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# Real-world usage and effectiveness of recombinant factor IX Fc in haemophilia B from the B-SURE study in France

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***Abstract***

**Background:** More real-world data are needed to complement existing phase III studies on the efficacy and safety of recombinant factor IX Fc fusion protein (rFIXFc) in people with haemophilia B.

**Objectives:** We report final data from the B-SURE study, evaluating the real-world usage and effectiveness of rFIXFc in France.

**Methods:** Previously treated patients (all ages/severities) received on-demand or prophylactic rFIXFc during B-SURE. Annualised bleeding rate (ABR), injection frequency (IF) and factor consumption (FC) were prospectively evaluated for patients on rFIXFc prophylaxis (primary endpoints). Six months of retrospective factor IX (FIX) data were collected for comparison; patients with ⩾3 months of treatment pre- and post-switch to rFIXFc were analysed.

**Design:** B-SURE was a 24-month, prospective, non-interventional, real-world study across haemophilia treatment centres in France.

**Results:** Ninety-one male patients enrolled across 21 centres (34% <18 years, 89% severe haemophilia B). Eighty-four patients received prophylaxis at rFIXFc initiation; mean prospective observation period was 21.5 months. Sixty-eight of 84 patients had prior FIX prophylaxis; on rFIXFc prophylaxis, these patients achieved low median ABR (1.2), IF (47.45 injections/year) and mean FC (2844 IU/kg/year). Compared with previous FIX, mean ABR was reduced by 40% ($n = 63$); mean IF and FC were reduced by 38.20 injections/year and 1008 IU/kg/year ($n = 57$). In patients with prior FIX on-demand ($n = 15$), mean ABR reduced by 84% on rFIXFc prophylaxis ($n = 14$), mean IF reduced by 2.13 injections/year and mean FC increased by 381.8 IU/kg/year ($n = 15$). Most physicians and patients were satisfied/highly satisfied with rFIXFc prophylaxis. rFIXFc was well tolerated with no new safety concerns.

**Conclusion:** Findings support the safety and effectiveness of rFIXFc, with reduced IF and FC while maintaining/improving bleed protection.

***Trial registration*:** NCT03655340.

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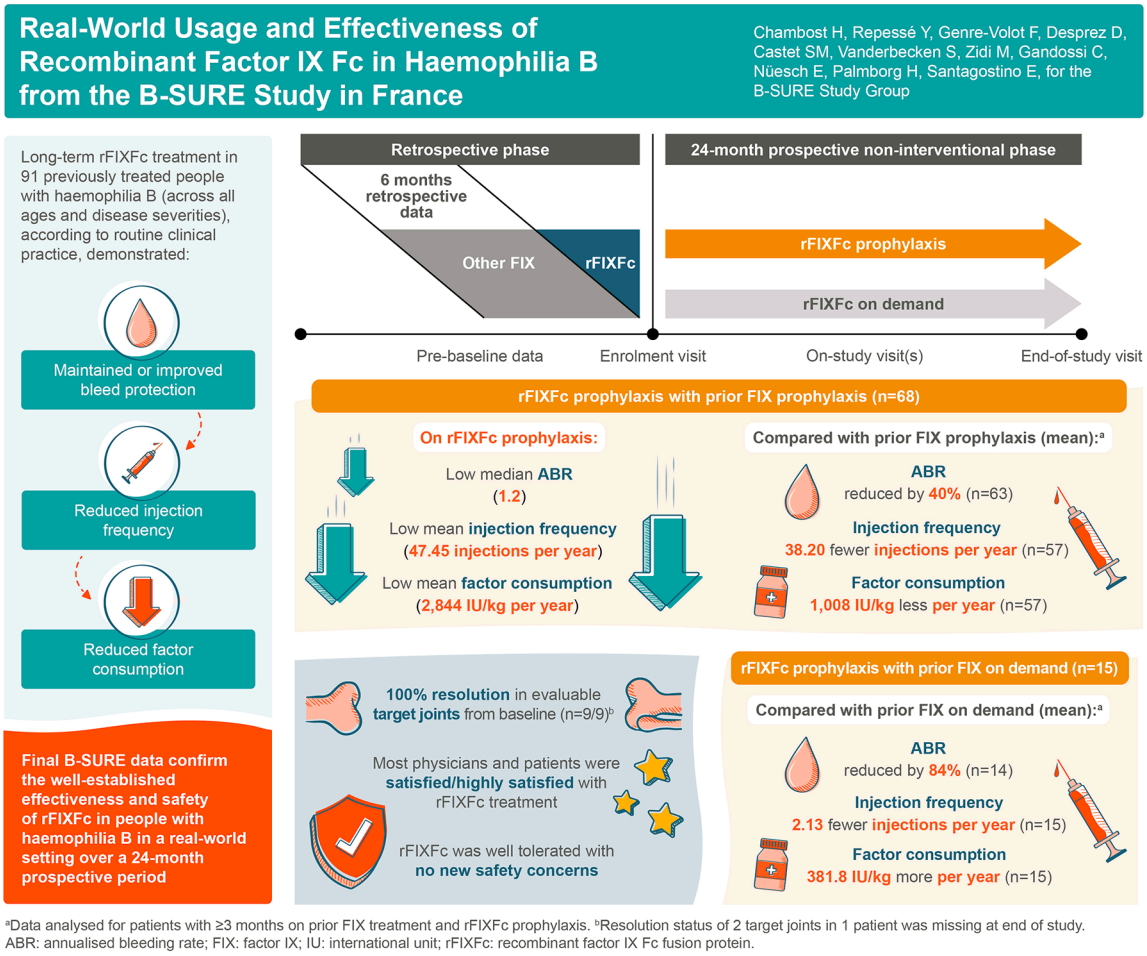
## Graphical abstract




aData analysed for patients with ≥3 months on prior FIX treatment and rFIXFc prophylaxis. bResolution status of 2 target joints in 1 patient was missing at end of study.
ABR: annualised bleeding rate; FIX: factor IX; IU: international unit; rFIXFc: recombinant factor IX Fc fusion protein.

