INTRODUCTION

Prophylactic factor replacement is a well-established standard of care for patients with severe haemophilia A, and routine prophylaxis with factor VIII (FVIII) has been shown to reduce the frequency of bleed episodes, prevent joint damage and improve health-related quality of life. However, optimal prophylaxis with conventional FVIII products requires frequent intravenous injections, a substantial burden that can negatively impact treatment adherence.

Several strategies have been employed to extend the half-life of FVIII in recombinant FVIII (rFVIII) products, thereby reducing the frequency of infusions. Fusion of the Fc domain of human immunoglobulin G (IgG) to a therapeutic protein is an established approach that leverages an existing physiologic pathway. Binding to the neonatal Fc receptor (FcRn), which is expressed in endothelial cells lining the vasculature, protects both endocytosed IgG and Fc fusion proteins from lysosomal degradation and moves them back into the circulation. Recombinant FVIII Fc fusion protein (rFVIIIFc), which comprises a single molecule of rFVIII fused to the Fc domain of human IgG1, was the first extended half-life FVIII approved in the European Union (Elocta®, Sobi) and the United States (Eloctate®, Sanofi) for the prophylaxis and treatment of bleeding in patients with haemophilia A.

Emerging benefits of Fc fusion technology in the context of recombinant factor VIII replacement therapy

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Abstract

Although the primary reason for recombinant factor VIII Fc fusion protein (rFVIIIFc) development was to reduce treatment burden associated with routine prophylaxis, new evidence suggests additional benefits of Fc fusion technology in the treatment of people with haemophilia A. Preclinical research has been utilized to characterize the potential immunomodulatory properties of rFVIIIFc, including an ability to reduce inflammation and induce tolerance to factor VIII. This has since been expanded into clinical research in immune tolerance induction (ITI) with rFVIIIFc, results of which suggest the potential for rapid tolerization in first-time ITI patients and therapeutic benefit in patients undergoing rescue ITI. The potential for improved joint health through the anti-inflammatory properties of rFVIIIFc has also been suggested. In addition, a new avenue of research into the role of rFVIIIFc in promoting bone health in patients with haemophilia A, potentially through reduced osteoclast formation, has yielded encouraging results that support further study. This review summarizes the existing preclinical and clinical studies of immunomodulation and tolerization with rFVIIIFc, as well as studies in joint and bone health, to elucidate the potential benefits of rFVIIIFc in haemophilia A beyond the extension of factor VIII half-life.

KEYWORDS
bone resorption (MeSH terms), FVIII, haemophilia A, immune tolerance, immunomodulation, inflammation, prophylaxis
with haemophilia A of all age groups. The extended circulating half-life of rFVIIIFc has been confirmed, and long-term efficacy and safety of rFVIIIFc have been extensively documented in clinical trials and in real-world studies.

The immunoregulatory properties of the Fc domain of IgG are an additional, albeit less well-known, characteristic of Fc fusion proteins. Decades ago, it was observed that coupling of haptens to IgG could induce antigen-specific tolerance, which was later understood to be mediated by the Fc domain as well as the F(ab′)2 fragment. IgG or Fc fusion proteins bound to the FcRn are diverted away from antigen presentation compartments, preventing an immune response. Later, hapten-IgG fusion proteins were also shown to induce hapten-specific tolerance and intravenously administered immunoglobulin to enhance the suppressive activity of regulatory T cells (Treg)—known for their contribution to the maintenance of immune self-tolerance. Since then, two T-cell epitopes, termed Tregitopes, have been identified in the Fc region of IgG1 that are capable of activating Tregs, tipping the resulting immune response towards tolerance. Consequently, Fc fusion proteins developed and utilized clinically to date appear to have low immunogenicity.

An improved understanding of the impact of the immunomodulatory properties of Fc fusion proteins in patients with haemophilia A is just now emerging, as well as the potential of rFVIIIFc to tackle some of the other key unmet needs of this therapy area beyond circulating half-life, such as immune tolerance induction, joint health and potentially bone health. The objective of this review was to summarize these potential broad effects of Fc fusion technology that have multiple mechanisms of action and go beyond the original intention of extended FVIII half-life.

