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Recombinant Factor VIII Fc Fusion Protein for First-time Immune Tolerance Induction: Final Results of the verITI-8 Study

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Abstract:
Inhibitor development remains a major challenge in factor VIII (FVIII) replacement therapy. verITI-8 is the first prospective study of a recombinant factor VIII Fc fusion protein (efmoroctocog alfa; rFVIIIFc) for first-time immune tolerance induction (ITI) in males with severe hemophilia A and high-titer inhibitors (historical peak ≥5 Bethesda units [BU]/mL). In this single-arm, open-label, multicenter study, screening was followed by ITI (rFVIIIFc 200 IU/kg/day until tolerization or maximum of 48 weeks). Those who achieved ITI success entered a tapering period, returning to standard prophylaxis, and then entered follow-up. Primary endpoint was time to tolerization with rFVIIIFc defined by inhibitor titer <0.6 BU/mL, incremental recovery (IR) ≥66% of expected IR (IR ≥1.32 IU/dL per IU/kg), and half-life ≥7 hours within 48 weeks. Sixteen subjects received ≥1 rFVIIIFc dose. Twelve (75%), 11 (69%), and 10 subjects (63%), respectively, achieved negative inhibitor titers, an IR ≥66%, and a half-life ≥7 hours (ie, tolerance) within 48 weeks. Median (IQR) times in weeks to achieve these markers of success were 7.4 (2.2–17.8), 6.8 (5.4–22.4), and 11.7 (9.8–26.2), respectively. All subjects experienced ≥1 TEAE (treatment-emergent adverse event [AE]), and 1 reported ≥1 related TEAE (injection site pain). Nine subjects experienced ≥1 treatment-emergent serious AE (TESAE). No thrombotic events, discontinuations due to AEs, or deaths were reported during the study. As the first extended half-life rFVIII with prospective data in ITI, rFVIIIFc offered short time to tolerization with durable responses in almost two-thirds of subjects and was well tolerated. Trial registered at www.clinicaltrials.gov (NCT03093480).

Conflict of interest: COI declared - see note

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Agreement to Share Publication-Related Data and Data Sharing Statement: Qualified researchers may request access to data and related documents (including, eg, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Any patient-level data provided will be anonymized, and study documents will be redacted, including to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

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verITI-8: first prospective study of first-time rFVIIIFc immune tolerance induction for severe hemophilia A and high historical peak titers.

A rFVIIIFc offered rapid time to tolerization with durable responses in almost two-thirds of subjects, no recurrence, and good tolerability.

Abstract (max. 250-word count)

Inhibitor development remains a major challenge in factor VIII (FVIII) replacement therapy. verITI-8 is the first prospective study of a recombinant factor VIII Fc fusion protein (efmoroctocog alfa; rFVIIIFc) for first-time immune tolerance induction (ITI) in males with severe hemophilia A and high-titer inhibitors (historical peak ≥5 Bethesda units [BU]/mL). In this single-arm, open-label, multicenter study, screening was followed by ITI (rFVIIIFc 200 IU/kg/day until tolerization or maximum of 48 weeks). Those who achieved ITI success entered a tapering period, returning to standard prophylaxis, and then entered follow-up. Primary endpoint was time to tolerization with rFVIIIFc defined by inhibitor titer <0.6 BU/mL, incremental recovery (IR) ≥66% of expected IR (IR ≥1.32 IU/dL per IU/kg), and half-life ≥7 hours within 48 weeks. Sixteen subjects received ≥1 rFVIIIFc dose. Twelve (75%), 11 (69%), and 10 subjects (63%), respectively, achieved negative inhibitor titers, an IR ≥66%, and a half-life ≥7 hours (ie, tolerance) within 48 weeks. Median (IQR) times in weeks to achieve these markers of success were 7.4 (2.2–17.8), 6.8 (5.4–22.4), and 11.7 (9.8–26.2), respectively. All subjects experienced ≥1 TEAE (treatment-emergent adverse event [AE]), and 1 reported ≥1 related TEAE (injection site pain). Nine subjects experienced ≥1 treatment-emergent serious AE (TESAE). No thrombotic events, discontinuations due to AEs, or deaths were reported during the study. As the first extended half-life rFVIII with prospective data in ITI, rFVIIIFc offered short time to tolerization with durable responses in almost two-thirds of subjects and was well tolerated. Trial registered at www.clinicaltrials.gov (NCT03093480).

Introduction

Prophylactic factor VIII (FVIII) replacement remains the standard treatment for severe hemophilia A (<1 IU/dL [1%] endogenous FVIII activity) to prevent bleeds, maintain musculoskeletal health, and promote quality of life.[1] However, development of inhibitors (immunoglobulin G alloantibodies to exogenous FVIII that neutralize the clotting factor's function, compromising treatment efficacy) continues to be a major challenge, resulting in increased hemophilia-related morbidities, including pain and physical limitations.[1-4]

Immune tolerance induction (ITI) is the standard of care for inhibitor eradication in patients with high-titer inhibitors (>5 Bethesda Units [BU]/mL).[2] ITI involves frequent exposure to FVIII over an extended period, typically from a minimum of 9 months to 2 or more years.[4] Intensive infusion schedules impose a high patient and caregiver burden, although, ultimately, successful ITI restores FVIII pharmacokinetics and sensitivity to FVIII treatment, allowing regular prophylactic therapy to be resumed.[1,5,6] However, ITI success rates are variable, and no clear consensus exists regarding the optimal dose or the most appropriate product.[1,3-5,7,8]

