Concomitant Use of rFVIIa and Emicizumab in People with Hemophilia A with Inhibitors: Current Perspectives and Emerging Clinical Evidence

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Abstract: Emicizumab, a humanized, bi-specific, monoclonal antibody subcutaneously administered, mimicking the function of FVIIIa, represents a milestone in treatment of patients affected by hemophilia A complicated with inhibitors. The HAVEN 1 and 2 studies have clearly established its superiority compared to bypassing agents for routine prophylaxis in preventing or reducing bleeding episodes in adult and pediatric patients with inhibitors. However, its protection against bleeding is only partial, and concomitant use of a bypassing agent may be required with potential thrombotic risk. The emicizumab Phase III trials (HAVEN 1, 2 and 4) have shown that the traditional bypassing agents, activated prothrombin complex concentrates or recombinant activated factor VII (rFVIIa), may be necessary for the treatment of breakthrough bleeds or surgery management. A post hoc analysis in particular has shown that the concomitant use of emicizumab and rFVIIa is safe and no thrombotic events have been described. The review describes the state of the art of the concomitant use of emicizumab and rFVIIa for treating acute bleeding and surgeries, its efficacy and safety and the lack of thrombotic events associated with this treatment modality. Data still derive mainly from HAVEN trials; however, the availability of emicizumab in clinical practice is progressively increasing the number of patients treated and no adverse events directly attributed to this agent have occurred. The availability of guidelines for the use and dosing of rFVIIa during emicizumab prophylaxis is useful in clinical practice for managing suspected or ongoing bleeding, emergency situations and elective invasive procedures. In the next years, careful prospective post-licensure surveillance to monitor safety of rFVIIa use during prophylaxis with emicizumab is highly recommended.

Keywords: hemophilia A, FVIII inhibitors, emicizumab, bypassing agents, recombinant FVIIa, safety

Introduction

The occurrence of neutralizing alloantibodies (inhibitors) following exposure to therapeutically infused factor VIII (FVIII) represents the most important complication of treatment of hemophilia A. The cumulative incidence of inhibitor may range from 20% to 40% in severe hemophilia A, usually within the first 10–15 days of exposure, and approximately 5–10% in moderate or mild disease. The inhibitor risk is significantly lower when patients are exposed to FVIII for more than 50–150 days. The pathophysiology of inhibitor development is a complex and multi-causal process, including the interaction of genetic and environmental determinants. As a result of the neutralizing alloantibodies onset, replacement therapy with FVIII

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concentrates becomes ineffective, and usual long-term prophylaxis is not feasible. Patients are hence at an increased risk of mortality, morbidity, and disability with a significantly worse quality of life because also bleeding episodes are more difficult to control. \(^6\) \(^7\) When inhibitors occur, patients with a low-responding inhibitor (<5 Bethesda Units) may still be treated with specific factor replacement at much higher doses to neutralize the antibody and to allow FVIII to increase to stop bleeding. On the other hand, patients with high-responding inhibitors (>5 Bethesda Units) present a high risk of anamnestic response upon treatment and must be treated with bypassing agents (BPAs), which represented the standard of care for many years. Two BPAs are available such as activated prothrombin complex concentrates (aPCC) \(^8\) or recombinant activated factor VII (rFVIIa). \(^9\) \(^10\) The efficacy of BPAs, however, is not 100% guaranteed and these patients often require frequent intravenous administrations, even on the same day, and the lack of suitable laboratory tests to monitor their efficacy makes clinical outcome more unpredictable. Therefore, immune tolerance induction (ITI) to eradicate inhibitors has represented the primary aim in patients with a high-responding inhibitor, to restore the use of FVIII replacement treatment. \(^11\) This approach requires daily, long-term administration of FVIII ultimately resulting in a down-regulation of the production of neutralizing antibodies in 60% to 80% of patients. \(^12\) \(^13\) \(^14\) However, ITI represents a very demanding treatment, both for the need of an easy and safe venous access and its considerable cost. \(^15\)

The development of agents targeting different key proteins in the coagulation process to restore thrombin generation in patients with hemophilia has been the focus of recent studies. These new agents aim at maintaining the coagulation to generate thrombin (Emicizumab) or at inhibiting natural anticoagulant pathways at different levels (Concizumab, Fitusiran and molecules targeting activated protein C or protein S). \(^16\) \(^17\)

The subcutaneous route of administration and the long half-life are additional novel potential advantages of these agents, resulting in an improved compliance and protection. Emicizumab (Hemlibra) has been recently approved as the first non-factor-based therapy for routine prophylaxis in patients affected by hemophilia A with inhibitors, thus representing a milestone in their treatment. However, the traditional BPAs may be still required for the treatment of breakthrough bleeds or to manage surgery, with a potential thrombotic risk.