2 | OVERVIEW OF THE rFVIIIFc MOLECULE AND ITS PHARMACOKINETIC (PK) PROFILE

rFVIIIFc is a recombinant fusion protein comprising a single molecule of rFVIII covalently fused to the Fc domain of human IgG1. It is produced in a human cell line using recombinant DNA technology, without the use of any animal-derived components. The active form of the FVIII component of rFVIIIFc is structurally and functionally comparable with native FVIII, allowing rFVIIIFc to bind normally to von Willebrand factor (VWF) and phospholipids. Clinical studies have confirmed that rFVIIIFc displays improved clearance-related PK parameters compared with conventional human rFVIII, with a 1.5-times longer terminal half-life on average (Table 1).

3 | IMMUNOMODULATORY PROPERTIES OF rFVIIIFc

The development of inhibitors is a serious treatment-related complication in patients with haemophilia A, occurring in up to 30% of patients with severe haemophilia A. Immune tolerance induction (ITI), involving the regular infusion of FVIII to induce FVIII antigen-specific tolerance, is the only strategy currently available to eradicate inhibitors in patients with high titres (>5 Bethesda units). While current ITI is successful in approximately 70% of patients with inhibitors, the treatment may take 1-2 years and is burdensome to patients and caregivers. Given the preliminary preclinical and clinical evidence, rFVIIIFc has the potential to address the current unmet need for ITI treatments that achieve faster responses.

3.1 | Preclinical evidence

Several key preclinical studies have been fundamental in characterizing the immunomodulatory properties of Fc fusion proteins in haemophilia A, laying the groundwork for further clinical assessments. Early evidence of Fc fusion protein immunomodulation in haemophilia A came from Lei and Scott in 2005. They transduced B cells with a fusion IgG containing the immunogenic A2 and C2 FVIII domains and demonstrated the induction of FVIII-specific tolerance in both naïve and FVIII-immunized haemophilia A mice, likely dependent on Tregs. Later, both Culina et al and Gupta et al demonstrated that the transplacental transfer of Fc-fused antigens induces an increase of thymic and peripherally derived Tregs in an antigen-specific manner. Furthermore, in a preclinical model of haemophilia A, Gupta et al found that transplacental transfer of Fc-fused immunodominant A2 and C2 FVIII domains

| TABLE 1 | Clearance-related pharmacokinetic parameters for rFVIIIFc (Eloctate®, Sanofi Genzyme) compared with a conventional rFVIII product (Advate®, Shire) in the Phase 3 A-LONG study in patients ≥12 y of age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>rFVIIIFc (n = 28)</th>
<th>rFVIII (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2 (h)</td>
<td>19.0</td>
<td>12.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CL (mL/h/kg)</td>
<td>2.0 (1.7-2.2)</td>
<td>3.0 (2.7-3.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AUC/dose (IU x h/dL per IU/kg)</td>
<td>51.2 (45.0-58.4)</td>
<td>32.9 (29.3-36.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time to 1 IU/dl (1%) FVIII trough level above baseline (days)</td>
<td>4.9 (4.4-5.5)</td>
<td>3.3 (3.0-3.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Data presented are geometric mean (95% confidence interval).

Abbreviations: AUC/dose, dose-normalized area under the curve; CL, systemic clearance; FVIII, factor VIII; rFVIII, recombinant factor VIII; rFVIIIFc, recombinant factor VIII Fc fusion protein; t1/2, terminal half-life.
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induced tolerance to FVIII in the progeny, attributable to FVIII-specific Tregs; however, the role of Fc in the induction of tolerance was not investigated (Table 2).

A key study for rFVIIIFc came from Krishnamoorthy et al,35 who reported decreased levels of inhibitor formation after rFVIIIFc treatment of haemophilia A mice with therapeutically relevant doses, compared with rFVIII treatment (Table 2). The reduced immunogenicity of rFVIIIFc was attributed to the development of regulatory T cells and a tolerogenic environment, potentially mediated by the interaction of the Fc domain of rFVIIIFc with the Fc receptors (FcR) on antigen-presenting cells. The authors proposed that a combination of the FcRn and Fcγ receptor signalling pathways, and potentially Fc Tregitopes, contributed to rFVIIIFc-mediated activation of tolerogenic pathways.

