]	5 (3.6)	3 (2.7)	
Unknown[d]	49 (26.3)	58 (34.1)	
Severity of hemophilia, *n* (%)			0.4412
Mild	4 (2.2)	0 (0.0)	
Moderate	7 (3.8)	5 (2.9)	
Severe	175 (94.1)	165 (97.1)	
History of inhibitors, *n* (%)	19 (10.2%)	32 (18.8)	0.0323
Presence of target joints prior to inclusion, *n* (%)[e]			0.9968
No	172 (92.5)	157 (92.4)	
Yes	14 (7.5)	13 (7.6)	

Abbreviations: FVIII, factor VIII; IQR, interquartile range; PwHA, patients with hemophilia A; rFVIIIFc, recombinant factor VIII Fc fusion protein; SHL, standard half-life.
[a]Unadjusted test of difference between the treatment groups based on univariate regression analysis.
[b]Body weight data were missing in four PwHA (rFVIIIFc *N* = 2, SHL FVIII *N* = 2).
[c]Percentages were based among non-missing/known data in patients from the analysis population (rFVIIIFc, *N* = 137; SHL FVII, *N* = 112).
[d]The unknown values for blood group were treated as a separate category in the propensity score model.
[e]Presence of target joints during the 12-month retrospective period, and percentages are based among non-missing data in patients from the analysis population.

(low-titer, < 5 Bethesda units/mL) was reported in one patient with an inhibitor history.

An illustrative summary of the main findings of this study is presented in Figure S1.

4 | Discussion

Prophylaxis with FVIII products remains the mainstay of hemophilia A treatment to prevent bleeds and preserve joint health [1, 23]. However, SHL FVIII products require frequent injections, which impose a substantial treatment burden [1, 6, 11]. The EHL of rFVIIIFc allows for enhanced flexibility and bleed protection, reduced factor consumption, and increased intervals between injections [11, 18, 24].

Clinical trial data evaluating rFVIIIFc in those with severe hemophilia A show the product to be efficacious and well tolerated in adults/adolescents and children [13–15, 25]. Although previous real-world studies have assessed the effectiveness of rFVIIIFc when switching from SHL FVIII therapy [22, 24, 26, 27], there is a lack of prospective and direct comparative evidence in larger populations. The results of this prospective matched comparative study demonstrate that for PwHA in clinical practice across Europe, compared with SHL FVIII products, prophylaxis with rFVIIIFc resulted in significantly lower ABR, annualized injection frequency, and annualized factor consumption. These primary endpoints were chosen because an effect on one can influence the others; for example, lower ABRs can be achieved with increased injection frequency and factor consumption, whereas convenience from reduced dosing frequency or cost savings from lower factor consumption may be prioritized over improved bleed protection. The study design aimed to emulate that of a randomized study, with matching, propensity score stratification, and prospective follow-up. To our knowledge, the use of a matched control group in an observational hemophilia study is unique. The process of patient matching by age and last prescribed SHL factor dose was successfully used to address potential sources of confounding by indication. As the two groups were well-matched prior to the application of propensity scores, the study results were not significantly impacted by them.

The clinically meaningful difference between mean ABRs was significant when comparing rFVIIIFc with SHL FVIII, with an average reduction of almost one bleeding event per year. The low ABR in the SHL FVIII group indicates that this patient population was well treated, and the additional effectiveness of rFVIIIFc is demonstrated by the further significant lowering of ABR. These findings are supported by the significantly lower AjBR in the rFVIIIFc group than in the SHL FVIII group. The significantly lower ABR with rFVIIIFc was achieved with a significantly lower mean annualized injection frequency and mean annualized factor consumption compared with SHL FVIII. These real-world results support the contribution of rFVIIIFc to address the unmet needs in patients on SHL factor prophylaxis.