Data from the prospective International ITI (I-ITI) study, which focused on subjects with a favorable risk profile, compared high-dose (HD) (200 IU/kg/day) and low-dose (LD) (50 IU/kg, 3 times per week) standard half-life FVIII ITI treatment regimens.[7] The overall success rate was 70% (~40% in the intent-to-treat [ITT] population), which was similar for HD and LD regimens.[7] Tolerization was achieved more quickly and bleed rates were lower in those patients on HD versus LD.[7] However, even in the HD group, median time to tolerance (from start of ITI, progressing through negative titer, first normal recovery, and finally, tolerance) was almost 2 years in the 66/115 patients who reached the defined study endpoints.[7]

Reports of clinical cases employing an extended half-life (EHL) recombinant factor VIII Fc fusion protein (efmoroctocog alfa, referred to in this paper as rFVIIIFc; Eloctate®/Elocta®, Sanofi, Cambridge, MA, and Sobi, Stockholm, Sweden) for ITI suggest rapid time to negative inhibitor titer, and it has been hypothesized that this may be partially attributed to its immunomodulatory Fc portion.[2,9,10] For example, 1 series included 2 first-time ITI patients who achieved negative inhibitor titer at 11 and 12 weeks at initial rFVIIIFc ITI doses of 100 IU/kg every other day (QOD) and 200 IU/kg QOD, respectively.[9] A further case study achieved a titer of 0.7 BU/mL over the course of 10 months with an rFVIIIFc regimen of 50 IU/kg 3 times weekly, after a brief trial of another product.[10] A retrospective chart review including 10 first-time ITI patients suggested that rapid tolerization and an 80% success rate could be achieved with rFVIIIFc ITI.[3] In that chart review, dosing regimens for rFVIIIFc ITI were median (range) dose 100 (50–200) IU/kg and median (range) weekly dose 700 (150–1400) IU/kg.[3] The median (range) time to achieve tolerization was 30 (3–99) weeks.[3] Additionally, a recent interim assessment of a retrospective chart review showed that use of rFVIIIFc ITI in first-time ITI was successful in nearly 50% (10 of 22) of patients; the remaining 10 patients were still receiving ITI at the time of cutoff for the interim analysis.[11] None of these reports highlighted any additional safety signals associated with using rFVIIIFc in a high-intensity regimen.[2,3,9,10]

While case reports and chart reviews provide an indication of the potential benefit of rFVIIIFc, they are limited by small patient numbers, their retrospective nature, heterogeneous treatment regimens (including dose and frequency), and differing response criteria used for ITI. Against this background, 2 Phase 4 studies were designed to prospectively evaluate ITI outcomes with rFVIIIFc. ReITIrate (NCT03103542) evaluated rFVIIIFc-based rescue ITI (ie, for those who had previously failed at least 1 ITI attempt).[12] The present work reports findings from verITI-8 (NCT03093480), the first prospective study of rFVIIIFc in first-time ITI in patients with severe hemophilia A and inhibitors.

Methods

Study design and participants

verITI-8 (NCT03093480) was a Phase 4, open-label, single-arm, interventional study conducted across Europe, USA, and Canada **(Supplementary Table 1)**. The protocol was approved by institutional review boards and/or ethics committees at participating institutions. Written informed consent was obtained from subjects or parents/legal guardians. verITI-8 was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.[13,14]

The primary objective of the study was to describe the time to tolerization (ITI success) in subjects within a maximum of 48 weeks of ITI treatment with rFVIIIFc. Secondary objectives included describing the outcome of ITI treatment, the relapse rate over the 48-week period following successful ITI performed with rFVIIIFc, bleed rates during the ITI period and during the 48-week period after successful ITI performed with rFVIIIFc, and finally the safety and tolerability of rFVIIIFc when used for ITI.

Enrolled subjects were male, of any age, with severe hemophilia A and high-titer inhibitors (historical peak ≥5 BU/mL based on medical records). Subjects had to have received prior treatment with any plasma-derived or recombinant conventional or EHL FVIII. Key exclusion criteria included the presence of other coagulation disorder(s) in addition to hemophilia A or receipt of previous ITI therapy. Concomitant immunomodulation or emicizumab were not permitted. Additional eligibility criteria are listed in the **Supplemental Methods**.

verITI-8 consisted of consecutive study periods: screening, ITI, tapering, follow-up, and safety follow-up **(Figure 1).** The initial screening period lasted up to 4 weeks and was followed by an ITI period, which had a maximum duration of 48 weeks. During the ITI period, rFVIIIFc was administered at a starting dose of 200 IU/kg/day. In the event of FVIII activity levels rising above 200 IU/dL, after reaching a negative inhibitor titer but prior to complete ITI success, the dose was to be adjusted on an individual basis according to investigator judgment to maintain peak FVIII activity levels between 100 and 200 IU/dL. Administration of bypassing agents was permitted during ITI to control acute bleeds.