This review analyzes the state of the art of concomitant use of emicizumab and BPAs, in particular rFVIIa.

### Agents for Treating Patients with Hemophilia A and Inhibitors

Today, in clinical practice, the available drugs for the treatment of patients affected by hemophilia A with inhibitors are emicizumab, aPCC and rFVIIa (Table 1).

#### Emicizumab

Emicizumab (Hemlibra, Roche Genentech, South San Francisco, CA, USA) is a recombinant, humanized, bispecific monoclonal antibody (Mab) which mimics the procoagulant activity of activated FVIII (FVIIIa). \(^18\) Bispecificity has been established by constructing an antigen-binding fragment (Fab) recognizing FIXa while the other Fab has FX as its substrate. The simultaneous binding of FX and FIXa by emicizumab facilitates the proteolytic activation of FX by FIXa without the cofactor activity of FVIII. \(^19\) \(^20\) thus increasing deficient thrombin generation with peak thrombin generation showing a bell-shaped curve and a close dose depending on emicizumab concentrations between 10 and 100 µg/mL. \(^20\) However, emicizumab and FVIII have some differences including the affinity for the antigen, topology, FIXa enhancing activity and regulation. \(^21\) While emicizumab binds to FIXa only at a single epidermal growth factor-1 like (EGF-1) domain site, FVIII binds to several heavy and light chain domains of FIXa. \(^21\) As a consequence, it has a lower affinity for FIXa and FX (10-fold and 6-fold, respectively) compared to FVIII. The antibody replaces partially FVIIIa cofactor activity and its activity is directly dependent on the amount of FIXa generated. Emicizumab-induced coagulation has no regulation at variance with the physiological FVIIIa-induced coagulation, characterized by exceeding concentrations of FIXa and FX. This imbalance disrupts the physiological on-and-off switch mechanism. \(^21\) Emicizumab has been approved in the United States in November 2017 for routine prophylaxis in patients with hemophilia A and inhibitors of all ages \(^22\) and in European Union in February 2018. \(^23\) The same dosing schedule consisting of 4 weekly loading doses of 3 mg/kg followed by weekly dosing of 1.5 mg/kg by subcutaneous injection is used in all the patients. Alternative treatment schemes are 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks after the initial 4-week loading schedule. Emicizumab half-life elimination is 24–30 days, but the complete disappearance of any drug-related effect can theoretically require as long as 150 days (5 half-lives). \(^24\) \(^25\) Apart from body weight, no dosage adjustment for age, renal or hepatic function is required.
and emicizumab concentration remains acceptably stable once the plateau has been achieved. Very few cases of immune response against emicizumab have been described. Most of these antibodies bind to emicizumab, without neutralizing its activity and treatment is usually continued. However, the onset of bleeding episodes previously prevented by emicizumab prophylaxis should suggest checking for emicizumab concentration or, if available, for the presence of anti-drug antibody (ADA).

In patients on emicizumab prophylaxis, routine assays are not useful to monitor treatment. The drug strongly influences activated partial thromboplastin time (aPTT), which normalises at concentrations well below the expected therapeutic range. Therefore, a normal aPTT in a patient on emicizumab does not reflect an in-vivo coagulation ability. In order to accurately measure FVIII and inhibitor titer in these patients, chromogenic assays using either human reagents (to assess emicizumab’s factor tenase activity) or bovine reagents (to assess tenase activity of residual FVIII) are required.

### aPCC

aPCC (FEIBA, Factor Eight Inhibitor Bypassing Activity, Takeda Pharmaceutical Company Limited, Lexington, MA, USA) is a plasma-derived BPA comprising activated coagulation factors, and in particularly high concentrations of FXa and FII. Typically, the recommended dose for treating bleeding episodes is 50–100 IU/kg every 8–12 h. A capped daily dose of ≤200 IU/kg is recommended to minimize the potential of thrombotic complications. Up to 30% of patients receiving aPCC may show a variable anamnestic increase of inhibitor levels caused by the presence in the product of small amounts of FVIII. However, inhibitor titer gradually decreases in more than 50% of patients on regular aPCC treatment and the anamnestic response is not associated with a reduction of clinical efficacy.