The results of this study corroborate the real-world German PREVENT study, which found a median (IQR) ABR of 0.5 (0.0–1.7) (mean value of 1.6 [SD 4.2]), mean (SD) injection frequency of 2.5 (0.7), and mean weekly factor consumption (IU/kg) of 91.9 (42.3) [28]. Other real-world studies of patients switching to EHL FVIII have also shown reduced injection frequency [22, 24, 26, 29] and reduced factor consumption [22, 24, 26, 27]. Similar bleeding events to those reported in this study have been reported by a retrospective analysis, which found lower ABR and AjBR following treatment with rFVIIIFc [22], compared

TABLE 2 | Primary endpoints—generalized linear model analysis and duration of observation.

	rFVIIIFc ($N=184$)[a]	SHL FVIII ($N=170$)[a]
ABR		
Mean (95% CI)	1.5 (1.0; 1.9)	2.3 (1.8; 2.8)
Treatment difference (95% CI)	−0.8 (−1.5; −0.2)	
p	0.0147	
Annualized injection frequency		
Mean (95% CI)	114.4 (100.6; 128.2)	169.2 (155.2; 183.2)
Treatment difference (95% CI)	−54.8 (−64.6; −45.0)	
p	< 0.0001	
Annualized factor consumption, IU		
Mean (95% CI)	243 024.2 (210 177.8; 275 870.5)	288 718.6 (255 261.0; 322 176.3)
Treatment difference (95% CI)	−45 694.5 (−70 414.6; −20 974.3)	
p	0.0003	
Duration of observation, months		
Mean (SD)	21.9 (4.3)	20.7 (5.9)
Median (Q1; Q3)	21.4 (19.4; 24.3)	21.0 (18.6; 24.6)

Note: Study visits occurred at baseline and during routine clinical visits. At each study visit, information about bleeds reported by the patient, prophylactic treatment prescribed, and the amount of dispensed factor product (IU) since the last visit were documented. Treatment differences were estimated with a general linear model. A predefined negative binomial regression model for ABR was considered; however, this was rejected due to poor model fit. The estimates from that model showed a mean (95% CI) ABR of 0.9 (0.6; 1.2) for rFVIIIFc and 1.2 (0.9; 1.6) for SHL FVIII, with a treatment effect ratio of 0.7 (0.5; 1.0) ($p=0.0548$).
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; FVIII, factor VIII; IU, International Units; Q, quartile; rFVIIIFc, recombinant factor VIII Fc fusion protein; SHL, standard half-life.
[a]Patients with < 3 months on initially prescribed treatment were excluded from analysis of annualized endpoints (rFVIIIFc $N=2$, SHL FVIII $N=0$) to support an accurate estimation of annualized outcomes.

with SHL treatment [22]. However, other studies have reported comparable bleeding rates upon switching to rFVIIIFc from SHL FVIII [24, 27]. A recent analysis of pooled real-world data from Germany, Italy, and the United States compared four different factor products for prophylaxis in hemophilia A—rVIII-SingleChain, octocog alfa, BAY 81–8973, and rFVIIIFc [30]. rFVIIIFc treatment was associated with a similar ABR to the other products, the highest proportion of patients with two or fewer injections per week, and the second lowest factor consumption [30].

In a recent study, physicians estimated ABR and weekly FVIII dose to decrease after switching to rFVIIIFc, with 62% agreeing that treatment burden improved [31]. Reduced injections, supporting patient lifestyle and convenience, were the top stated reasons for the switch [31].

In this study, rFVIIIFc was well tolerated, AEs were consistent with the established safety profile, and no new safety concerns were identified. The device-related thrombosis and deep vein thrombosis SAEs observed in one patient following catheter removal resolved and were assessed by the investigator as not related to rFVIIIFc. No inhibitors were detected during treatment with rFVIIIFc, in line with results reported by previous clinical trials [13–15].

Overall, our findings show clear benefits of rFVIIIFc compared with SHL FVIII prophylaxis, with improved protection against bleeds, fewer injections, and lower factor product consumption. These results confirm those of previous clinical trials (A-LONG, Kids A-LONG, ASPIRE) [13–15] and show how rFVIIIFc can meet the unmet needs of patients on SHL factor prophylaxis in a real-world setting.