ITI success was defined as achieving an inhibitor titer <0.6 BU/mL and rFVIIIFc incremental recovery (IR) ≥1.32 IU/dL per IU/kg (representing ≥66% of the expected IR 2 IU/dL per IU/kg); each criterion had to be met at 2 consecutive visits taking place 2 weeks (±3 days) apart, in addition to a reported half-life ($t_{½}$) ≥7 hours. Partial success was also recorded in subjects completing 48 weeks of ITI and was defined as achieving negative inhibitor titer and 1 of the pharmacokinetic (PK) parameters of ITI success (IR ≥1.32 IU/dL per IU/kg *OR* $t_{½}$ ≥7 hours). Treatment failure was defined as fulfilling 1 of the following criteria: no downward trend of ≥20% in inhibitor titer in a 24-week period after the initial 12 weeks of the ITI period, presence of a sustained positive inhibitor (≥0.6 BU/mL) after 48 weeks of ITI treatment, or negative inhibitor titer without achieving either of the 2 PK parameters.

Only subjects who achieved ITI success within the maximum 48-week timeframe entered tapering and follow-up periods lasting ≥16 weeks and 32 weeks, respectively, followed by a final safety follow-up visit/call within a further 2 weeks. During tapering, doses were adjusted to achieve effective prophylaxis.

Subjects with successful ITI were monitored during the tapering and follow-up periods for the occurrence of relapse. Relapse was defined as positive inhibitor titer (≥0.6 BU/mL) and IR <1.32 IU/dL (representing <66% of the expected IR), each reported on 2 consecutive assessments

performed within 2 to 4 weeks, and a $t_{½}$ <7 hours. In the event of relapse, subjects were to proceed to the end of treatment visit.

Endpoints

The primary endpoint of the verITI-8 study was time to tolerization (ITI success) with rFVIIIFc ITI within a maximum of 48 weeks.

Secondary endpoints included the number of subjects achieving ITI success. Additional secondary endpoints included the number of bleeding episodes during the ITI period and during the 48-week period after successful ITI with rFVIIIFc, adverse events and serious adverse events, and rFVIIIFc consumption.

Data collection and analysis

Samples for inhibitor testing, IR, and $t_{½}$, were analyzed at the local laboratory as well as centrally. A washout period of at least 24 hours was required prior to assessments for incremental recovery and half-life. Analysis of ITI outcomes was based on the investigator's assessment of local laboratory data unless results could not be interpreted, in which case central laboratory results were used.

Statistical analysis

No formal sample size calculation was performed based on the limited population. All analyses describing efficacy and safety during ITI treatment were based on the ITI full analysis set including all subjects receiving ≥1 infusion of rFVIIIFc. The tapering period and follow-up period full analysis sets included all subjects entering the tapering and follow-up phases, respectively. All analyses describing efficacy and safety during the tapering or follow-up periods used these analysis sets.

Due to the sample size, descriptive statistics were performed rather than inferential hypothesis testing.

Data sharing statement

Qualified researchers may request access to data and related documents (including, eg, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Any patient-level data provided will be anonymized, and study documents will be redacted, including to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

Results

Subject characteristics

Sixteen subjects with a median (range) age of 2.1 (0.8–16) years were enrolled into and completed the study. Baseline characteristics and demographics demonstrated presence of risk factors for poor ITI outcome in many subjects, including extended time from inhibitor diagnosis to ITI treatment, high historical peak titers, and high-risk mutations **(Table 1)**.[5,7,15] The median (range) time from inhibitor diagnosis to the start of rFVIIIFc ITI was 23.1 (3.8–744.9) weeks, with 1 subject having a 14-year gap from diagnosis to start of ITI. Median (range) historical peak inhibitor titer (pre-ITI) was 22.4 (6.2–256) BU/mL; 2 subjects had peak titers >200 BU/mL. *F8* genotyping showed that over half (n=10) of the cohort had a large structural change involving >50 base pairs, most of which were intron-22 inversions. Medical and surgical histories of enrolled subjects were characteristic of individuals with severe hemophilia A. The most common surgery among subjects prior to the study was central venous catheterization placement (n=11, 69%).

Time to tolerization and ITI success

Twelve (75%) subjects achieved a negative inhibitor, of which 11 (69%) achieved an IR of ≥66% of expected, and 10 subjects (63%) a $t_{½}$ ≥7 hours within 48 weeks. Median (interquartile range [IQR]) times in weeks to achieve these markers of success were 7.4 (2.2–17.8), 6.8 (5.4–22.4), and 11.7 (9.8–26.2), respectively, meaning subjects achieved tolerance in a median of 11.7 weeks **(Table 2)**. All patients who achieved a normal recovery had first achieved a negative Bethesda titer, and those patients who achieved $t_{½}$ ≥7 hours had to first achieve a negative titer and IR ≥66% **(Supplementary Table 2).** Ten subjects (63%) achieved complete success, 1 subject (6%) achieved partial success (negative inhibitor titer and IR ≥66% of expected), and 5 subjects (31%) failed ITI **(Figure 2)**. The patient who achieved partial success had a negative inhibitor titer and normal IR. Of those who failed, 2 (13%) had a reduction in titer from Week 12 to 36 of <20%, 2 (13%) completed 48 weeks of rFVIIIFc ITI and had positive inhibitor, and 1 (6%) had completed 48 weeks of ITI and had a negative inhibitor titer but did not reach normal IR or $t_{½}$. The Kaplan-Meier estimate of ITI success rate was 67.2%, with an estimated median time to tolerization of 29 weeks (95% confidence interval [10.3, not estimable]) **(Supplemental Figure 1)**. No relapses were reported during the tapering or follow-up periods (during which time rFVIIIFc was tapered to a prophylactic dose [**Supplementary Table 3**]) in subjects who achieved ITI success. The time course of milestone achievement in individual subjects is represented graphically in **Figure 3**. The detailed information regarding ITI for individual subjects is included in **Supplementary Table 2.**

