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To cite this article: María Teresa Álvarez Román, Olga Benítez, Maria Isabel Canaro, María Fernanda López Fernández, Francisco J. López Jaime, José Mateo Arranz, Ramiro Núñez, Manuel Rodríguez López, Cristina Sierra Aisa & Victor Jiménez-Yuste (2021) Expert opinion paper on the treatment of hemophilia B with albutrepenonacog alfa, Expert Opinion on Biological Therapy, 21:9, 1165-1171, DOI: [10.1080/14712598.2021.1932811](https://doi.org/10.1080/14712598.2021.1932811)

To link to this article: <https://doi.org/10.1080/14712598.2021.1932811>



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Published online: 06 Jul 2021.



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## Expert opinion paper on the treatment of hemophilia B with albutrepenonacog alfa

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### ABSTRACT

**Introduction:** Current guidelines recommend prophylactic treatment of hemophilia B with the missing coagulation factor IX, either with standard half-life or extended half-life products. Extended half-life products have half-lives three to six times longer than the former, allowing a reduction in the number of weekly injections and therefore, potentially impacting on treatment adherence and quality of life. Albutrepenonacog alfa is an extended half-life fusion protein of coagulation factor IX with recombinant human albumin, indicated for both on-demand and prophylactic treatment for bleeding in patients with hemophilia B of all ages.

**Areas covered:** The authors review the clinical and pharmacokinetic characteristics of albutrepenonacog alfa, as well as the available information regarding trough levels and real-world evidence. Given the availability of other factor IX products in the market, indirect comparisons of clinical and pharmacokinetic characteristics are presented.

**Expert opinion:** The authors exhibit their expert opinion on which patient profiles are candidates for prophylactic treatment with albutrepenonacog alfa, and on the management of patients in terms of dosing, regimens of administration and protocols for switching the treatment.

### ARTICLE HISTORY

Received 8 February 2021  
Accepted 17 May 2021

### KEYWORDS

Albutrepenonacog alfa;  
blood coagulation factors;  
factor IX; hemophilia B;  
qualitative research

## 1. Introduction

Hemophilia B is a congenital bleeding disorder caused by a deficiency of coagulation factor IX (FIX), manifested by either spontaneous bleeding or bleeding after trauma or surgery [1,2]. According to the World Federation of Hemophilia, hemophilia B affects approximately 3.75 per 100,000 males, and rates vary considerably between different countries [3,4]. The severity of hemophilia depends on the blood levels of clotting factor – levels of 5–40% have been correlated with mild disease; 1–5%, with moderate disease; and less than 1%, with severe disease [5].

According to current guidelines, prophylaxis with FIX concentrates should be the goal of therapy to preserve normal musculoskeletal function, since it prevents bleeding and joint destruction, and it is a cost-effective intervention. Both plasma-derived (pd-FIX) and recombinant FIX (rFIX) concentrates are recommended options for replacement therapy [2]. However, rFIX concentrates are the preferred choice in some countries, due to a negligible risk of pathogen contamination [6–8].

Current prophylactic treatment options include either standard half-life FIX (SHL-FIX) or extended half-life FIX (EHL-FIX)

products (Table 1). SHL-FIX products typically need to be administered two or three times per week. On the other hand, EHL-FIX have half-lives three to six times longer than SHL-FIX, and therefore entail less injections and a potential improvement in adherence [1,2,9,10].

The clinical development program of albutrepenonacog alfa (recombinant fusion protein linking FIX with albumin -rIX-FP-), initiated in 2010, has provided promising clinical data and has brought up new prophylactic regimens for patients with hemophilia B.

The authors of this publication held a virtual meeting to review the available evidence and provide expert opinion on the new scenario of prophylaxis of bleeding in patients with hemophilia B treated with rIX-FP.

## 2. Characteristics of albutrepenonacog alfa (recombinant fusion protein linking FIX with albumin, rIX-FP)

The rIX-FP molecule was designed to improve the biological characteristics of rFIX in vivo. To that purpose, rFIX was genetically fused to albumin via a peptide linker that undergoes

**Article highlights**

- Albutrepenonacog alfa is a fusion protein of recombinant FIX with human albumin, which extends the product circulation time.
- Albutrepenonacog alfa is an effective and safe option for the prophylactic treatment of patients with hemophilia B of all ages.
- Optimal dosing of FIX products relies on accurately monitoring plasma factor levels. High trough levels can be achieved with the administration of albutrepenonacog alfa, regardless of the administration regimen (7-, 10-, 14- or 21-day regimens), which represents an advantage for patients with bleeding episodes, arthropathies, high physical activity, and those undergoing surgery or invasive procedures.