Additional work has since been undertaken to characterize the interaction between rFVIIIFc and antigen-presenting cells. An in vitro study published by Kis-Toth et al36 showed that rFVIIIFc, but not rFVIII, elicits an alternatively activated regulatory macrophage phenotype, further elucidating on the mechanisms of potential rFVIIIFc immunomodulatory properties (Table 2). rFVIIIFc was shown to induce human monocyte-derived macrophages to polarize to a Mox/M2 phenotype in vitro, without need for a danger signal or interleukin 4. This report suggests that rFVIIIFc drives regulatory macrophage polarization in an FcR-dependent way, resulting in an antioxidant state and anti-inflammatory molecular profile.

### 3.2 Clinical evidence

ITI with rFVIIIFc has been examined in case reports,37-39 small cohort studies40,41 and in prospective studies and chart reviews (some of which are still ongoing; NCT03951103) (Table 3).42-44 The definition of success with ITI should be taken into account when interpreting the data. While successful tolerization is typically defined as achieving...
### TABLE 3  Clinical studies and case reports evaluating ITI with rFVIIIFc

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Patient(s)</th>
<th>rFVIIIFc ITI dose</th>
<th>ITI outcomes</th>
<th>Safety outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groomes 2016&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Case report</td>
<td>15-mo-old with severe haemophilia A who received prior ITI with Kogenate and Xyntha</td>
<td>50 IU/kg TIW</td>
<td>Inhibitor titre decreased from 11 to 0.7 BU/mL over 308 d</td>
<td>NR</td>
</tr>
<tr>
<td>Batsuli 2019&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Case report</td>
<td>12-y-old with severe haemophilia A and four prior ITI attempts; concomitant treatment with emicizumab</td>
<td>100 IU/kg TIW</td>
<td>Inhibitor titre decreased from a historical peak titre of 198 BU/mL to &lt;0.6 BU/mL after 37 wk of rFVIIIFc treatment</td>
<td>NR</td>
</tr>
<tr>
<td>Malec 2016&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Case series</td>
<td>Children with severe haemophilia A undergoing their first ITI treatment (n = 2) or who failed prior ITI (n = 1)</td>
<td>100 IU/kg QOD; 200 IU/kg TIW/QOD</td>
<td>3/3 achieved negative inhibitor status in 11, 4 and 12 wk; no patients had recurrence of detectable inhibitor at mean follow-up of 13-14 mo</td>
<td>No patients experienced treatment complications</td>
</tr>
<tr>
<td>Carcao 2019&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Non-interventional, retrospective chart review</td>
<td>Children with severe haemophilia A undergoing their first ITI treatment or who have failed previous ITI attempts</td>
<td>43 IU/kg TIW to 200 IU/kg/d</td>
<td>Interim results (8 November 2018): 9/10 first-time ITI patients tolerated in median (range) of 30 (3-99) weeks; 9/18 rescue ITI patients achieved Bethesda negativity with 3 transitioned to prophylaxis</td>
<td>No adverse events reported</td>
</tr>
<tr>
<td>Nagao 2019 (FACTs study)&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Prospective, multicentre, observational study</td>
<td>Adolescents and children with haemophilia A undergoing their first ITI treatment (n = 5) or who have failed previous ITI attempts (n = 3)</td>
<td>39.7 IU/kg TIW to 227.3 IU/kg/d</td>
<td>Interim results (October 2018): Decreased inhibitor titre to &lt;1 BU/mL in 2/5 first-time ITI patients at 6 mo; ITI ongoing in all patients</td>
<td>No severe adverse events reported</td>
</tr>
<tr>
<td>Abraham 2018&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Prospective, multicentre, observational study</td>
<td>Patients with haemophilia A (N = 38)</td>
<td>50 IU/kg TIW to 200 IU/kg/d</td>
<td>Interim results: 17/38 achieved negative inhibitor status in a median (range) of 20 (10-60) weeks</td>
<td>NR</td>
</tr>
<tr>
<td>Malec 2019 (verITI-8 study)&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Open-label, single-arm, interventional, multicentre, Phase 4 study</td>
<td>Patients with severe haemophilia A undergoing their first ITI treatment (N = 16)</td>
<td>200 IU/kg/d</td>
<td>Interim results (23 January 2019): 6/15 tolerized in median (range) of 11.7 (9.9-12.3) weeks; ITI ongoing in 8/15; ITI failure in 1/15</td>
<td>No adverse events related to rFVIIIFc reported</td>
</tr>
<tr>
<td>ReITIrate study&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Open-label, single-arm, interventional, multicentre, Phase 4 study</td>
<td>Patients with severe haemophilia A who have failed previous ITI attempts</td>
<td>200 IU/kg/d</td>
<td>NA (study ongoing)</td>
<td>NA (study ongoing)</td>
</tr>
<tr>
<td>NCT03951103</td>
<td>Observational, retrospective and prospective chart review</td>
<td>Patients with haemophilia A who have been, or who are currently, treated with rFVIIIFc for ITI (N = ~50)</td>
<td>NR</td>
<td>NA (study ongoing)</td>
<td>NA (study ongoing)</td>
</tr>
<tr>
<td>NCT04303572 (The Hemophilia Inhibitor Eradication Trial)</td>
<td>Open-label, randomized, interventional, multicentre, Phase 3 study</td>
<td>Male adults or children &gt;4 mo of age with severe haemophilia A and current or past high-responding FVIII inhibitors</td>
<td>Eloctate 100 IU/kg QOD with or without emicizumab 1.5 mg/kg QOD</td>
<td>NA (planned start in June 2020)</td>
<td>NA (planned start in June 2020)</td>
</tr>
</tbody>
</table>