Bleeds

In an analysis including subjects with ≥90 days of data within a study period, most bleeds occurred in the ITI period when median (IQR) annualized bleed rates (ABRs) (n=13) were 3.8 (0–10.1) overall. Corresponding ABRs for tapering and follow-up in subjects with successful ITI were low **(Table 3).** No bleeds occurred in 7 subjects during ITI, and in subjects in whom bleeds occurred, the counts suggested a trend towards reduced bleeds from Month 1 to Month 12. Bleeding episodes during ITI are presented by type (overall, spontaneous, trauma, unknown) **(Supplementary Figure 2)** and by location (overall, joint, muscle, other) **(Supplementary Figure 3)**.

rFVIIIFc consumption and bypassing agent use

Median (IQR) annualized rFVIIIFc consumption was, as expected, highest during the ITI period (70,677 [59,996–72,466] IU/kg; n=13). Lower values were reported for the tapering (22,342 [19,106–27,220] IU/kg; n=10) and follow-up periods (9210 [8205–12,544] IU/kg; n=10) **(Table 4)**. Across the ITI, tapering, and follow-up periods, subjects were able to maintain excellent adherence

(Supplementary Table 4). Half of all subjects (n=8) used bypassing agents during the ITI period to treat bleeding events. Four of 16 subjects (25%) received activated prothrombin complex concentrate, and 5 of 16 subjects (31%) received recombinant factor VIIa (rFVIIa) within the ITI period, during which bypassing agent use was permitted to treat active bleeds **(Table 4)**. Individual listings of bypassing agent use during the ITI period are presented in **Supplementary Table 5**.

Safety

A total of 220 treatment-emergent adverse events (TEAEs) occurred in 16 subjects. All subjects experienced ≥1 TEAE. The most frequently reported TEAEs (incidence ≥15%) are reported in **Supplementary Table 6**. All but 3 TEAEs were assessed as mild to moderate in severity; the 3 assessed as severe were vascular device infection, mouth injury, and arthropathy (all considered serious). Twenty-eight treatment-emergent serious adverse events (TESAEs) were reported in 9 subjects (56%); none were considered related to rFVIIIFc ITI treatment by the investigator. The most common TESAEs were vascular device infection in 4 of 16 (25%), contusion in 2 of 16 (13%), and hemarthrosis in 2 of 16 subjects (13%) within the study. No thrombotic events or serious allergic reactions were reported. No adverse events led to treatment discontinuation, and no deaths occurred. One mild non-serious TEAE of injection site pain was reported and assessed as related by the investigator.

Discussion

The present work describes findings from verITI-8, the first prospective study of rFVIIIFc in first-time ITI therapy. While this study used strict success criteria, requiring all 3 endpoints to be met, rFVIIIFc had a notable success rate of 63% in patients with severe hemophilia A with high historical peak inhibitor titers and a rapid time to tolerization, with a median time to tolerance of 11.7 weeks. rFVIIIFc was well tolerated as ITI treatment. The timeframe for achieving tolerance was shorter than observed in the I-ITI study, where similar success rates were observed despite the I-ITI study only including subjects with a favorable risk profile.[7] In total, 70% achieved tolerance in I-ITI, although the success rate appears lower (40%) when considering success among the intent-to-treat (ITT) population of the I-ITI study.[7] In addition, 6 tolerized I-ITI subjects experienced a partial relapse, 2 of which were transient and 4 were permanent.[7] Three of the I-ITI subjects with partial relapse originated from the group that received HD therapy, and 3 subjects had received LD therapy.[7] Relapse in the I-ITI study was defined as inhibitor recurrence during the 12-month follow-up period on prophylaxis after tolerance was achieved, as evidenced by recurrent positive Bethesda titer or a decline in FVIII recovery or $t_{½}$ below study limits.[7] This contrasts with the absence of relapse observed in successfully tolerized subjects in verITI-8. However, differences in study design make direct comparisons difficult. The duration of cutoff for ITI success (48 weeks) in verITI-8 was much shorter than in previous ITI study designs, and it is conceivable that the success rate could have been higher if the timeframe had been extended. Of note, 1 patient did achieve Bethesda negativity within the 48-week period but had not shown a normal recovery or $t_{½}$ prior to study termination at Week 48. It is possible that this patient could have subsequently achieved success with longer treatment.