### rFVIIa

rFVIIa (Novoseven, eptacog alfa, NovoNordisk, Bagvaerd, Denmark) is a single-chain glycoprotein produced in baby hamster kidney (BHK) cell line, genetically modified. During purification, rFVII is converted in its activated form. rFVIIa is able to directly activate FX and increases thrombin generation on the surface of activated platelets in the absence of FVIII or FIX. The platelet-specific generation of FIIa by rFVIIa is thought to localize the hemostatic process to the sites of active bleeding and tissue injury.

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Table 1 Drugs for Treatment of Patients Affected by Hemophilia A with Inhibitors

| Mechanism of action | Emicizumab | aPCC | rFVIIa |
|---------------------|------------|------|--------|
| Dose: on demand | n.a. | 50–100 U/kg every 6–12 h until hemostasis | 90–120 μg/kg every 2–3 h until hemostasis |
| Dose: prophylaxis | 1.5 mg/kg per week or 3 mg/kg every 2 week or 6 mg/kg once monthly | 85 U/kg 3–5 times per week | 90 μg/kg or 270 μg/kg daily |
| Maximum safe dose | n.a. | 100 U/kg per dose; 200 U/kg daily | Individual doses rarely greater than 300 μg/kg |
| Administration | s.c. injection | Up to 30 min i.v. infusion | 2–5 min i.v. infusion |
| Thrombotic or thromboembolic adverse events | Thrombotic microangiopathy and venous thrombotic events when aPCC is used at ≥100 IU/kg/day for ≥24 hours | Thromboembolic events | Arterial and venous thrombotic events |
| Laboratory monitoring | Emicizumab interferes with aPTT and aPTT-based assays. One-stage FVIII measurement is not reliable. PT-based or chromogenic assays (bovine reagents for FVIII and inhibitor titration by Bethesda method) are not influenced by emicizumab | No assays clinically validated to determine coagulation status | No assays clinically validated to determine coagulation status |

Abbreviations: n.a., not applicable; i.v., intravenous; s.c., subcutaneous; aPTT, activated partial thromboplastin time; PT, prothrombin time.
children, with significant individual variations, and thus it must be infused every 2–6 h. Recently, an automated pump for the administration of rFVIIa has been developed to simplify the administration of rFVIIa in the future. rFVIIa has been initially approved at a dose of 90 μg/kg every 2–3 h until clinical evidence of good hemostasis is achieved; then, a single bolus 270 μg/kg has been also used in clinical practice to meet the requirement of less infusions, especially in pediatric populations, faster response rates, thus allowing longer intervals between infusions. Prospective clinical studies on rFVIIa efficacy have demonstrated that a single 270 μg/kg dose is comparable to three 90 μg/kg doses administered every 3 h. Moreover, the higher dose is safe, with a low risk of thrombosis risk in patients with inhibitors.

With regard to hemostatic efficacy, the FENOC study showed similar overall results with resolution in 70–80% of bleeding events in a controlled head-to-head comparison of aPCC and rFVIIa. An improved response to one BPA versus the other, changing over time also in the same patient, has been frequently observed. Moreover, sequential regimens of both aPCC and rFVIIa may be required to control 10–20% of bleeds not effectively managed with a single BPA.

Both BPAs are associated with a potential risk of thrombotic complications, including venous thromboembolism, disseminated intravascular coagulation and myocardial infarction. These events are very rare in hemophilia patients, but they could be theoretically increased in patients with preexisting conditions (atherosclerotic disease, liver disease, prolonged immobilization).

aPCC and rFVIIa are used in prophylactic regimens in patients with inhibitors, even if their benefits are not as evident as with the usual FVIII prophylaxis for patients without inhibitor. Prophylaxis with BPAs may be considered before starting ITI, during ITI or in those patients who failed ITI. Two prospective, randomized trials, the Pro–FEIBA and PROOF studies demonstrated a 60–72% reduction of bleeding episodes compared to on-demand treatment with aPCC. Only a single prospective, randomized trial has evaluated the efficacy of rFVIIa, showing up to 60% reduction of bleeding episodes compared to the pre-prophylactic period. However, the short half-life of the BPAs, their variable efficacy and the relevant costs are important drawbacks limiting their use in the real-world practice.