This box summarizes key points contained in the article.

cleavage in parallel with FIX activation. Therefore, the molecule remains intact until activation and cleavage of albumin, which makes the circulation time of the product longer than that of SHL-FIX [11,12]. Albumin is a convenient fusion protein, since its half-life is around 20 days, it lacks enzymatic and immune activity, it is a natural carrier of other proteins and peptides, it is already abundant in plasma, and it is a very stable molecule [13]. Besides, albumin recycles via the neonatal Fc receptor pathway, which is an additional mechanism responsible for prolonging the half-life of rIX-FP in vivo [14].

rIX-FP is approved for long-term prophylaxis to prevent bleeding in patients with severe hemophilia B, at a weekly dose of 35–50 IU/kg of body weight. Adult patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days. When control is also achieved with these regimens, further extension of the treatment interval to 21 day with a dose of 100 IU/kg may be considered in some adult patients [15].

### 3. Pharmacokinetics

rIX-FP was first studied in a phase I, multicenter, dose-escalation trial that assessed pharmacokinetics (PK) and safety of the molecule in 25 adult patients with hemophilia B. rIX-FP produced an increase of FIX activity levels, compared to the same dose of rFIX or pd-FIX. The mean terminal half-life and the mean area under the curve (AUC) were higher with rIX-FP than with rFIX – 5.3- and 7-fold increase, respectively. Other PK parameters, such as incremental recovery and clearance, were also improved with rIX-FP [16,17]. In the phase III study, a 14-day PK evaluation was also performed, and rIX-FP displayed a better PK profile when compared to SHL-FIX products; the mean terminal half-life was 4.3 times longer than with the previous FIX treatment [18]. In the pediatric population, when compared to the previous FIX treatment, the mean

terminal half-life of rIX-FP was 4.3 times longer, and the clearance was 6.4 times slower [19].

### 4. Trough levels

In patients with hemophilia B, maintaining appropriate trough levels of the clotting factor helps to reduce the incidence of bleeds, and consequently, to reduce joint disease and improve quality of life and life expectancy [2,20]. However, due to phenotype variability among patients, current recommendations tend to individualized prophylaxis approaches, rather than considering specific trough levels for all patients. Besides, the time that a patient remains above certain levels can be as important as the trough level itself [20,21]. Achieving high trough levels is particularly important in patients with bleeding episodes, with arthropathies, with high physical activity, and those undergoing surgery or invasive procedures [21].

Trough levels higher than 5 IU/dL can be maintained 7 days after the administration of 25 IU/kg of rIX-FP, or 14 days after 50 IU/kg in adults [17], and 10 days after 50 IU/kg in children [19]. In contrast, the mean FIX activity is around 5 IU/dL 48 hours after the administration of 50 IU/kg of either rFIX or pd-FIX, both in adults and pediatrics [17,19]. For the adult and adolescent population, the mean steady-state trough FIX activity level was 20.9% when receiving 35-50 IU/kg every 7 days, and 12.76% when receiving 50-75 IU/kg every 14 days. In pediatrics treated with 35-50 IU/kg every 7 days, it was 12.8% [22]. In the extension study that evaluated the efficacy of rIX-FP in adult patients previously enrolled in the phase III study or who initiated prophylaxis following surgery, mean steady-state trough FIX activity was 22.0%, 19.8%, 13.6%, and 7.6% with 7-, 10-, 14-, and 21-day regimens, respectively [23].