The rationale for dose selection included maintaining consistency with current US ITI guidance in which supportive evidence for use of 200 IU/kg/day is strongest in patients <8 years with adequate venous access and favorable risk factors.[16] The present dose regimen also aligns with that employed in the HD arm of the I-ITI study. Although the I-ITI study predated the introduction of EHL products and therefore used standard $t_{½}$, it provided a historical comparator.[7] The current dose is also consistent with but less intensive than the 300 IU/kg/day advocated by the Bonn protocol.[17] LD ITI has been explored and is associated with higher bleed rates and longer time to tolerance than HD regimens, with cumulative median time from start of ITI through negative titer, first normal recovery, and tolerance extending for approximately 3 years.[7] HD ITI regimens, although more intensive, may be associated with greater patient acceptability based on their shorter duration. This in turn may be reflected in high adherence throughout the verITI-8 study when calculated relative to the prescribed daily dose of rFVIIIFc.

The $t_{½}$ threshold of 7 hours exceeds the 6 hours recommended by World Federation of Hemophilia (WFH) guidelines for standard FVIII clotting factor concentrates[1]; however, using 7 hours reduces the burden in young children and has been considered the lower limit of normal in the pediatric population.[16,18] However, updated guidelines from UK Haemophilia Centre Doctors Organization (UKHCDO) and pediatric working party on the management of FVIII inhibitors in congenital hemophilia recommend a threshold of the lower end of normal for the age of the child undergoing ITI for the particular extended half-life product used during ITI.[19] In light of these recommendations, 7 hours may be an underestimate; however, for rFVIIIFc, since it was the first extended half-life FVIII at the time of verITI-8 study design, evidence suggested that use of 7-hour or greater half-life as an indicator of tolerance would be applicable.

When attempting to draw comparisons between verITI-8 and I-ITI study outcomes, it is important to note that participants in the I-ITI were described by the authors as a "good-risk cohort."[7] Some of

the subjects failing ITI in the verITI-8 study would not have been included in earlier studies, in particular 2 subjects with a historical peak inhibitor titer >200 BU/mL, and notably the I-ITI study reported an inverse association between historical peak inhibitor titer and successful ITI, although this was not significant upon multivariate analysis.[7] Regarding historical peak titer, all 10 subjects who were successfully tolerized in verITI-8 had values ≤40 BU/mL. In comparison, the results from a recent retrospective chart review of rFVIIIFc ITI in first-time patients showed that 50% of rFVIIIFc first-time ITI patients who were successfully tolerized had historical peak inhibitor titer values ≤40 BU/mL).[3] One subject with a historical peak of 1126 BU/mL was also successfully tolerized, with ITI starting within 1 week of inhibitor diagnosis.[3]

The majority of the verITI-8 study population harbored high-risk mutations for inhibitor development. Furthermore, the time from inhibitor diagnosis to start of ITI was greater than 6 months in half of the subjects (although 1 subject with an interval of 744.9 weeks [~14 years] achieved ITI success and another subject with an interval of >202 weeks achieved partial success). Retrospective evidence from 2 US treatment centers suggests that a long interval between inhibitor diagnosis and start of ITI can negatively influence the outcome of ITI by permitting the accumulation of long-lived plasma cells.[5]

In the context of patient and caregiver treatment burden associated with ITI, it is interesting to note the shorter time to tolerization observed in verITI-8 than in the I-ITI study. Times to achieve each sequential milestone towards tolerization in the I-ITI study were longer than the overall time to tolerization in verITI-8. Whereas in verITI-8, median (IQR) time to tolerization was 11.7 (9.8–26.2), weeks corresponding to 2.7 (2.3–6.0) months, and the I-ITI study median (IQR) time (months) to negative titer in the HD group was 4.6 (2.8–13.8) (n=31), negative titer to normal recovery was 6.9 (3.5–12.0) (n=23), and normal recovery to tolerance was 10.6 (6.3–20.5) (n=22).[7] With the advent of nonfactor therapies such as emicizumab, the burden associated with ITI has come into focus. Eradication of inhibitors is still considered an appropriate goal,[18] and the use of emicizumab concurrently with ITI is being investigated (NCT04303572,[20,21] NCT02196207, NCT04030052). Considering that emicizumab is licensed for bleed prevention in patients with hemophilia A with and without inhibitors,[1] ITI treatment regimen durations similar to those employed in the I-ITI study are less likely to be favored. Indeed, it will be critical to select the best ITI regimen and corresponding factor product.[18] Selecting a regimen that provides for a more rapid time to tolerization, such as that observed in the verITI-8 trial, could contribute to a reduction in ITI treatment burden. Prospective studies of first-time ITI using recombinant standard half-life or EHL FVIII apart from I-ITI are lacking, although ObsITI, a prospective observational study, reported a median time to success of 11.25 months using plasma-derived products.[22] Registry and retrospective studies were not considered appropriate for comparison; however, the efficacy observed in achieving tolerance and favorable safety profiles in verITI-8 are consistent with published chart review data with rFVIIIFc ITI.[2,3,11] No new safety concerns were identified, despite the intensity of the ITI treatment. Strengths of the study include the prospective design and broad inclusion criteria that increase generalizability of the findings. For example, limits were not imposed on potential risk factors such as time from inhibitor to start of rFVIIIFc, historical peak titer, or inhibitor titer at start of ITI. A major limitation of the study includes the small study population.