***Keywords:*** factor IX, haemophilia B, prophylaxis, recombinant fusion proteins

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## Introduction

Treatment for haemophilia B consists of replacement therapy with factor IX (FIX) products, administered either prophylactically as regular injections (standard of care) to prevent or minimise the occurrence of bleeding episodes and subsequent joint damage, or on demand when bleeding episodes occur.[1,2]

Extended half-life (EHL) products were developed to reduce treatment burden, maintain higher factor trough levels and improve bleed protection compared to standard half-life (SHL) products.[2]

The efficacy and safety of eftrenonacog alfa, a recombinant factor IX Fc fusion protein (herein referred to as rFIXFc), were established across phase III pivotal and extension studies in previously-treated patients with severe haemophilia B.[3–7] These studies demonstrated low annualised bleeding rates (ABRs) with prophylactic rFIXFc dosing intervals of 7 to ⩾14 days.[3–5,7] rFIXFc was also effective in the treatment of acute bleeding and perioperative management.[3–6,8] rFIXFc is approved in the United States, Europe and other regions of the world for the treatment and prophylaxis of bleeding in all age groups of people with haemophilia B.[9–13]

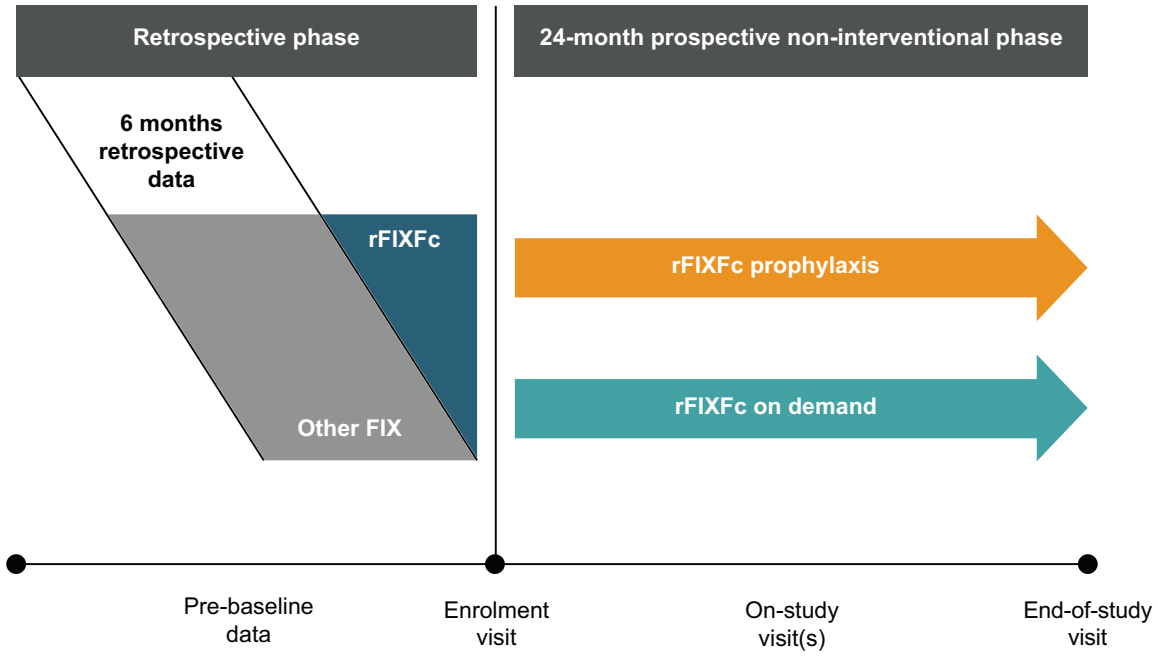


**Figure 1.** B-SURE study design.
FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein.

However, clinical trials can be inherently limited due to mandated dose or treatment intervals, and restrictions in the populations and/or treatment duration. As such, there is a need for more real-world data on the effectiveness and usage of rFIXFc in clinical practice to complement existing data and bridge evidence gaps.[14–20]

B-SURE (NCT03655340) was a 24-month, multicentre, prospective, non-interventional study, which enrolled a large cohort of patients with haemophilia B treated with rFIXFc according to routine practice in France. Here, we report the final data from the B-SURE study evaluating the real-world usage and effectiveness of treatment with rFIXFc.

## Methods

### *Study design and participants*

B-SURE (NCT03655340) was a non-interventional study across haemophilia treatment centres in France, which primarily aimed to evaluate the real-world effectiveness and usage of rFIXFc in patients with haemophilia B over a 24-month prospective period.

Patients across all ages and severities of haemophilia B who had previously been treated with a FIX product were eligible for enrolment in B-SURE. There were no specific requirements or restrictions regarding prior or concomitant therapy during the study. However, participation in any other investigational medicinal product trial at enrolment was not permitted.

Patients switched from previous FIX products to on-demand or prophylactic treatment with rFIXFc prior to or at enrolment (Figure 1). For patients who initiated rFIXFc treatment before enrolment, retrospective data on previous FIX treatment were collected from the 6-month period before the first rFIXFc injection. For patients who initiated rFIXFc treatment at enrolment, retrospective data were collected for 6 months prior to enrolment. The 24-month period from enrolment to the last study visit contributed to the prospective period. The total observation period per patient was $24 \pm 6$ months, calculated from the enrolment visit. rFIXFc was prescribed based on the treating physician's judgement and in discussion with the patient.

### *Outcome measures and data collection*

At enrolment, baseline characteristics and 6 months of retrospective data prior to the switch

to rFIXFc were collected. Prospective data were collected at the enrolment visit and at routine clinical visits up to the 24-month visit.

The primary objective was to evaluate the real-world effectiveness and usage of rFIXFc treatment over the 24-month prospective period.

For patients treated prophylactically with ⩾3 months prospective follow-up on rFIXFc, primary endpoints included ABR (based on bleeding episodes reported by the healthcare professional at study visits), annualised injection frequency (IF; assessed by prescription and usage at regular visits) and annualised factor consumption (FC; assessed by prescription and usage). Data on treatment and bleeding were collected from patient diaries during routine clinical practice and entered into an electronic case report form. For patients treated on demand, primary endpoints included the amount of rFIXFc and the number of injections to treat a bleeding episode.