Furthermore, notwithstanding many years of experience with BPAs, there is no laboratory test easily available for monitoring their hemostatic efficacy, and dose and duration of treatment is mainly decided by clinical assessment.

### Emicizumab in HAVEN Trials

Data on the efficacy of emicizumab derives by an extensive clinical program of phase III trials (HAVEN 1, HAVEN 2 and HAVEN 4) in patients with hemophilia A with inhibitors (Table 2).

#### Table 2 Emicizumab Clinical Program of Phase III Trials in Hemophilia A with Inhibitors

| Study | Study Design | Efficacy | Safety |
|-------|--------------|----------|--------|
| HAVEN 1 | 2 randomized arms 2 non-randomized arms | 87% reduction in randomized arm between emicizumab prophylaxis vs no prophylaxis 63% with no treated bleeding | 2 thrombotic events 3 thrombotic microangiopathy events 2 anti-drug antibodies 0 neutralizing antibodies |
| HAVEN 2 | Single arm, all patients receiving emicizumab prophylaxis | 95% of patients with no treated bleeding 99% bleeding reduction in subset of patients in comparison to prior BPA prophylaxis | 0 thrombotic events 0 thrombotic microangiopathy events 4 anti-drug antibodies 1 neutralizing antibodies 1 allergy reaction |
| HAVEN 4 | Pharmacokinetic trial evaluating an every 4 week dosing regimen | Preliminary data shows that this dosing regimen follows the pre-study pharmacokinetic model, suggesting that this may be an effective alternative dosing regimen | 0 thrombotic events 0 thrombotic microangiopathy events 2 anti-drug antibodies 0 neutralizing antibodies |

**Abbreviation:** BPA, bypassing agent.
In HAVEN 1, an inter-individual comparison of the number of treated bleeds during 24 weeks between patients with hemophilia A and high titer inhibitors aged ≥12 years receiving episodic BPA treatment compared to emicizumab prophylaxis was the primary end point. The median annualized bleeding rate (ABR) was 2.9 (95% confidence interval [CI]: 1.7–5.0) in patients on emicizumab prophylaxis versus 23.3 (95% CI: 12.3–43.9) among those treated on on-demand with BPAs, with a 87% difference favoring emicizumab (p<0.001). Secondary bleeding-related end points, including all bleeding, spontaneous bleeding, joint bleeding and target joint bleeding also were significantly lower in patients on emicizumab prophylaxis and 63% of them did not experience any bleeding episodes requiring treatment with BPAs compared to only 6% of those on episodic BPAs treatment. In the intra-individual analysis, emicizumab prophylaxis showed a 79% reduction of bleeds requiring treatment (p<0.001) compared to previous prophylaxis with BPAs. Furthermore, there was a significant improvement in overall health-related quality of life and the physical health subscores.

HAVEN 2 was a single-arm trial evaluating the efficacy, safety and pharmacokinetic profile of emicizumab prophylaxis in pediatric hemophilia A patients with high titer inhibitors. Eighty-eight children, previously receiving episodic or mostly prophylactic BPAs, were treated with emicizumab 1.5 mg/kg weekly (n=68), 3 mg/kg every 2 weeks (n=10) or 6 mg/kg every 4 weeks (n=10). With once-weekly emicizumab prophylaxis, the ABR was 0.3 (95% CI, 0.17–0.50) and 77% of patients experienced no treated bleeds. A 99% reduction of the number of treated bleeds in the intra-patient analysis of those on BPAs prophylaxis before enrollment was observed, with a drop of ABR from 21.1 (95% CI: 15.99–27.82) to 0.3. The ABRs in participants receiving emicizumab every 2 weeks or every 4 weeks were 0.2 (95% CI:0.03–1.72) and 2.2 (95% CI:0.69–6.81), respectively, with 90% and 60% of patients having reporting zero treated bleeds.