In conclusion, the final data from verITI-8 demonstrate benefit of rFVIIIFc as first-time ITI to eradicate inhibitors in patients with severe hemophilia A. Despite the limited number of subjects enrolled in the study (N=16), rFVIIIFc is the first EHL product with data available for this therapeutic application. As evaluated within a 48-week timeframe, rFVIIIFc offered a rapid time to tolerization in a shorter timeframe than previous reports, combined with durable responses in almost two-thirds of

subjects.[7] Furthermore, recurrence of inhibitors was not observed after successful tolerization during the tapering and follow-up periods, lasting ≥16 weeks and 32 weeks, respectively. Optimizing ITI to eradicate inhibitors remains a priority for people with severe hemophilia A and inhibitors.

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Contributions

LM, AKCC, NJ, JD, SL, and MC contributed substantially to the design of the work and/or the preparation of the manuscript for publication. LM, AVD, AKCC, MS, JD, SL, MC, and FP contributed substantially to data acquisition. LM, AVD, AKCC, CS, JD, SL, MC, and FP contributed substantially to data analysis or interpretation of data. All authors provided critical revision of the manuscript and had final approval of the manuscript for publication.

Conflicts-of-interest disclosure

LM has presented in advisory boards and/or received consultancy fees or investigator-initiated grant funding from Bioverativ, a Sanofi company, Shire, and/or Bayer. AVD has received honoraria for advisory board participation from Bayer, Pfizer, and Shire outside the submitted work. AKCC has participated in an advisory board for Bioverativ, a Sanofi company. MS has received honoraria for advisory board participation from Bayer, Sobi, and Roche outside the submitted work. NJ is a former employee of Sanofi and a current employee of Takeda and may hold shares and/or stock options in the company. CS and JD are employees of Sanofi and may hold shares and/or stock options in the company. SL is an employee of Sobi and may hold shares and/or stock options in the company. MC has received research support and/or honoraria for speaking/participating in advisory boards from Bayer, CSL Behring, LFB, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, and/or Takeda. FP has received personal fees from Ablynx, Grifols, Kedrion, Novo Nordisk, Roche, Shire, and Sobi outside the submitted work.

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Tables and Figures

Table 1. Baseline demographics and characteristics of subjects enrolled in verITI-8 (ITI full analysis set)

Characteristic	Enrolled subjects (N=16)
Median (range) age at informed consent, years	2.1 (0.8–16)
Median (range) time from inhibitor to start of rFVIIIFc ITI, weeks	23.1 (3.8–744.9*)
Median (range) historical peak inhibitor titer (pre-ITI), BU/mL	22.4 (6.2–256)
Median (range) inhibitor titer at rFVIIIFc ITI start, BU/mL	9.7 (0.7–144)
Number of FVIII exposure days at first confirmed inhibitor development, n (%)	
<25	8 (50.0)
25–50	5 (31.3)
51–100	2 (12.5)
>100	1 (6.3)
Family history of inhibitor, n (%)	
Yes	3 (18.8)
No	13 (81.3)
Race, n (%)	
White	12 (75.0)
Black or African American	2 (12.5)
Other	2 (12.5)
Ethnicity, n (%)	
Hispanic or Latino	2 (12.5)
Not Hispanic or Latino	14 (87.5)
F8 genotype, n (%)	
Frameshift	2 (12.5)
Large structural change (>50 bp)	10 (62.5)
Intron-22 inversion	7 (43.8)
Intron-1 inversion	1 (6.3)
Deletion	2 (12.5)
Small structural change (in-frame, <50 bp)	1 (6.3)
Nonsense	2 (12.5)
Missing genotype data	1 (6.3)

bp, base pair; BU, Bethesda unit; FVIII, factor FVIII; ITI, immune tolerance induction; rFVIIIFc, recombinant factor VIII Fc fusion protein.

*14.3 years.

Table 2. Time to achieve ITI success endpoints from start of ITI (ITI full analysis set)

Time to endpoint	n	Median (weeks)	IQR
Negative-inhibitor titer*	12	7.4	2.2–17.8
Normal IR	11	6.8	5.4–22.4
$t_{½}$ ≥7 hours	10	11.7	9.8–26.2

IQR, interquartile range; IR, incremental recovery; ITI, immune tolerance induction; $t_{1/2}$, half-life.

*Defined as time to first negative inhibitor titer recorded.

Table 3. Summary of ABRs during each period of the study*,†,‡

Period	n	Overall,§ median (IQR)	Spontaneous, median (IQR)	Traumatic, median (IQR)	Joint, median (IQR)
During ITI‖	13	3.8 (0–10.1)	0 (0–2.6)	1 (0–4)	0 (0–3.1)
During tapering¶	10	0 (0–2.4)	0 (0–0)	0 (0–1.3)	0 (0–0)
During follow-up#	10	0 (0–1.5)	0 (0–0)	0 (0–0)	0 (0–0)

ABR, annualized bleed rate; IQR, interquartile range; ITI, immune tolerance induction.

∗ABR is defined as the number of bleeding episodes divided by length of the noted period in days × 365.25.

†Excludes patients observed <90 days within the period.

‡Only subjects who achieved tolerization entered the tapering and follow-up periods.

§Overall includes those with 0 ABR.

‖There were 7 patients (44%) with no bleeds during the ITI period.

¶There were 6 patients (60%) with no bleeds during the tapering period.