Secondary objectives were to describe the effectiveness and annual usage of rFIXFc since initiation compared to the period with other FIX products. Therefore, data from both the prospective and retrospective periods were analysed.

The change in primary endpoints since rFIXFc initiation compared with prior treatment were assessed as the secondary endpoints for prophylactically treated patients with ⩾3 months on prior FIX treatment and rFIXFc. Other secondary endpoints for prophylactically treated patients included: annualised joint bleeding rate (AJBR) since rFIXFc initiation and change in AJBR since rFIXFc initiation; target joints at enrolment (defined as a joint in which ⩾3 spontaneous bleeding episodes occurred within a consecutive 6-month period in the last year) and target joint resolution at the end of study (⩽2 bleeding episodes into the joint within a consecutive 12-month period); prescribed IF and dose prior to and since rFIXFc initiation; change in weekly number of injections and/or weekly dose (prescribed and usage) since rFIXFc initiation; reason for change in prescribed dose and/or IF; occurrence of a change in treatment regimen; and surgery data, including surgery type and rFIXFc consumption across the perioperative period (prior to, during and post-surgery until return to usual treatment), stratified by major and minor surgeries. In addition, physician satisfaction with the outcomes of rFIXFc treatment was assessed using a 5-point scale (highly satisfied/satisfied/neutral/dissatisfied/highly dissatisfied). Hemophilia Joint Health Scores (HJHS)© were recorded at all study visits, if performed as part of normal clinical practice.

Patient-reported outcomes (PROs) were recorded for all study participants: EuroQoL-5 Dimension 5 levels (EQ-5D-5L; visual analogue scale range 0–100, with low scores indicating worse health states), Haemophilia Activities List (HAL)/Paediatric HAL (PedHAL) with range 0–100 (low scores indicating worse functional status and patient satisfaction of rFIXFc treatment using the aforementioned 5-point scale). Self-reported questionnaires were administered at the enrolment visit and at all routine clinical visits to evaluate and compare changes in the patient's perceptions of quality of life and treatment satisfaction. Further details on PROs are provided in the Supplemental Methods.

Secondary endpoints for patients treated with rFIXFc on demand and with ⩾3 months follow-up included: ABR, AJBR, change in ABR and AJBR since rFIXFc initiation, and physician and patient satisfaction with outcomes of rFIXFc treatment using the 5-point scale.

Only serious adverse events (SAEs) and non-serious adverse events (non-SAEs) that led to rFIXFc discontinuation were collected, from the first rFIXFc dose to the patient's last study visit.

### *Statistical analysis*

Study outcomes were summarised using descriptive statistics; no formal statistical hypothesis testing was performed. On-demand and prophylactically treated patients were evaluated separately; subgroup presentations were performed as appropriate.

For calculation of annualised endpoints, the minimum documented treatment duration was set to 3 months within the respective period. This refers to all treatment periods (prior to rFIXFc, since rFIXFc initiation and during both the retrospective and prospective rFIXFc treatment periods). Comparisons with previous SHL FIX therapy

were only made for patients where sufficient retrospective data were available to calculate annualised endpoints.

Mean ABR and AJBR prior to and since rFIXFc initiation were estimated using a negative binomial model, with the total number of treated bleeding episodes during the respective period as the response variable and the log-transformed duration (in years) of the observation period as an offset variable. Rate ratios (RRs) were estimated using a repeated negative binomial model with treatment period (prior versus post rFIXFc initiation) as a covariate.

PROs were analysed by visit, applying a window algorithm where assessments were assigned to the predefined visit schedule and the assessment closest to the predefined schedule was analysed.

## Results

### *Study location, population and treatment regimens*

A total of 22 haemophilia treatment centres across France participated in B-SURE and 21 centres successfully enrolled patients; participating centres are listed in the Supplemental Material. Of the 98 patients screened, 91 male patients were enrolled between September 2018 and September 2019. Eighty-six patients (94.5%) completed the 24-month study period.

Most patients enrolled in B-SURE had severe haemophilia B (89.0%, $n = 81/91$; Table 1). Median (range) age of the enrolled patients was 34.2 (4–84) years; 31 patients (34.1%) were <18 years. Most enrolled patients received prophylactic treatment at rFIXFc initiation (92.3%; $n = 84/91$); 7 patients (7.7%) received on-demand treatment (Figure 2).

For patients treated with rFIXFc prophylaxis, the most common reasons for rFIXFc treatment initiation were to 'reduce injection frequency while maintaining protection from bleeds' (47.6%; $n = 40/84$) and to 'provide protection from bleeds' (40.5%; $n = 34/84$). For the 7 patients treated on demand, 3 (42.9%) initiated rFIXFc to 'reduce the number of injections to treat a bleed'; the reason for initiating rFIXFc for the remaining patients was classified as 'other' (57.1%; $n = 4/7$).

Prior to the switch to rFIXFc prophylaxis, 64 patients were treated with FIX prophylaxis and 16 patients had FIX on-demand treatment (Figure 2). Four patients received both prophylaxis and on-demand treatment before initiating rFIXFc prophylaxis.

Most patients who received rFIXFc prophylaxis at initiation remained on a prophylactic regimen throughout B-SURE to their last documented rFIXFc treatment ($n = 83$; 98.8%). One patient had multiple switches between prophylaxis and on-demand treatment during the study, but the final regimen was rFIXFc on-demand. This patient initiated rFIXFc treatment for protection from bleeds; reasons for the switch between treatment regimens were not recorded.

Of the 23 patients with prior on-demand treatment, 7 continued to receive on-demand treatment after the switch to rFIXFc. Of these, 4 patients switched from on-demand treatment to prophylaxis during the study and remained on prophylaxis as their final rFIXFc regimen.

In the overall study population, the mean (range) prospective observation period was 21.6 (3.1–30.6) months. The mean (range) prospective observation period was 21.5 (3.1–30.6) months for the 84 patients on rFIXFc prophylaxis at initiation and 23.6 (17.9–29.9) months for the 7 patients treated with rFIXFc on-demand at initiation.