To our knowledge, this study is the first to prospectively compare the effectiveness of an EHL rFVIII product with SHL FVIII for prophylaxis of PwHA in a real-world setting. Indirect comparisons between rFVIIIFc and other hemophilia products have reported [32, 33] that it can achieve a similar ABR with lower injection frequency and factor consumption [32]. Further real-world studies comparing products directly are warranted and would be important to help inform physicians and guide decision-making. This study has limitations inherent to observational studies, including risk of selection bias and confounding; records of non-participating centers and patients were maintained to address this. Potential confounding by indication was addressed using patient matching locally as well as adjustments by a propensity score, as previously mentioned. Consequently, the study population was deemed representative of the general hemophilia A population, with patients well-managed and receiving personalized prophylaxis. The centers included in the study (European Haemophilia Treatment Centres and European Haemophilia Comprehensive Care Centres) treat the majority of PwHA in Europe, and the comparison of included and non-included patient characteristics highlighted that age and severity were similar between groups.

TABLE 3 | Primary endpoints and secondary endpoints supporting primary objective—descriptive analysis.

	rFVIIIFc ($N=184$)[a]	SHL FVIII ($N=170$)[a]
ABR		
Mean (SD)	1.5 (3.1)	2.2 (5.1)
Median (IQR)	0.6 (0.0; 1.6)	0.6 (0.0; 1.9)
Annualized injection frequency		
Mean (SD)	115.7 (31.4)	170.9 (65.2)
Median (IQR)	104.4 (104.4; 121.8)	156.5 (139.3; 182.6)
Annualized factor consumption, IU[b]		
Mean (SD)	245,468.4 (117,564.9)	291,590.7 (150,384.7)
Median (IQR)	225,044.6 (155,754.3; 318,797.5)	262,400.0 (206,416.4; 362,626.5)
AjBR—secondary endpoint supporting primary objective		
Mean (SD)	1.0 (2.4)	1.5 (4.1)
Median (IQR)	0.0 (0.0; 1.0)	0.0 (0.0; 1.3)
AtjBR—secondary endpoint supporting primary objective	**rFVIIIFc ($N=14$)**[c]	**SHL FVIII ($N=13$)**[c]
Mean (SD)	2.7 (4.5)	2.8 (6.0)
Median (IQR)	0.6 (0.0; 1.6)	1.3 (0.0; 1.9)
Duration of observation (months)	**rFVIIIFc ($N=184$)**[a]	**SHL FVIII ($N=170$)**[a]
Mean (SD)	21.9 (4.3)	20.7 (5.9)
Median (Q1; Q3)	21.4 (19.4; 24.3)	21.0 (18.6; 24.6)

Abbreviations: ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AtjBR, annualized target joint bleeding rate; FVIII, factor VIII; IQR, interquartile range; IU, International Units; PwHA, patients with hemophilia A; Q, quartile; rFVIIIFc, recombinant factor VIII Fc fusion protein; SD, standard deviation; SHL, standard half-life.

[a] Patients with < 3 months on initially prescribed treatment were excluded from analysis of annualized endpoints (rFVIIIFc $N=2$, SHL FVIII $N=0$) to support an accurate estimation of annualized outcomes.

[b] Annualized factor consumption data were missing in three PwHA (rFVIIIFc $N=1$, SHL FVIII $N=2$).

[c] Patients with target joints during the past 12 months prior to inclusion.

TABLE 4 | Analysis of AEs in the rFVIIIFc cohort.

	Prospective period ($N=210$)		Retrospective period ($N=159$)	
	***N* (%)**	**Events**	***N* (%)**	**Events**
Any non-serious AE leading to rFVIIIFc permanent discontinuation	1 (0.5)	1	NA	NA
Any SAE	25 (11.9)	35	3 (1.9)	4
Any SAE related to rFVIIIFc	0 (0.0)	0	0 (0.0)	0
Any SAE leading to rFVIIIFc permanent discontinuation	1 (0.5)	1	NA	NA
Any fatal SAE	1 (0.5)	1	NA	NA

Abbreviations: AE, adverse event; NA, not applicable; rFVIIIFc, recombinant factor VIII Fc fusion protein; SAE, serious adverse event.