#There were 7 patients (70%) with no bleeds during the follow-up period.

Table 4. rFVIIIFc consumption on study and bypassing agent use during the ITI period

	Total*,† (N=16)	ITI period* (N=16)	Tapering period‡ (N=10)	Follow-up period§ (N=10)
Annualized rFVIIIFc consumption‖,¶,#				
n	16	13	10	10
Median (IQR), IU/kg/year	36,717 (25,646–62,841)	70,677 (59,996–72,466)	22,342 (19,106–27,220)	9210 (8205–12,544)
Subjects receiving bypassing agents, n (%)**				
aPCC	4 (25.0)	4 (25.0)	0	0
rFVIIa	5 (31.3)	5 (31.3)	0	0
Median (IQR) annualized bypassing agent consumption¶,††				
aPCC, U/kg/year	4866 (211–26,437)	9463 (154–43,411)	N/A	N/A
rFVIIa, µg/kg/year	2345 (229–23,642)	5691 (714–23,642)	N/A	N/A

aPCC, activated prothrombin complex concentrate; IQR, interquartile range; ITI, immune tolerance induction; N/A, not applicable; rFVIIa, recombinant activated factor VII; rFVIIIFc, recombinant factor VIII Fc fusion protein.

*Total study and ITI period based on the ITI full analysis set.

†The total column includes a subject's entire study period for annualized consumption calculations.

‡Tapering period is based on the tapering period full analysis set.

§Follow-up period is based on the follow-up period full analysis set.

‖Annualized rFVIIIFc consumption for a treatment period is the (total nominal rFVIIIFc [IU/kg]/length of period in days) × 365.25.

¶Annualized analysis excludes subjects who were observed for <90 days in the period.

#Surgical-related consumption was not included.

**Bypassing agents were used only during the ITI period.

††Annualized bypassing agent consumption is the (total consumption/length of period in days) × 365.25.

Figure 1. verITI-8 study design

ITI, immune tolerance induction; rFVIIIFc, recombinant factor VIII Fc fusion protein.

*Only subjects who achieved tolerization entered the tapering and follow-up periods.

†Subjects with bleeding episodes during the tapering and follow-up periods were tested for recurrence of inhibitors and monitored for relapse. In the event of relapse, subjects were to proceed to the end of treatment visit.

Figure 2. Success rates among subjects undergoing rFVIIIFc ITI

BU, Bethesda unit; ITI, immune tolerance induction; IR, incremental recovery; rFVIIIFc, recombinant factor VIII Fc fusion protein; t½, half-life.

*Successful tolerization was defined as attaining negative inhibitor titer (<0.6 BU/mL), rFVIIIFc IR ≥66% of expected IR, and $t_{1/2}$ ≥7 hours.

†Total values exceed 100% following rounding.

‡Partial success was defined as receiving 48 weeks of ITI treatment and achieving a negative inhibitor status and 1 normal pharmacokinetic parameter (IR ≥1.32 IU/dL per IU/kg *OR* $t_{1/2}$ ≥7 hours).

§Subject achieved a negative inhibitor titer and normal IR.

‖Subjects were considered to have failed ITI if there was reduction of inhibitor titer <20% within a 6-month period following the initial 12 weeks of rFVIIIFc ITI, presence of a positive inhibitor (≥0.6 BU/mL) after 48 weeks of ITI with rFVIIIFc, or a negative-inhibitor titer without achieving either an IR ≥1.32 IU/dL per IU/kg (representing ≥66% of expected IR) or $t_{1/2}$ ≥7 hours after 48 weeks of rFVIIIFc ITI.

¶Two (12.5%) had a titer change of <20% from Weeks 12 to 36; 2 (12.5%) had completed 48 weeks of ITI and maintained a positive inhibitor titer; and 1 (6.3%) completed 48 weeks of ITI and achieved a negative inhibitor titer without attaining either normal pharmacokinetic parameter (IR or $t_{1/2}$ ≥7 hours).

Figure 3. Swimmer plot of patients' time to criteria of success and time in each period during the study

BU, Bethesda unit; FVIII, factor VIII; IR, incremental recovery; ITI, immune tolerance induction; rFVIIIFc, recombinant factor VIII Fc fusion protein; t½, half-life.

*Subjects were considered to have failed ITI if there was a reduction of inhibitor titer <20% within a 6-month period following the initial 12 weeks of rFVIIIFc ITI, presence of a positive inhibitor (≥0.6 BU/mL) after 48 weeks of ITI with rFVIIIFc, or a negative inhibitor titer without achieving either an IR ≥1.32 IU/dL per IU/kg (representing ≥66% of expected IR) or $t_{1/2}$ ≥7 hours after 48 weeks of rFVIIIFc ITI.

†Partial success was defined as receiving 48 weeks of ITI treatment and achieving a negative inhibitor status and 1 normal pharmacokinetic parameter (IR ≥1.32 IU/dL per IU/kg *OR* $t_{1/2}$ ≥7 hours).

‡Successful tolerization was defined as attaining negative inhibitor titer (<0.6 BU/mL), rFVIIIFc IR ≥66% of expected IR, and $t_{1/2}$ ≥7 hours.

§>202 weeks.