### 5. Clinical efficacy of rIX-FP

A phase III study evaluated the efficacy and safety of rIX-FP in 63 previously treated adolescent and adult patients with severe hemophilia B. The median annualized spontaneous bleeding rate (AsBR) was reduced from 15.43 to 0.00 after switching from on-demand to weekly prophylaxis treatment ( $p < 0.0001$ ). Median AsBR was also 0.00 on 10- and 14-day regimens. The annualized bleeding rate (ABR) was 0.00 in patients on 7- and 10-day regimens, and 1.08 in patients with 14-day regimens. The annualized joint bleeding rate (AjBR) was 0.00 on all prophylaxis regimens [18]. In the extension study, median AsBR was 0.00, 0.28, 0.37 and 0.00 for the 7-, 10-, 14- and 21-day regimens, respectively [23], meaning that 14- and 21-day regimens have comparable efficacy to the 7-day regimen.

**Table 1.** Current recombinant prophylactic treatment options for hemophilia B approved by the EMA.

Classification according to half-life	Product	Fusion protein	Brand	Manufacturer
Standard	rFIX (nonacog alfa)		BeneFIX®	Pfizer
	BAX 326 (nonacog gamma)		Rixubis®	Baxalta Innovations GmbH
Extended	rIX-FP (albutrepenonacog alfa)	Albumin	Idelvion®	CSL Behring
	rFIX-Fc (eftrenonacog alfa)	Fragment crystallizable	Alprolix®	Biogen Inc
	N9-GP (nonacog beta pegol)	Polietilenglicol	Refixia®	Novo Nordisk

In children under 12 who were treated with rIX-FP on a prophylaxis weekly regimen, median AsBR turned out to be 0.00 [19]. The extension study for the pediatric population showed a very low median AsBR on any regimen: 0.00 for the 7- and 10-day regimens, and 1.10 for the 14-day regimen [24].

## 6. Comparison to other EHL-FIX

A systematic review conducted by Davis and collaborators compared, through indirect statistical comparison, the efficacy of rIX-FP to that of other SHL-FIX and EHL-FIX for prophylaxis treatment of adult patients [9]. On a 7-day regimen, the mean ABR was significantly lower with 35–50 IU/kg of rIX-FP than with 50 IU/kg of rFIX-Fc (1.2 [1.8] vs 3.1 [2.9],  $p < 0.001$ ). Mean AsBR and AjBR values were not provided in the rFIX-Fc pivotal study, so an indirect comparison was not possible. However, and although data come from different studies, the median AsBR and AjBR values were lower with rIX-FP than with rFIX-Fc (median AsBR was 0.00 with all regimens of rIX-FP vs 1.0 for weekly and 0.9 for individualized administration of rFIX-Fc; the median AjBR was 0.00 with all regimens of rIX-FP vs 1.1 for weekly and 0.4 for individualized administration of rFIX-Fc) [18,25]. No indirect comparison has been performed in pediatric patients, since mean bleeding rates were not reported in the pivotal study of rFIX-Fc [26].

An indirect comparison with N9-GP was neither possible, since mean ABR, AsBR, and AjBR were not provided in the pivotal study [27]; however, rIX-FP achieved a lower median ABR than N9-GP, on 7-day regimen (0.00 vs 1.04). rIX-FP also achieved lower mean ABR values than the SHL-FIX products encompassed in the systematic review [9,28,29].

## 7. Real-world evidence using rIX-FP

A retrospective study collected data from preexisting medical records of patients treated with rIX-FP for 8 weeks or more in Germany, and compared its efficacy with the patient's prior FIX product. The mean ABR decreased from 2.6 (2.9) with the prior product to 0.3 (0.6) with rIX-FP, and the proportion of patients with zero bleeds increased from 24% to 81%. The mean factor consumption was nearly half with rIX-FP than with prior prophylaxis (44.2 vs 82.3 IU/kg/week) [30].

A similar study was performed with patients from Italy, Belgium and the United Kingdom. Mean ABR reductions after the switch ranged from 67.7% to 94.3%, depending on the doses administered in each country. The administration of rIX-FP increased the proportion of patients experiencing zero spontaneous bleeds from 41% to 88%. Dosing and frequency of administration were also reduced after the switch [31].

In the United States, 145 patients treated with rIX-FP were included in a study to evaluate utilization and bleeding rates. The mean ABR changed from 8.9 to 0.7 when switching from rFIX-Fc to rIX-FP, and from 4.5 to 1.5 when switching from rFIX to rIX-FP. Mean and median consumption was also diminished with rIX-FP, when compared to previous FIX, and specifically to rFIX or rIX-Fc [32,33].