HAVEN 4 trial evaluated prophylaxis with emicizumab 6 mg/kg every 4 weeks in hemophilia A patients aged ≥12 years, with or without inhibitors. Data on 41 patients have shown a consistent high efficacy and acceptable safety profile of such schedule dosing with a median ABR for treated bleeds of 0.0 with 56.1% (95% CI: 39.7–71.5) of patients without treated bleeds and 90.2% (95% CI: 76.9–97.3) having ≤3 treated bleeds. Data on emicizumab efficacy are undoubtedly significant to recommend its use for prophylaxis in patients with inhibitors. However, it should be kept in mind that protection against bleeding is not absolute and the risk of bleeding could be roughly estimated to be similar to that of patients with mild hemophilia. Breakthrough bleeds may still occur (trauma, emergency surgery, etc.) and co-administration of a BPAs required, with potential prothrombotic risk. In HAVEN 1 four serious thrombotic events (2 venous thrombosis and 2 thrombotic microangiopathy (TMA)), occurred in subjects who received aPCC at high doses (>100 IU/kg/day) for ≥24 hours for the treatment of breakthrough bleeds. A fifth patient developed TMA and died of rectal hemorrhage after the refusal of blood transfusions. However, TMA was improving before he died, and the death was judged unrelated to emicizumab.

The synergistic interaction between emicizumab and aPCC and the inherent thrombotic risk are well explained by the presence in aPCC of FIX and FX and their activated forms, which are the substrates for the bi-specific antibody, thus exceedingly increasing thrombin generation. In fact, the enzymatic activity of FIXa in aPCC can be increased in an unregulated manner up to 20,000-fold by emicizumab. Thus, some guidelines have been provided about the dosing of BPAs during emicizumab prophylaxis and the avoidance of aPCC or choosing the lowest dose approved BPAs.

No thrombotic complications have been reported when using emicizumab alone or in combination with rFVIIa. The lack of events when co-administrating the two drugs may be explained by the short half-life of rFVIIa, the fact that emicizumab does not bind to rFVIIa and the physiologic antithrombin-mediated inactivation process able to prevent excessive rFVIIa-mediated thrombin generation.

Co-Administration of Emicizumab and rFVIIa

Management of Bleeding Episodes

Recently, an extensive analysis assessing the safety of emicizumab and rFVIIa co-administration in HAVEN 1, 2 and 4 clinical trials was jointly performed by Roche and Novo Nordisk. Overall, 61 enrolled patients received rFVIIa for one or more events to manage or as prophylaxis of bleeding episodes. A total of 210 bleeding episodes for which rFVIIa treatment was used were analysed.
The large majority of bleeds were observed in HAVEN 1, in which 46/113 patients had at least one rFVIIa treatment. A total of 193 bleeds (84% in joints or muscles) in 37 patients were managed with rFVIIa and. A 100 ± 20 µg/kg initial dose of rFVIIa was given in the majority of cases. Dosing interval and cumulative dosing were in keeping with prescribing information and current practice. The median duration of treatment per bleed was 1 day for more than half (61.7%) of events.

In HAVEN 2, 11 patients received rFVIIa to treat a bleed (10 bleeding trauma-related) and 4 as a prophylaxis before activity. The cumulative median dose per bleed was 164.21 µg/kg and the median number of infusions was one. The dosing interval was at least 2 h.

In HAVEN 4, a single patient out of five with inhibitors was treated with rFVIIa for three bleeds, two of which occurring at the start of treatment, when emicizumab concentration was still not at the steady state yet. The rFVIIa cumulative dose per bleed was 276.94 µg/kg for the first bleeding and 449.15 µg/kg for the second bleeding.

Overall, it appeared that the co-administration of rFVIIa for treating breakthrough bleeds in patients on emicizumab was safe and control of bleeding excellent.

Management of Surgery
In HAVEN trials, patients with surgeries already planned were not enrolled, with the exception of minor procedures. However, unplanned emergency surgeries have been required in some enrolled patients receiving emicizumab. Perioperative management was left at the investigator’s discretion on clinical judgement and specific guidance (per protocol) on surgical management with regard to BPAs use was provided.

Only preliminary information on the management of surgeries and procedures are described so far and final data are going to be presented.

In HAVEN 1, 13 patients underwent surgical procedures using perioperatively rFVIIa. Two surgeries were major (a total hip replacement and a knee arthroscopy with synovectomy, chondroplasty, and debridement). The others were minor surgeries or procedures as dental surgery, radiosynovectomy, endoscopy and central venous access devices (CVADs) placement or removal. In HAVEN 2, 21 patients underwent CVADs removal with rFVIIa prophylaxis only in 4 of them.