Abbreviations: BU, Bethesda unit; ITI, immune tolerance induction; NA, not available; NR, not reported; QOD, every other day; TIW, three times per week.
negative Bethesda titre (≥0.6 BU) as well as normal FVIII recovery (≥66%) and half-life (≥6 hours), a minority of studies have described negative Bethesda titres alone as a successful outcome.

Case reports from Groomes et al and Malec et al demonstrate successful ITI with rFVIIIFc and the potential to achieve tolerance with a regimen of shorter duration and at a lower dose frequency than ITI utilizing conventional half-life products. In addition, there is a case report of successful ITI with rFVIIIFc after multiple failed attempts in the setting of emicizumab prophylaxis.

Carcao et al reported outcomes from a non-interventional, retrospective chart review of patients with severe haemophilia A and high-titre inhibitors treated with rFVIIIFc for ITI, the most recent analysis of which includes 28 patients. Nine of 10 first-time ITI patients were tolezerized with a median time to tolerization of 30 (range 3–99) weeks. Nine of 18 rescue ITI patients achieved Bethesda negativity, and of these, 3 patients were tolezerized at 21.7, 35.0 and 101.1 weeks, respectively, and transitioned to rFVIIIFc prophylaxis. Despite the majority of patients in this study having poor-risk features for ITI success, rFVIIIFc use demonstrated a rapid decrease in inhibitor titres and rapid tolerization in first-time ITI patients and showed therapeutic benefit in patients undergoing rescue ITI. Nagao et al and Abraham et al have both reported interim results from observational analyses with promising outcomes (Table 3).

Two prospective open-label, single-arm, interventional, multicentre studies are now underway to examine the efficacy of rFVIIIFc in ITI (Table 3). The verITI-8 study (NCT03093480) will assess the time to tolerization with rFVIIIFc over a 48-week study period in 16 patients undergoing primary ITI treatment. Interim results show that, as of the 23 January 2019 data cut-off, 6 out of 15 patients were successfully tolezerized in a median of 11.7 (range 9.9–12.3) weeks. rFVIIIFc ITI is ongoing in 8 patients, and 1 patient failed to achieve ITI success by Week 48. The RetITIrate study (NCT03103542) will assess the rate of ITI success using rFVIIIFc over a 60-week study period in 16 patients undergoing rescue ITI therapy having failed at least one previous ITI attempt.