In summary, prophylactic treatment with rFVIIIFc is an effective and well tolerated treatment option for PwHA. The A-SURE study established that rFVIIIFc has clear benefits compared with SHL FVIII products, with improved bleed protection, fewer injections, and lower factor consumption, thereby meeting the key unmet needs associated with SHL FVIII prophylaxis. No new inhibitor development was seen in patients treated with rFVIIIFc, including in those with previous inhibitor history. The A-SURE study design successfully met the requirements for a direct prospective comparison in a real-life setting and may serve as an example for future hemophilia studies aiming to study product class comparisons.

Author Contributions

Conceptualization of the study: Linda Bystrická and Stefan Lethagen. Data curation: Stefan Lethagen. Performed statistical analysis: Håkan Malmström and Stefan Lethagen. Funding acquisition: Stefan Lethagen. Investigation: Stefan Lethagen. Methodology: Håkan Malmström, Stefan Lethagen, and Charles Hay. Project administration: Stefan Lethagen. Supervision: Stefan Lethagen and María Teresa Álvarez-Román. Validation: Linda Bystrická, Stefan Lethagen, and María Teresa Álvarez-Román. Visualization: Linda Bystrická, Stefan Lethagen, and Charles Hay. All authors were involved in the writing and critical review of the manuscript.

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Conflicts of Interest

J.O. declares grants or contracts from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Sobi, and Takeda paid to the Medical Faculty University of Bonn; payment or honoraria from Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, and Takeda; and support for attending meetings/travel from Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, and Takeda; has participated in data safety monitoring/advisory boards for Bayer, Biogen Idec, Biomarin, Biotest, CSL Behring, Chugai, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Spark Therapeutics, Sobi, and Takeda; leadership or fiduciary role in other board, society, committee or advocacy, paid or unpaid for the GTH, and foundation "Hämotherapie Forschung"; and receipt of equipment materials, drugs, medical writing, gifts, or other services from Bayer to the Medical Faculty University of Bonn. C.H. has received consulting fees from Sobi, CSL Behring, and Roche, declares payment or honoraria from Roche, Sobi, and Biotest; support for attending meetings and/or travel for Roche, CSL Behring, and Sobi; and leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid as Director of the UK Haemophilia Database. F.P. declares honoraria from Grifols, Roche, and Sobi, as well as participation in data safety monitoring/advisory boards for Biomarin, Roche, Sobi, and Takeda. A.T. has received consulting fees from Bayer and support for attending meetings from Bayer and Sobi. P.A.H. declares grants or contracts from Bayer, Pfizer, Roche, and Sobi paid to their institution; payment or honoraria for lectures and advisory boards from Bayer, BMS, CSL Behring, NovoNordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda; support for attending meetings and/or travel from Bayer, CSL Behring, NovoNordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda; and leadership or fiduciary role in other board, society, committee or advocacy, paid or unpaid as a member of the executive committee of ACHIEVE group and ADVANCE group. M.T.Á.-R. has participated as a speaker and in advisory boards and sponsored symposia, with Amgen, CSL Behring, Novartis, NovoNordisk, Octapharma, Pfizer, Roche, Sobi, and Takeda. C.B.-A. has received consulting fees from CSL Behring, Takeda, and LFB and declares payment or honoraria for LFB. S.L. is a shareholder of stock or stock options of Sobi. S.L., H.M., and L.B. are employees of Sobi.

Data Availability Statement

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by the European Medicines Agency and/or US Food and Drug Administration, while protecting individual participant integrity and compliance with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi, and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity, and commitment to publication of the results. To request access to study data, a data sharing request form (available on www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at: https://www.sobi.com/en/policies.

References

1. A. Srivastava, E. Santagostino, A. Dougall, et al., "WFH Guidelines for the Management of Hemophilia," *Haemophilia* 26 suppl. 6 (2020): 1–158.

2. S. Lobet, C. Hermans, and C. Lambert, "Optimal Management of Hemophilic Arthropathy and Hematomas," *Journal of Blood Medicine* 5 (2014): 207–218.

3. A. L. Forsyth, M. Witkop, A. Lambing, et al., "Associations of Quality of Life, Pain, and Self-Reported Arthritis With Age, Employment, Bleed Rate, and Utilization of Hemophilia Treatment Center and Health Care Provider Services: Results in Adults With Hemophilia in the HERO Study," *Patient Preference and Adherence* 9 (2015): 1549–1560.