‖Time to negative inhibitor titer was the time interval (in weeks) from the start date of ITI treatment with rFVIIIFc to date of first negative inhibitor titer, which was subsequently confirmed by a sample from a consecutive visit.

¶Time to FVIII normal recovery was the time interval (in weeks) from the date of ITI treatment with rFVIIIFc to date of first normal IR (≥66%), which was subsequently confirmed by a sample from a consecutive visit.

#Time to FVIII $t_{1/2}$ of ≥7 hours was the time interval (in weeks) from start date of ITI treatment with rFVIIIFc to date of $t_{1/2}$ ≥7 hours.

Figure 1

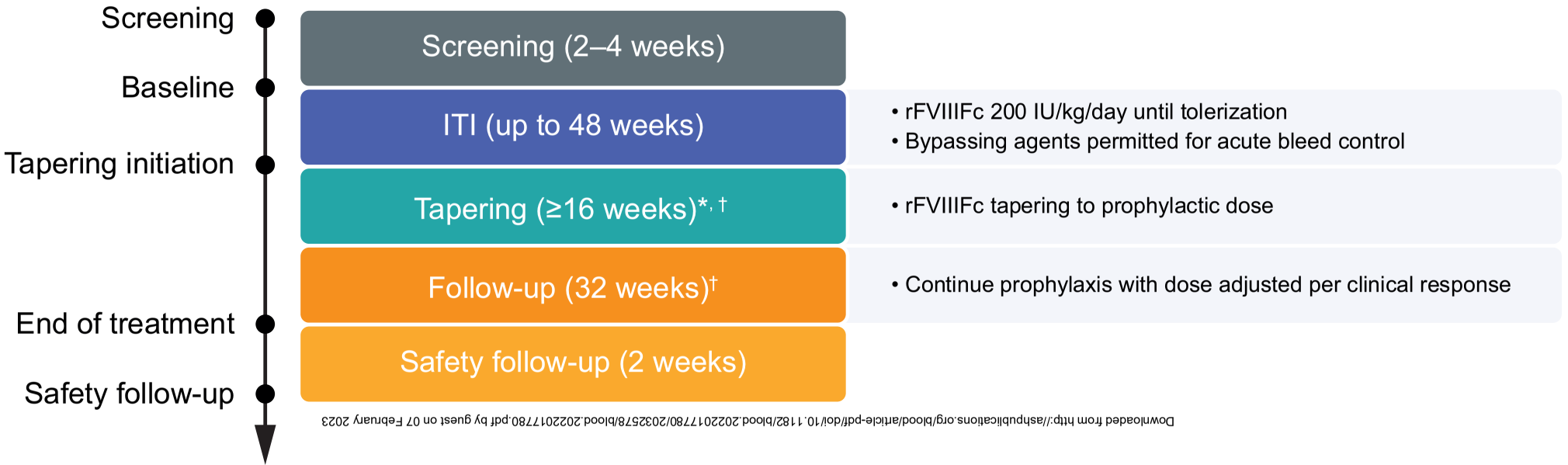

Figure 2

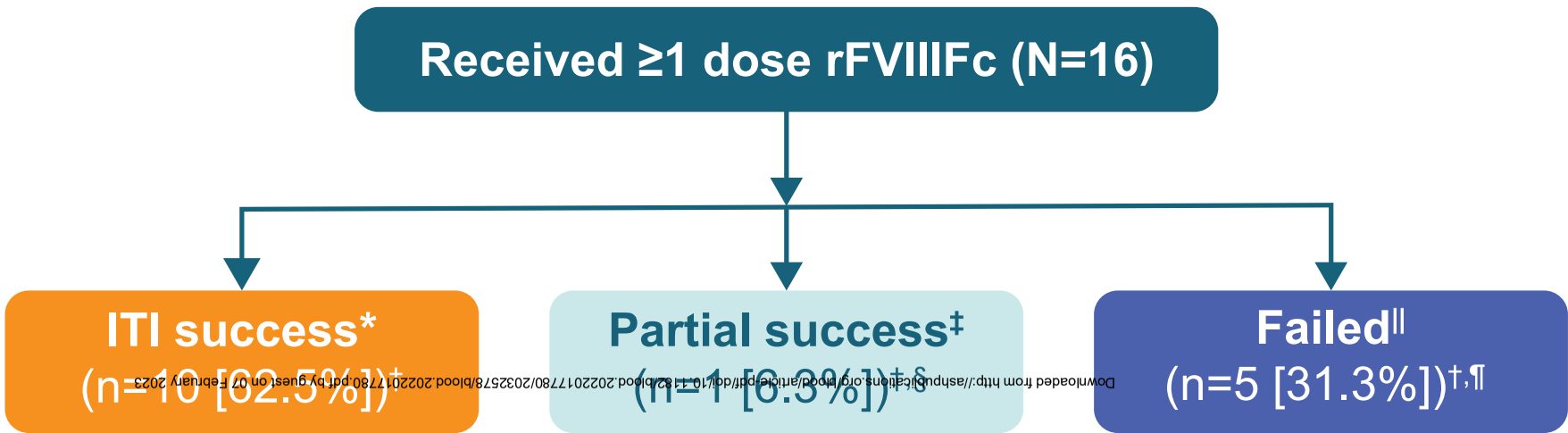

Figure 3