### *Prophylactic rFIXFc treatment*

*ABRs, IF and FC.* In patients with prior prophylaxis ($n = 68$), the mean/median (interquartile range [IQR]) total ABR during the prospective treatment period on rFIXFc prophylaxis was 1.6/1.2 (0.0–2.5). The mean/median (IQR) total AJBR during the prospective period was 0.8/0.5 (0.0–1.2). For the 63 patients with ⩾3 months available data pre- and post-switch to rFIXFc prophylaxis, there was a mean reduction of 40% in ABR (RR: 0.60; 95% confidence interval (CI): 0.39–0.92) and 36% in AJBR (RR: 0.62; 95% CI: 0.34–1.11) since rFIXFc initiation (Figure 3[a]).

**Table 1.** Baseline characteristics and demographics of patients enrolled in B-SURE.

| ***n* (%), unless otherwise stated** | **rFIXFc prophylaxis at initiation (*n* = 84)** | **rFIXFc on demand at initiation (*n* = 7)** | **Total (*N* = 91)** |
|---|---|---|---|
| Gender | | | |
| Male | 84 (100.0) | 7 (100.0) | 91 (100.0) |
| Severity of haemophilia | | | |
| Severe | 76 (90.5) | 5 (71.4) | 81 (89.0) |
| Moderate | 3 (3.6) | 1 (14.3) | 4 (4.4) |
| Mild | 5 (6.0) | 1 (14.3) | 6 (6.6) |
| Age (years), median (range) | 33.5 (4–78) | 51.9 (17–84) | 34.2 (4–84) |
| Age category (years) | | | |
| <12 | 16 (19.0) | 0 (0.0) | 16 (17.6) |
| 12–17 | 14 (16.7) | 1 (14.4) | 15 (16.5) |
| ⩾18 | 54 (64.3) | 6 (85.7) | 60 (65.9) |
| Weight (kg), median (range) | 64.0 (15–152) | 78.0 (60–90) | 65.0 (15–152) |
| History of inhibitors[a] | 2 (2.4) | 0 (0.0) | 2 (2.2) |
| Low-titre, *n* (peak titre, BU/mL) | 1 (4.75) | – | 1 (4.75) |
| High-titre, *n* (peak titre, BU/mL) | 1 (16.00) | – | 1 (16.00) |
| Target joints[b] | | | |
| 0 | 75 (89.3) | 6 (85.7) | 81 (89.0) |
| ⩾1 | 9 (10.7) | 1 (14.3) | 10 (11.0) |
| Prior FIX treatment regimen | | | |
| Prophylaxis | 64 (76.2) | 0 (0.0) | 64 (70.3) |
| On-demand | 16 (19.0) | 7 (100) | 23 (25.3) |
| Both (prophylaxis and on-demand) | 4 (4.8) | 0 (0.0) | 4 (4.4) |
| Prior treatment | | | |
| Plasma-derived | 41 (48.8) | 4 (57.1) | 45 (49.5) |
| Recombinant | 35 (41.7) | 3 (42.9) | 38 (41.8) |
| Investigational medicinal product | 3 (3.6) | 0 (0.0) | 3 (3.3) |
| Missing | 5 (6.0) | 0 (0.0) | 5 (5.5) |

*(Continued)*

**Table 1.** (Continued)

| *n* (%), unless otherwise stated | rFIXFc prophylaxis at initiation (*n* = 84) | rFIXFc on demand at initiation (*n* = 7) | Total (*N* = 91) |
|---|---|---|---|
| Prior relevant comorbidities | | | |
| Human immunodeficiency virus | 17 (20.2) | 1 (14.3) | 18 (19.8) |
| Hepatitis C virus | 3 (3.6) | 0 (0.0) | 3 (3.3) |
| Clinically significant cardiovascular disease | 9 (10.7) | 1 (14.3) | 10 (11.0) |
| Clinically significant liver disease | 4 (4.8) | 1 (14.3) | 5 (5.5) |
| Depression | 1 (1.2) | 0 (0.0) | 1 (1.1) |
| Non-haemophilic acute or chronic medical conditions causing mobility/ joint problems | 6 (7.1) | 1 (14.3) | 7 (7.7) |
| Other[c] | 13 (15.5) | 2 (28.6) | 15 (16.5) |

Percentage values may not sum to 100% due to rounding. Prior refers to the 6-month retrospective period before rFIXFc initiation.
[a]Low-titre inhibitor defined as ⩾0.60 to <5 BU/mL; high-titre inhibitor defined as ⩾5 BU/mL.
[b]Target joints were defined as major joints with ⩾3 bleeding episodes into the same joint in a consecutive 3-month period.
[c]As judged by the physician.
FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein.

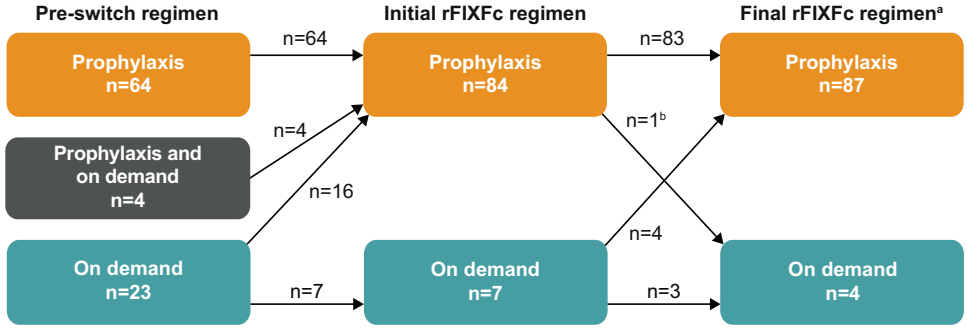


**Figure 2.** Treatment regimens pre- and post-switch to rFIXFc.
[a]Final rFIXFc regimen refers to the last documented regimen.
[b]One patient had multiple switches between prophylaxis and on-demand treatment regimens since rFIXFc prophylaxis initiation; final regimen was on-demand treatment.
FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein.

The mean (SD) annualised IF and dispensed FC during the prospective treatment period in patients with prior prophylaxis (*n* = 68) was 47.45 (13.13) injections/year and 2,844 (1,043) IU/kg/year. In those with available data pre- and post-switch to rFIXFc prophylaxis (*n* = 57), the mean annualised IF reduced by 38.20 injections/year and annualised FC reduced by 1,008 IU/kg/year (Table 2).