A 5-year observational chart review (NCT03951103) in an estimated 50 patients who have been, or who are currently, treated with rFVIIIFc for ITI is also ongoing in Europe and the Middle East (Table 3). The Hemophilia Inhibitor Eradication Trial (NCT04303572), planned to start in June 2020, is an open-label, randomized, interventional, multicentre, 48-week Phase 3 trial that will compare weekly rFVIIIFc ITI plus weekly emicizumab with weekly rFVIIIFc ITI alone to eradicate inhibitor formation in approximately 90 patients (Table 3).

It is encouraging that in clinical trials evaluating a prophylaxis regimen in previously treated patients, no major signals of immunogenicity for rFVIIIFc have been observed. For instance, there was no inhibitor development, nor any reports of anaphylaxis or serious vascular thrombotic events, or deaths or serious adverse events considered related to rFVIIIFc. However, it should be acknowledged that previously treated patients are at a lower risk of developing an alloimmune response to exogenous FVIII as compared with previously untreated patients (PUPs).

Results from clinical trials in PUPs, a population for whom clinical data are currently limited, are expected to answer key questions on the immunomodulatory properties of this molecule. In a case report of two cousins with severe haemophilia A and the same high-risk genotype, the patient treated with rFVIIIFc developed low-titre inhibitors not requiring ITI whereas the patient treated with full-length FVIII developed high-titre inhibitors requiring ITI within a similar timeframe. The tolerogenic potential of rFVIIIFc was offered as a possible explanation for the findings of this report. The Phase 3 PUPs A-LONG trial (NCT02234323) investigating the safety and efficacy of rFVIIIFc in PUPs with haemophilia A was recently completed (September 2019) and is the only study, to date, of rFVIIIFc in this population. This was an international, open-label, interventional single-group, multicentre, 3-year study in 108 PUPs aged up to 5 years, the primary outcome for which was the number of participants with inhibitor development over the duration of the study. Data from an interim analysis (N = 95), presented recently, indicate that rFVIIIFc was well tolerated and efficacious for prevention of bleeds in a PUP population in which 80% of subjects had a high-risk genotype. While the development of inhibitors in 31% of subjects is within the expected range in PUPs with severe haemophilia A (ie 25%–40%), there was a low risk for development of high-titre inhibitors (15% in subjects with ≥10 exposure days or who had an inhibitor).

It has been suggested that activation of the immune system (ie, via bleeds, infection, trauma and vaccination) must be minimized at the time of first FVIII exposure to achieve tolerance in PUPs. This approach will be assessed in The Hemophilia Inhibitor Prevention Trial (NCT04303559), a multicenter, randomized, controlled Phase 3 trial that compares weekly rFVIIIFc with weekly emicizumab in PUPs with severe haemophilia A, 4 months of age or older.

4 | JOINT AND BONE HEALTH

While haemophilic arthropathy is the leading cause of morbidity in haemophilia A, osteopenia (low bone mineral density) and osteoporosis are highly prevalent, and fracture rates are also elevated. In a retrospective cohort of 382 patients, there was a significantly greater relative risk of fracture in patients with haemophilia A and haemophilia B compared with the control population (relative risk: 10.7, 95% confidence interval: 8.2–14.1; P < .0001), with risk increasing with age and with haemophilia severity. The exact aetiology behind both the elevated osteopenia and increased fracture risk, and the interplay between these comorbidities, has not yet been elucidated; nevertheless, it is clear that joint and bone health in patients with haemophilia A remains a significant unmet need beyond successful prevention of joint bleeds.