A total knee replacement in a patient enrolled in HAVEN 1 and perioperative management with rFVIIa have been described. A preoperative rFVIIa bolus of 200 µg/kg was infused, followed by doses of 100 µg/kg every 2 h during surgery and for the first postoperative day. A bolus dose of 100 µg/kg was administered every 3 h on day 2 and then the infusion intervals were prolonged up to every 4 and 6 h, respectively, on days 3 and 4. The patient remained on every 6-h dosing until postoperative day 11, with a subsequent tapered treatment every 8 h until day 14. Hemostatic efficacy was excellent, without clinical evidence of thrombosis or TMA. Another case report describes the perioperative management of a total hip arthroplasty with a preoperative rFVIIa bolus of 180 µg/kg followed by a bolus of 90 µg/kg every 3 h until day 3, when the frequency of administration was tapered to every 6 h on postoperative days 4–7. Since day 8 to 12, rFVIIa was infused every 8 h, then every 12 h until day 14. No additional rFVIIa was given.

Conclusions
Emicizumab represents a milestone in hemophilia. A treatment, offering the opportunity to improve the prophylactic approach even in patients with inhibitors. HAVEN trials have shown that the concomitant use of traditional BPAs may be required for the treatment of breakthrough bleeds or for surgery with a potential thrombotic risk. The same studies have also shown that the concomitant use of emicizumab and rFVIIa is safe and effective and no thrombotic events have been described. However, the modulation of usual therapeutic plans to manage suspected or ongoing bleeding or scheduled invasive procedures has been required. This also for the issues related to monitoring emicizumab therapy, as routine assays cannot be used. Emicizumab strongly shortens the aPTT, even very low concentrations, far from the theoretical therapeutic range. This spurious effect may be misinterpreted as a normalization of the coagulation potential in the patients. The concomitant use of rFVIIa makes it currently impossible to perform a laboratory monitoring that reflects the in vivo activation of hemostasis.

Therefore, due to thrombotic episodes observed in HAVEN 1 in patients receiving aPCC at doses ≥100 IU/kg/day for 24 h or longer to treat breakthrough bleeds and according to the guidance released by the manufacturer for the use and dosing of BPAs in patients on emicizumab prophylaxis, the indication to avoid aPCC and to prescribe the lowest doses of approved BPA is commonly accepted.

rFVIIa represents the first-line option for bleeds requiring hemostatic replacement therapy in patients with inhibitors on emicizumab. An initial dose of 90–120 µg/Kg is
suggested, to be repeated 2–4 h apart according to the clinical severity and response. rFVIIa megadose (270 µg/kg) should be avoided, even as a single infusion. Even in surgery with major bleeding risk, is rFVIIa represents the first-line treatment, at a dose of 90–120 µg/Kg starting 15 min preoperatively and then post-surgery every 2–3 h with a progressive interval between injections.8,49

The availability of emicizumab in clinical practice is progressively increasing the number of patients treated and the knowledge of the drug by clinicians. No new thrombosis or TMA events have been reported when concomitant use of BPAs, according to available practical guidance. Post-licensure carefully designed prospective together with registry data will be of utmost importance to continue monitoring the safety of concomitant use of rFVIIa and Emicizumab in a real-world scenario as well in guiding the best clinical practice.

**Author Contributions**

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

**Disclosure**

GC acted as a speaker at company satellite symposia during scientific meetings for Roche, Sobi, Novo Nordisk, Werfen, and Kedrion; is a member of the steering committee of Uniqure; and funding research was directly provided to his Institution from CSL Behring, Pfizer and SOBI. He participated in advisory boards of Ablynx, Alexion, Bayer, Baxalta/Shire, CSL Behring, Novo Nordisk, Pfizer, Roche, SOBI and Uniqure. He also reports grants and personal fees from CSL Behring and Sobi, personal fees from Roche, Novo Nordisk, Bayer, Kedrion, Shire, Sanofi, Werfen, and Uniqure, and grants from Pfizer, outside the submitted work.

SL participated in advisory boards of CSL Behring, Roche, Sobi, and Novo Nordisk.

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