In patients with prior on-demand treatment (*n* = 15; 1 missing), the mean/median (IQR) total ABR during the prospective treatment

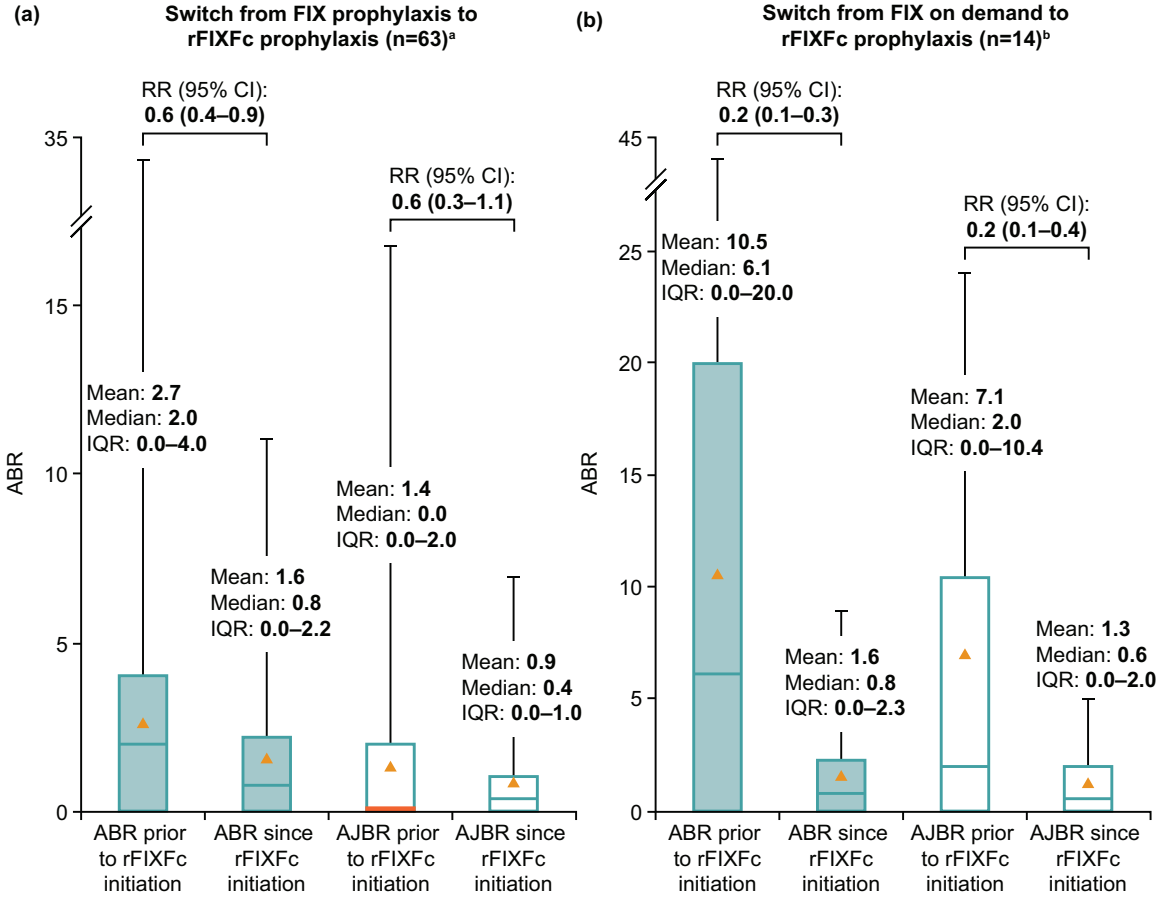


**Figure 3.** ABR of patients with available data both pre- and post-switch to rFIXFc prophylaxis from (a) FIX prophylaxis ($n=63$) or (b) FIX on-demand treatment ($n=14$).
Figure shows means (triangles), IQR (box boundaries) and ranges (error bars); orange line indicates equal median/quartile. The period prior to rFIXFc initiation refers to the 6 months prior to the first rFIXFc injection; the period since rFIXFc initiation refers to the period from the first rFIXFc injection to the end of the prospective period. Means were estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed period duration (in years) as an offset variable. RRs were estimated using a repeated negative binomial model with treatment period (prior versus post rFIXFc initiation) as a covariate.
[a]$n=63/65$ patients with available data both pre- and post-switch to rFIXFc prophylaxis were included.
[b]$n=14/18$ patients with available data both pre- and post-switch to rFIXFc prophylaxis were included.
ABR, annualised bleeding rate; AJBR, annualised joint bleeding rate; FIX, factor IX; IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein; RR, rate ratio.

period on rFIXFc was 1.4/1.0 (0.0–1.6). The mean/median (IQR) total AJBR during the prospective period was 1.2/0.6 (0.0–1.6). For those with ⩾3 months available data both pre- and post-switch to rFIXFc prophylaxis ($n=14$), the mean ABR and AJBR reduced by 84% and 82% (RR: 0.16; 95% CI: 0.08–0.33 and RR: 0.18; 95% CI: 0.08–0.38), respectively (Figure 3[b]).

Mean (SD) annualised IF and dispensed FC of rFIXFc during the prospective period in patients with prior on-demand treatment ($n=15$) was 31.00 (13.52) injections/year and 1,900 (944) IU/kg/year. In those with available data pre- and post-switch to rFIXFc prophylaxis ($n=15$), the mean annualised IF reduced by 2.13 injections/year and the mean annualised FC increased by 381.8 IU/kg/year (Table 2).

For those with available pre- and post-switch data, the median (IQR) weekly number of injections in patients with prior prophylaxis and prior on-demand treatment since rFIXFc initiation was 0.98 (0.79–1.05; $n=57$) and 0.58 (0.46–0.84; $n=15$) injections/week, respectively (Table 2).