Some case series and case reports from patients receiving prophylactic treatment with rIX-FP in Spain have been recently presented. In a case series of six patients treated for two years,

the median ABR was 0.50, the median AsBR was 0.25, and patients reported good quality of life [34]. A case report of a patient with severe hemophilia B treated with rFIX from the age of 15 months to 7 years with poor venous access and repetition infections, using rFIX and then switching to rIX-FP, showed a reduction of 64.8% in FIX consumption, and no hospitalizations were observed after 6 months with rIX-FP [35]. Another patient, a 3-year-old with moderate hemophilia B, was switched from rFIX to rIX-FP due to difficult venous access and mobility reasons (health emergency secondary to COVID-19): the efficacy was maintained, the reported quality of life was improved, and the number of injections administered was reduced [36]. A recent case series has described the efficacy and safety of rIX-FP in two previously untreated pediatric patients in Italy [37].

A few recent reported real world experiences have associated prophylaxis with rIX-FP with spontaneous bleeding and poor response [38–41]. In a single center case series, the recommendations of the European Summary of Product Characteristics (SmPC) to perform the switches to rIX-FP were not followed in none of the three patients reported with poor bleed control. All of them started with a 2-week regimen, without ensuring well-control in the previous weekly regimen, as recommended in the SmPC, which may explain the clinical outcome in these three patients [38]. On the other hand, the authors reported that 25 other patients had been switched to rIX-FP since its licensure, with similar dosing to the three reported cases and had positive outcomes. In another report, key information was missing: no data on the dose or dose regimens were provided, neither, for example, regarding the patients' baseline bleeding rate, physical activity levels and joint health. Furthermore, patients ranged in age from a few months to 23 years. The mean or median ages of patients on each product were not provided and, as children typically have higher bleeding rates than adults, this could have had an impact on the findings [39,40]. The authors thereof speculated that a poor distribution of rIX-FP to the extravascular space could be the key contributor for these results, although it has been published that extravascular distribution of rIX-FP is comparable to that of natural FIX [42,43]. Moreover, evidence to ensure that biodistribution of FIX is related to bleeding rates is still lacking, and clinical efficacy is still the most relevant outcome to assess treatment success [44,45]. In a third report, 3 out of the 7 patients treated with rIX-FP reported unexpected bleeding episodes. However, mean doses used were lower than those currently recommended in the product label [41].

## 8. Safety

rIX-FP was well tolerated by adult and pediatric patients included in the clinical trials of the development program. Of the reported adverse events (AEs), most were mild or moderate in severity [16,18,19,46]. As described in the SmPC, the common ( $\geq 1/100$  to  $< 1/10$ ) mild/moderate AEs are headache, dizziness and injections site reactions. Other adverse reactions as rash, hypersensitivity or eczema are uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) [15]. In the pivotal study, the most frequently reported treatment-emergent AEs were

nasopharyngitis, headache, arthralgia, and influenza; only two patients experienced serious AEs (SAEs), and were classified as not related to rIX-FP treatment [18]. In the extension study, the majority of treatment-emergent AEs were also mild to moderate. About 17% of adults experienced SAEs, and only one was considered to be related to the treatment: arterial thrombosis after undergoing knee replacement surgery, followed by persistent postoperative complications, although the patient's history was also considered a contributing factor. 29.1% of pediatric patients experienced SAEs, but none was related to treatment [23,24]. The safety profile of the 21-day regimen was similar to that of the 14-day regimen [23]. No inhibitors or antibodies were detected in any patient participating in these studies. However, an isolated case of a young patient with hemophilic arthropathy, mainly due to a delay in the initiation of an adequate prophylactic treatment, treated with prophylactic rIX-FP and developing a low-titer inhibitor has been reported [47]. This patient started with an off-label prophylactic regimen (50 IU/kg every 14 days).

## 9. Conclusions

rIX-FP has an excellent efficacy in the prophylactic treatment of patients with hemophilia B, with very low median values of ABR, AsBR and AjBR, which can positively impact joint protection, preservation of physical activity and quality of life, as observed in real-world data. Clinical trials have also demonstrated that over 95% of treated patients can achieve a steady-state FIX activity trough level higher than 5%, and a good bleeding control under 7-, 14- and even 21-day regimens; all this data translates in a decrease in the burden of treatment administration, less factor consumption and higher adherence rates.