4. J. O'Hara, S. Walsh, C. Camp, et al., "The Impact of Severe Haemophilia and the Presence of Target Joints on Health-Related Quality-Of-Life," *Health and Quality of Life Outcomes* 16, no. 1 (2018): 84.

5. E. Berntorp, G. Dolan, C. Hay, et al., "European Retrospective Study of Real-Life Haemophilia Treatment," *Haemophilia* 23, no. 1 (2017): 105–114.

6. M. Carcao, "Changing Paradigm of Prophylaxis With Longer Acting Factor Concentrates," *Haemophilia* 20, no. suppl. 4 (2014): 99–105.

7. J. Oldenburg, "Optimal Treatment Strategies for Hemophilia: Achievements and Limitations of Current Prophylactic Regimens," *Blood* 125, no. 13 (2015): 2038–2044.

8. J. Oldenburg, H. Tran, F. Peyvandi, et al., "Health-Related Quality of Life and Health Status in Adolescent and Adult People With Haemophilia A Without Factor VIII Inhibitors-a Non-interventional Study," *Haemophilia* 27, no. 3 (2021): 398–407.

9. "European Medicines Agency. Elocta - Summary of Product Characteristics," 2019, https://www.ema.europa.eu/en/documents/product-information/elocta-epar-product-information_en.pdf.

10. J. S. Powell, N. C. Josephson, D. Quon, et al., "Safety and Prolonged Activity of Recombinant Factor VIII fc Fusion Protein in Hemophilia A Patients," *Blood* 119, no. 13 (2012): 3031–3037.

11. E. Berntorp, C. Negrier, P. Gozzi, P. M. Blaas, and S. Lethagen, "Dosing Regimens, FVIII Levels and Estimated Haemostatic Protection With Special Focus on rFVIIIFc," *Haemophilia* 22, no. 3 (2016): 389–396.

12. P. M. Mannucci, "Hemophilia Therapy: The Future Has Begun," *Haematologica* 105, no. 3 (2020): 545–553.

13. G. Young, J. Mahlangu, R. Kulkarni, et al., "Recombinant Factor VIII fc Fusion Protein for the Prevention and Treatment of Bleeding in Children With Severe Hemophilia A," *Journal of Thrombosis and Haemostasis* 13, no. 6 (2015): 967–977.

14. J. Mahlangu, J. S. Powell, M. V. Ragni, et al., "A-LONG Investigators. Phase 3 Study of Recombinant Factor VIII fc Fusion Protein in Severe Hemophilia A," *Blood* 123, no. 3 (2014): 317–325.

15. B. Nolan, J. Mahlangu, I. Pabinger, et al., "Recombinant Factor VIII fc Fusion Protein for the Treatment of Severe Haemophilia A: Final Results From the ASPIRE Extension Study," *Haemophilia* 26, no. 3 (2020): 494–502.

16. J. Oldenburg, R. Kulkarni, A. Srivastava, et al., "Improved Joint Health in Subjects With Severe Haemophilia A Treated Prophylactically With Recombinant Factor VIII fc Fusion Protein," *Haemophilia* 24, no. 1 (2018): 77–84.

17. J. Pasi, C. Hermans, Z. Hakimi, et al., "Improvement in Pain-Related Quality of Life in Patients With Hemophilia A Treated With rFVIIIFc Individualized Prophylaxis: Post hoc Analysis From the A-LONG Study," *Therapeutic Advances in Hematology* 13 (2022): 20406207221079482.

18. A. D. Shapiro, M. V. Ragni, R. Kulkarni, et al., "Recombinant Factor VIII fc Fusion Protein: Extended-Interval Dosing Maintains low Bleeding Rates and Correlates With von Willebrand Factor Levels," *Journal of Thrombosis and Haemostasis* 12, no. 11 (2014): 1788–1800.

19. J. Blatny, E. M. Nielsen, S. B. Reitzel, et al., "Real-World Evidence on Efmoroctocog Alfa in Patients With Haemophilia A: A Systematic Literature Review of Treatment Experience in Europe," *Haemophilia* 29, no. 4 (2023): 963–974.