**Table 2.** IF and annualised FC for patients with available data pre- and post-switch to rFIXFc during B-SURE.

| Statistic | Switch from prior FIX prophylaxis to rFIXFc prophylaxis ($n = 57$)[a] | | | Switch from prior FIX on demand to rFIXFc prophylaxis ($n = 15$)[b] | | |
|---|---|---|---|---|---|---|
| | Pre-switch | Post-switch | Change[c] | Pre-switch | Post-switch | Change[c] |
| Weekly IF (injections/week) | | | | | | |
| Mean (SD) | 1.66 (0.61) | 0.93 (0.26) | −0.73–(0.54) | 0.70 (1.21) | 0.66 (0.28) | −0.04 (1.20) |
| Median | 1.82 | 0.98 | −0.85 | 0.43 | 0.58 | 0.06 |
| IQR | 1.08–2.00 | 0.79–1.05 | −1.02–0.34 | 0.19–0.58 | 0.46–0.84 | −0.12–0.50 |
| Range | 0.34–3.46 | 0.39–1.99 | −2.44–0.14 | 0.00–4.97 | 0.32–1.30 | −4.13–1.11 |
| Annualised IF (injections/year) | | | | | | |
| Mean (SD) | 86.55 (31.60) | 48.31 (13.33) | −38.20 (28.24) | 36.39 (63.28) | 34.26 (14.38) | −2.13 (62.73) |
| Median | 94.84 | 51.22 | −44.10 | 22.20 | 30.27 | 3.29 |
| IQR | 56.19–104.40 | 41.06–54.93 | −53.00–17.50 | 9.98–30.44 | 24.07–43.80 | −6.37–26.28 |
| Range | 17.60–180.60 | 20.41–103.90 | −127.00–7.31 | 0.00–259.50 | 16.60–67.87 | −216.00–57.89 |
| Weekly FC (IU/kg/week) | | | | | | |
| Mean (SD) | 75.34 (40.87) | 56.03 (19.86) | −19.31 (32.50) | 31.18 (59.29) | 38.50 (18.13) | 7.32 (58.89) |
| Median | 66.13 | 51.67 | −8.36 | 15.50 | 34.39 | 16.67 |
| IQR | 49.26–86.66 | 45.56–64.09 | −35.12–5.54 | 8.13–22.04 | 23.20–47.63 | −0.27–39.47 |
| Range | 14.50–252.30 | 22.00–161.20 | −133.10–25.80 | 0.00–242.60 | 20.10–90.90 | −189.70–76.10 |
| Annualised FC (IU/kg/year) | | | | | | |
| Mean (SD) | 3,931 (2,132) | 2,924 (1,036) | −1,008 (1,696) | 1,627 (3,094) | 2,009 (945.92) | 381.8 (3,073) |
| Median | 3,451 | 2,696 | −436.40 | 809.00 | 1,789 | 869.60 |
| IQR | 2,570–4,522 | 2,377–3,344 | −1,833–289.20 | 424.20–1,150 | 1,211–2,485 | −14.20–2,060 |
| Range | 754.00–13,162 | 1,150–8,410 | −6,946–1,344 | 0.00–12,657 | 1,049–4,743 | −9,898–3,973 |

Pre-switch refers to the period prior to rFIXFc initiation; post-switch refers to the period since rFIXFc initiation.
[a]57/65 patients with available data both pre- and post-switch to rFIXFc prophylaxis were included.
[b]15/18 patients with available data both pre- and post-switch to rFIXFc prophylaxis were included.
[c]Data were calculated from the date of rFIXFc initiation, including retrospective data.
FC, factor consumption; FIX, factor IX; IF, injection frequency; IQR, interquartile range; IU, international unit; rFIXFc, recombinant factor IX Fc fusion protein.

A median decrease in weekly IF of 0.85 was seen in patients with prior prophylaxis following switch to rFIXFc, while those with prior on-demand treatment had a median increase of 0.06 injections/week.

Since rFIXFc initiation, the median (IQR) weekly rFIXFc consumption for patients with prior prophylaxis and prior on-demand treatment (with available pre- and post-switch data) was 51.67 (45.56–64.09; $n = 57$) and 34.39 (23.20–47.63; $n = 15$) IU/kg/week, respectively (Table 2). A median decrease in weekly FC of 8.36 IU/kg/week was observed in patients with prior prophylaxis following switch to rFIXFc prophylaxis, while those with prior on-demand treatment had a

median increase of 16.67 IU/kg/week. Of the 57 patients who switched from prior prophylaxis to rFIXFc prophylaxis with ⩾3 months available data, 91.2% had severe haemophilia, 5.3% had moderate and 3.5% had mild. Of the 15 patients who switched from prior on-demand treatment to rFIXFc prophylaxis with ⩾3 months available data, 13 (86.7%) had severe haemophilia and 2 (13.3%) had mild.

*Prescribed IF and dose.* Median (IQR) change in prescribed annualised IF, weekly dose and number of injections since rFIXFc initiation in patients treated with rFIXFc prophylaxis (with data available pre- and post-switch to rFIXFc; $n=58$) was −53.0 (−63.1−5.95) injections/year, −11.1 (−33.8−6.7) IU/kg/week and −1.02 (−1.21−0.11) injections/week, respectively. Prescribed IF and dose prior to and since rFIXFc initiation are presented in the Supplemental Results.

During the observation period, more than half of the patients treated with rFIXFc prophylaxis ($n=49/84$; 58.3%) had a change in the frequency and/or dose of prescribed prophylactic treatment. The most common reasons for changes in prescription were to improve 'protection from bleeds' ($n=19/49$ patients; 38.8%), 'reduce injection frequency while maintaining protection from bleeds' ($n=19/49$; 38.8%), 'weight adjusting' ($n=8/49$; 16.3%) and 'improve protection to increase physical activity level' ($n=3/49$; 6.1%).

Over the observation period, the proportion of patients with a rFIXFc IF of >7 days increased (Figure S1). Most patients on rFIXFc prophylaxis ($n=58/84$; 69.0%) had a prescribed IF of every 7 days at rFIXFc initiation; 27.4% of patients ($n=23$) had a prescribed frequency of >7 days, increasing to 34.5% ($n=29$) at last documentation.

*Target joints.* Most patients who initiated rFIXFc prophylaxis had no target joints at enrolment (89.3%; $n=75/84$; Table 1). The remaining 9 patients had at least 1 target joint with 11 target joints in total ($n=7$ patients had 1 target joint; $n=2$ had 2), which were localised to the ankles, elbows or knees.