4.1 | Anti-inflammatory properties of rFVIIIFc: Clinical evidence in joint health

The largest body of evidence to date on the impact of rFVIIIFc prophylaxis on joint health in patients with haemophilia A comes from a post hoc analysis of A-LONG and Kids A-LONG studies and...
the ASPIRE extension study.59-61 Joint health showed continued improvement, as reflected by changes in Hemophilia Joint Health Score in children and modified Hemophilia Joint Health Score (mHJHS) in adolescents and adults (domains include swelling, pain, strength, flexion and extension loss), from A-LONG/Kids A-LONG baseline to ASPIRE Year 2.59,61 Resolution of at least one target joint (defined as ≤2 spontaneous bleed episodes in 12 consecutive months) was achieved in 99.6% of evaluable patients in A-LONG/ASPIRE (n = 235) and 100% of evaluable patients in Kids A-LONG (n = 9). Improvements in joint health and 100% target joint resolution were also reported in patients who did not reach optimum haemostatic control (ie had an annualized bleed rate in the top 25%) in the first year of treatment with rFVIIIFc in the A-LONG study and who continued prophylaxis with rFVIIIFc in ASPIRE.60 The mechanism behind this improvement in joint health and target joint health resolution with prolonged rFVIIIFc treatment most likely relates to low bleed rates. Changes in mHJHS that contributed most to improvements in total score were swelling, range of motion and strength.59 The contribution of increased adherence to prophylaxis and the potential anti-inflammatory properties of the Fc-fused rFVIII (described earlier) remain to be fully elucidated.59

Interestingly, a prospective study in 26 adult patients with haemophilia A and haemophilia B with arthropathic joints receiving various factor replacement therapies found that acute painful bleed episodes were not associated with expected PK parameters (ie not associated with more time spent below certain clotting factor thresholds in the days preceding the bleed). However, joint bleeds were found to be associated with prominent vascularity changes, indicating that vascular remodelling and leakiness—probably a result of previous joint bleeds—may contribute to joint bleeds. Given that the patients receiving rFVIIIFc experienced fewer painful episodes than did those receiving conventional products, the potential anti-inflammatory properties of rFVIIIFc were proposed to play a role.62

4.2 Impact of rFVIIIFc on osteoclast formation: Preclinical evidence in bone health

The role of FVIII and/or thrombin in bone health is currently unclear. While animal models support a direct role for FVIII in bone remodelling, whereby RANKL (which increases bone breakdown) expression is decreased by FVIII treatment, bone formation may also be indirectly affected by FVIII via thrombin generation.58 It is, therefore, interesting to note the findings of a recent in vitro study presented by Rajani et al,63 where rFVIIIFc, but not FVIII, was shown to inhibit monocyte-derived osteoclast formation, suggesting a potential effect on bone resorption in patients with haemophilia. In this study, the bone resorption capabilities of rFVIIIFc-treated, monocyte-derived osteoclasts were compromised compared with untreated, human IgG1- or rFVIII-treated cells. Furthermore, gene and protein expression of rFVIIIFc-treated cells showed upregulation of NRF2 pathway-related molecules and subsequent downregulation of molecules involved in osteoclast formation and function.63 These findings lend support to further study of the potential benefits of rFVIIIFc for bone health in patients with haemophilia A.

5 CONCLUSION

Further to its prolonged half-life compared with conventional rFVIII products, the Fc domain of rFVIIIFc may confer additional benefits to patients with haemophilia A owing to its immunomodulatory and non-immunomodulatory effects. Based on the available preclinical and clinical evidence, these may include reduced immunogenicity and inflammation, and an enhanced ability to induce tolerance. An additional emerging role for rFVIIIFc in promoting bone health, potentially through reduced osteoclast activation and, consequently, bone resorption, lends further support to the belief that the Fc fragment of rFVIIIFc confers benefits, beyond those originally intended in the molecule's design, that have yet to be fully characterized. The Fc domain continues to be incorporated into novel haemophilia therapeutics, such as BIVV001 (rFVIIIFc-VWF-XTEN), a new class of FVIII replacement.64 Whether these emerging benefits of the Fc fragment persist in highly bio-engineered proteins remain to be elucidated.

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REFERENCES


International Society on Thrombosis and Haemostasis (ISTH), July 6-10, 2019; Melbourne, Australia.

44. Königs CMS, Jain N, Lethagen S. Study design for reitirate—a prospective study of rescue ITI with recombinant factor VIII Fc (rFVIIIFc) in patients who have failed previous ITI attempts. Haemophilia. 2018;24:32-135.


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