20. J. Oldenburg, C. R. M. Hay, V. Jimenez-Yuste, et al., "Design of a Prospective Observational Study on the Effectiveness and Real-World Usage of Recombinant Factor VIII Fc (rFVIIIFc) Compared With Conventional Products in Haemophilia A: The A-SURE Study," *BMJ Open* 9, no. 5 (2019): e028012.

21. ICH, "International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised guideline," Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Current Step 4 version 2016, https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.

22. C. Wang and G. Young, "Clinical Use of Recombinant Factor VIII fc and Recombinant Factor IX fc in Patients With Haemophilia A and B," *Haemophilia* 24, no. 3 (2018): 414–419.

23. E. Berntorp, C. Hermans, A. Solms, L. Poulsen, and M. E. Mancuso, "Optimising Prophylaxis in Haemophilia A: The ups and Downs of Treatment," *Blood Reviews* 50 (2021): 100852.

24. A. Tagliaferri, A. Matichecchia, G. F. Rivolta, et al., "Optimising Prophylaxis Outcomes and Costs in Haemophilia Patients Switching to Recombinant FVIII-Fc: A Single-Centre Real-World Experience," *Blood Transfusion* 18, no. 5 (2020): 374–385.

25. B. A. Konkle, J. Oldenburg, J. Pasi, et al., "Prophylaxis With a Recombinant Factor VIII fc in Hemophilia A: Long-Term Follow-Up on Joint Health, Efficacy, and Safety From Phase 3 Studies in Children and Adults," *Res Pract Thromb Haemost* 7, no. 6 (2023): 102180.

26. J. Oldenburg, G. Goldmann, N. Marquardt, et al., "Real-World Clinical Experience of Extended Half-Life Recombinant Factor VIII fc Fusion Protein (rFVIIIFc) in Comparison to Conventional Factor Products in Patients With Severe Hemophilia A," *Current Medical Research and Opinion* 4, no. 5 (2021): 950–960.

27. M. Holmstrom, E. Olsson, J. Astermark, et al., "Real-World Prophylactic Usage of Recombinant Factor VIII fc in Sweden: A Report From the Swedish National Registry for Bleeding Disorders," *Haemophilia* 27, no. 4 (2021): e554–e558.

28. C. Bidlingmaier, C. Heller, F. Langer, et al., "Final Data From the PREVENT Study Evaluating Real-World Usage and Effectiveness of a Recombinant Factor VIII fc and Recombinant Factor IX fc in Haemophilia A or B in Germany," *Haemophilia* 29, no. S1 (2023): 24–202.

29. F. Peyvandi, I. Garagiola, M. Boscarino, A. Ryan, C. Hermans, and M. Makris, "Real-Life Experience in Switching to New Extended Half-Life Products at European Haemophilia Centres," *Haemophilia* 25, no. 6 (2019): 946–952.

30. M. Olivieri, M. Simpson, S. Yan, et al., "Analysis of Pooled Real-World Data From Germany, Italy, and the United States of rVIII-SingleChain Compared With Standard- and Long-Acting FVIII Products for Prophylaxis of Hemophilia A," *Current Medical Research and Opinion* 38, no. 7 (2022): 1133–1139.

31. M. van der Sluijs, N. Huyghe, C. Wood, and S. Tawil, "A Survey of physicians' Treatment Switching Practice in People on Long-Term Prophylaxis for Hemophilia in Five European Countries," *Current Medical Research and Opinion* 38, no. 1 (2022): 65–73.

32. A. Iorio, S. Krishnan, K. J. Myren, et al., "Indirect Comparisons of Efficacy and Weekly Factor Consumption During Continuous Prophylaxis With Recombinant Factor VIII fc Fusion Protein and Conventional Recombinant Factor VIII Products," *Haemophilia* 23, no. 3 (2017): 408–416.

33. R. Klamroth, P. Wojciechowski, S. Aballea, et al., "Efficacy of rFVIIIFc Versus Emicizumab for the Treatment of Patients With Hemophilia A Without Inhibitors: Matching-Adjusted Indirect Comparison of A-LONG and HAVEN Trials," *Journal of Blood Medicine* 12 (2021): 115–122.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.