At the end of the observation period, nine target joints were resolved. The resolution status for two target joints from one patient were not assessed as he ended the study less than 12 months after the enrolment visit.

*Physician and patient satisfaction.* Physicians were highly satisfied or satisfied with the outcome of rFIXFc prophylaxis at the last assessment for most patients (83.3%; $n=70/84$) and highly dissatisfied or dissatisfied for 6.0% of patients ($n=5/84$; $n=7$ were neutral; $n=2$ had missing data). For patients who initiated rFIXFc for 'protection from bleeds', 94.1% ($n=32/34$) of physicians were highly satisfied or satisfied with treatment outcomes. For those who initiated rFIXFc treatment to 'reduce injection frequency while maintaining protection', 75.0% ($n=30/40$) of physicians were highly satisfied or satisfied with the treatment outcome.

Most patients (77.4%; $n=65/84$) were satisfied or highly satisfied with the outcome of rFIXFc prophylaxis at the last assessment, while 8 patients (9.5%) were highly dissatisfied or dissatisfied ($n=5$ were neutral; $n=6$ had missing data). Of the patients who initiated rFIXFc to 'reduce injection frequency while maintaining protection', 80% ($n=32/40$) were highly satisfied or satisfied with the treatment outcome. For those who initiated rFIXFc for the 'protection from bleeds', 73.5% ($n=25/34$) of patients were highly satisfied or satisfied with rFIXFc treatment.

Most patients ($n=66/84$) completed the questionnaires themselves; for 16 patients, the questionnaires were completed by a caregiver ($n=2$ had missing data).

*Patient-reported outcomes.* The number of patients on rFIXFc prophylaxis with an available EQ-5D-5L assessment decreased from 86.9% ($n=73/84$) patients at enrolment to 40.5% ($n=34/84$) at month 18 (Figure S2[a]). Mean (SD) score was 74.0 (19.77) at enrolment and 77.0 (20.59) at month 18.

The number of patients with an available HAL or PedHAL score also declined throughout the prospective period (Figure S2[b] and [C]). Mean (SD) HAL score varied slightly throughout the study period from 67.9 (21.22) at enrolment ($n=54$) to 65.9 (20.61) at month 18 ($n=25$). Mean (SD) PedHAL score was 96.3 (4.83) at

enrolment ($n = 20$) and 98.7 (2.16) at month 18 ($n = 9$).

*HJHS.* HJHS data were only available for a limited number of patients and as a result, were not included in this analysis (data are available on request).

### *On-demand rFIXFc treatment*

*Amount of rFIXFc and number of injections to treat a bleeding episode.* Six of the 7 patients treated with rFIXFc on demand experienced a total of 18 bleeding episodes during the prospective period (14 traumatic in $n = 5$ patients; 4 spontaneous in $n = 3$). Median (IQR) amount of rFIXFc used to treat a bleeding episode during the prospective period was 42.7 (41.4–51.7) IU/kg/injection (event-based; Table S1).

Median (IQR) number of injections to treat a bleeding episode during the prospective period was 1.0 (1.0–1.0; Table S1). The median (IQR) number of injections to treat spontaneous bleeding episodes was higher than for traumatic bleeding episodes (1.5 [1.0–6.0] versus 1.0 [1.0–1.0]).

Secondary endpoints for patients treated with rFIXFc on demand are summarised in the Supplemental Results.

### *Surgery*

In the overall study population, 16 major (in $n = 13$ patients) and 61 minor surgeries (in $n = 32$ patients) were performed. Most common major surgeries were knee arthroplasty ($n = 8$ surgeries) and synovectomy ($n = 2$). Most common minor surgeries were joint injections ($n = 21$ surgeries) and tooth extractions ($n = 13$). Data on the surgery outcomes were not collected in this study.

Since rFIXFc initiation, 47.6% of patients treated with rFIXFc prophylaxis ($n = 40/84$) and 71.4% of patients treated on demand ($n = 5/7$) had at least one surgery (69 and 8 surgeries, respectively).

Overall, the median (IQR) number of rFIXFc injections and median (IQR) consumption prior to and during surgery was 9.5 (8.5–18.5) injections and 534.74 (396.32–843.28) IU/kg for major surgeries, and 1.0 (1.0–2.0) injection and 80.40 (60.24–128.57) IU/kg for minor surgeries.

The median (IQR) total number of injections across the perioperative period was 18.0 (11.5–26.0) for major surgeries and 1.0 (1.0–3.0) for minor surgeries. Median (IQR) total consumption during the perioperative period was 864.66 (545.30–1,607) IU/kg for major surgeries and 98.88 (61.54–166.67) IU/kg for minor surgeries.

### *Safety*

In the overall population, 26.4% of patients ($n = 24/91$) experienced at least one SAE ($n = 48$ SAEs were recorded in total). The most frequently reported SAEs were fall, rectal haemorrhage, chest pain and haematuria (each reported for $n = 3$ patients).

One patient with severe haemophilia B (aged 32 years), who received prior on-demand FIX treatment and switched to 50 IU/kg rFIXFc weekly prophylaxis, developed two SAEs (hypersensitivity and a low-titre FIX inhibitor) which were assessed by the investigator as related to treatment and led to discontinuation of rFIXFc. Recovery from the hypersensitivity reaction occurred on the day of the event. After study withdrawal, treatment with rFVIIa was initiated.

The patient had a family history of inhibitors and a previous history of low-titre inhibitors associated with an allergic reaction. Previous haemophilia treatments included bypassing agents, plasma-derived prothrombin complex concentrate for approximately 13 years and plasma-derived FIX for approximately 17 years. Past medical history included asthma and ankle arthropathy.

No other adverse events were assessed as treatment-related during the prospective period. One patient experienced a fatal SAE (acute pulmonary oedema) which was deemed unrelated to rFIXFc treatment.

## Discussion

Final data from B-SURE support the effectiveness and safety of rFIXFc treatment in people with haemophilia B in a real-world setting. rFIXFc usage in this clinical practice setting was

consistent with clinical trial experience and in line with dosing recommendations in product labels.[3–7,9,10]

Long-term data, across a mean prospective follow-up of 21.5 months for patients receiving prophylaxis at B-SURE initiation, supports the possibility to reduce IF and FC whilst maintaining or improving bleed protection with rFIXFc. Low ABRs were achieved on rFIXFc prophylaxis regardless of the pre-study treatment regimen (on-demand or prophylaxis). For patients switching to rFIXFc prophylaxis, ABR, annualised injection frequencies and annualised consumption were reduced since rFIXFc initiation, compared to previous prophylactic FIX treatment. The median dispensed frequency and dose of rFIXFc were generally similar to that prescribed for patients treated with rFIXFc prophylaxis. Additionally, most patients treated with rFIXFc prophylaxis, and their physicians, were satisfied/highly satisfied with treatment. The study also confirmed that rFIXFc was effective in the management of bleeding episodes on demand.

rFIXFc was well tolerated with no new safety concerns observed in the real-world setting, consistent with the established safety profile from phase III clinical trials (B-LONG, Kids B-LONG and B-YOND).[3–6] One previously treated patient, who had a family history of inhibitors and a previous history of low-titre inhibitors, developed a hypersensitivity reaction and a low-titre inhibitor on rFIXFc prophylaxis and discontinued the study. Indeed, hypersensitivity reactions and inhibitor development are identified as adverse reactions with FIX replacement therapy.[9,10]

This study adds to the growing body of real-word evidence demonstrating the effectiveness and safety of rFIXFc prophylaxis for patients of all ages across different clinical settings. Several studies in other countries have demonstrated the benefits of switching to rFIXFc prophylaxis from SHL FIX products, including improvements in bleed control, health-related quality of life and treatment adherence.[14,16–22] Reducing treatment burden has previously been identified as a key reason for switching from SHL FIX to rFIXFc, which is in line with the findings from B-SURE.[19,20] Across real-world studies, factor utilisation was decreased following the switch to rFIXFc prophylaxis, with most patients achieving injection intervals of once weekly or longer.[14,17–22] The possibility to use rFIXFc in the perioperative setting has also been established from real-world data and the rFIXFc clinical trial programme.[8,15,23]

A key strength of B-SURE was the non-interventional study design, which allowed investigation of rFIXFc in real-world conditions, accommodating individualised treatment and dosing flexibility. The findings of this study are therefore expected to align with clinical practice. Furthermore, the B-SURE study population can be considered representative of the French haemophilia population given the extent of participating haemophilia treatment centres. The patient population was also generally consistent with the FranceCoag cohort, a large national register in France, including over 1,000 people with haemophilia B.[24]

The limitations of this study should be considered when interpreting the findings. Firstly, there were some missing data pre- and post-switch to rFIXFc, and differences between retrospectively and prospectively collected data may limit comparisons. The number of patients completing the PRO questionnaires also declined across the study period. Further, there was insufficient joint evaluation before and after rFIXFc initiation to be able to draw conclusions on joint health outcomes. A limited number of patients were also treated on demand with rFIXFc so these results should be interpreted with caution.

## Conclusion

In conclusion, results from B-SURE, a 24-month, multicentre, prospective, non-interventional study in France, confirm the well-established effectiveness and safety of rFIXFc treatment for patients with haemophilia B in a real-world setting and provide valuable data to allow physicians and patients to make informed decisions about switching to rFIXFc treatment. Findings also indicate that FIX replacement continues to be the cornerstone of haemophilia B treatment with excellent effectiveness and safety profiles, as well as highlighting the role of prophylaxis with an EHL FIX as the standard of care for people with severe haemophilia B.

## Author's note

A complete list of members of the B-SURE Study Group appears in the Supplemental Material.

## Declarations

### *Ethics approval and consent to participate*

The B-SURE study protocol was approved by an independent ethics committee at participating institutions. B-SURE was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and ethical principles that comply with the Declaration of Helsinki, and is registered with ClinicalTrials.gov (NCT03655340).[25,26] Sobi performed statistical analyses of the data; all data analyses included in this manuscript were shared with all authors. Patients/their legal guardians provided written informed consent prior to participation; if appropriate, adolescent/paediatric patients also provided assent.

### *Consent for publication*

Patients/their legal guardians provided written informed consent prior to participation; if appropriate, adolescent/paediatric patients also provided assent.

### *Author contributions*

**Hervé Chambost:** Conceptualisation; Visualisation; Writing – original draft; Writing – review & editing.

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**Dominique Desprez:** Conceptualisation; Visualisation; Writing – original draft; Writing – review & editing.

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### *Competing interests*

H.C.: consulting fees from BioMarin, CSL Behring, Novo Nordisk, Pfizer, Roche Chugai and Sobi; payment/honoraria for lectures/

speakers bureau from BioMarin, CSL Behring, Novo Nordisk, Roche Chugai and Sobi; payment for expert testimony from BioMarin; support for attending meetings from BioMarin, Novo Nordisk, Roche and Sobi. Y.R.: grant/research support from CSL Behring and Octapharma; consultant for (scientific advisory board honoraria) Sobi; invitation as speaker in symposia for CSL Behring, LFB, Novo Nordisk, Octapharma, Roche, Sobi and Takeda; participation in data safety monitoring or advisory board for CSL Behring and LGB. F.G.-V.: investigator in clinical trials for CSL Behring, Roche, Sobi and Takeda; consultant for LFB, Pfizer, Roche, Sobi and Takeda; payment/honoraria for lectures/speakers bureau from CSL Behring, Roche Chugai, Sobi and Takeda. D.D.: grant or honoraria or invitation as speaker in symposia for CSL Behring, Novo Nordisk, Roche, Sobi and Takeda. S.M.C.: consultant (advisory board honoraria or invitation as speaker in symposia) for CSL Behring, LFB, Novo Nordisk, Roche, Sobi and Takeda. S.V.: investigator in clinical trials for Sobi. M.Z.: employee of Sobi. C.G., E.N., H.P., E.S.: employees and shareholders of Sobi.

### *Availability of data and materials*

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by EMA and/or FDA 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 at 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

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## Supplemental material

Supplemental material for this article is available online.

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