In summary, rIX-FP is an excellent choice for the prophylactic treatment of any patient with hemophilia B, providing benefits in terms of efficacy, adherence and quality of life.

## 10. Expert opinion

According to the authors' opinion, and based on its clinical efficacy, rIX-FP is a convenient option for prophylactic treatment of hemophilia B in all patients, in any age group. Its PK profile allows an extension of the dosing interval up to 14 or even 21 days, and a reduction in the number of intravenous injections, which may have a positive impact on patient's quality of life. In fact, substantial improvements have been observed in the quality of life of pediatric patients, as well as in the satisfaction of their caregivers [48]. Extended dosing intervals can also have a positive impact on adherence, which in turn can lead to improved clinical outcomes. Excellent adherence rates have been observed in both clinical trials and clinical practice with rIX-FP [49].

Specifically, rIX-FP can be a good option in pediatric and teenage patients, since they usually have higher physical activity, more difficult venous access, higher number of traumatic bleeds and higher FIX clearance. Additionally, the fact of receiving intravenous injections can be more unpleasant and burdensome in pediatric and young patients, so reducing their frequency may be advisable. Likewise, adult patients who have

poor venous access or a high level of physical activity can obtain an extra benefit from rIX-FP administration.

Adult patients who require a high number of infusions or those poorly controlled with the former treatment can also especially benefit from rIX-FP, since the reduction in the number of injections can entail an even larger increase in quality of life, and it could be a cost-effective option. Actually, a recent pharmacoeconomic model assessed the budget impact of treating severe hemophilia B with reimbursed rIX-FP over 3 years in Italy, concluding that rIX-FP is expected to decrease pharmaceutical costs [50]. A recent real world study found that the cost per success (defined as patients experiencing no spontaneous bleeding) in patients switching from nonacog alfa to rIX-FP was reduced by 29% in Italy, 55% in Belgium, and 50% in the United Kingdom. The reduction continued to be true even when the price of nonacog alfa or when the efficacy of rIX-FP were reduced by 20% [31]. Patients with complications, such as arthropathies, severe muscle hematomas, and life-threatening hemorrhages, or those who are to undergo surgery, are also good candidates for prophylaxis with rIX-FP (Figure 1).

Optimal dosing of FIX products relies on accurately monitoring plasma factor levels [51]. The authors agreed that trough levels need to be individualized according to each patient's characteristics. Higher trough levels should be considered in patients with joint concerns, uncontrolled patients, patients undergoing surgery or on secondary prophylaxis after muscle hematomas or life-threatening hemorrhages. Likewise, children and adolescents with a high clearance and high physical activity would also be candidates for higher trough levels. Current recommendations include factor target levels of 5–15% for children and adults performing high-risk activity, 15–30% for patients performing intensive sport activity, and 50–80% for patients performing very high impact physical activity [21]. Schedules involving weekly dosing or dosing every two weeks are feasible with rIX-FP, and it is a good option for patients requiring high trough levels.

As stated in the summary of product characteristics, the usual dose of rIX-FP for long-term prophylaxis to prevent bleeding is 35–50 IU/kg once a week, and well-controlled adolescent and adult patients on a once-weekly regimen can receive up to 75 IU/kg dose every 10 or 14 days. In 18-year-old or older patients, a greater extension of the treatment interval can be considered [15]. In order to help practitioners to switch patients from other FIX products to rIX-FP, the authors designed an algorithm, where decisions are prompted by hemostatic efficacy after a period under a specific regimen (Figure 2). According to the opinion of the experts, and based on recent recommendations [20,52], a PK assessment can be done before switching to estimate the dose and frequency of infusion for maintaining appropriate trough levels; and/or two weeks after switching, to assess whether the dose and frequency of infusion are adequate. The Web Accessible Population Pharmacokinetic Service for Hemophilia (WAPPS-Hemo) is a free tool to make PK evaluations easier [53]. The authors also suggest to assess trough levels at the discretion of the treating clinician, and perform further PK studies when changes in trough levels are identified. The one-stage (OS) assay is



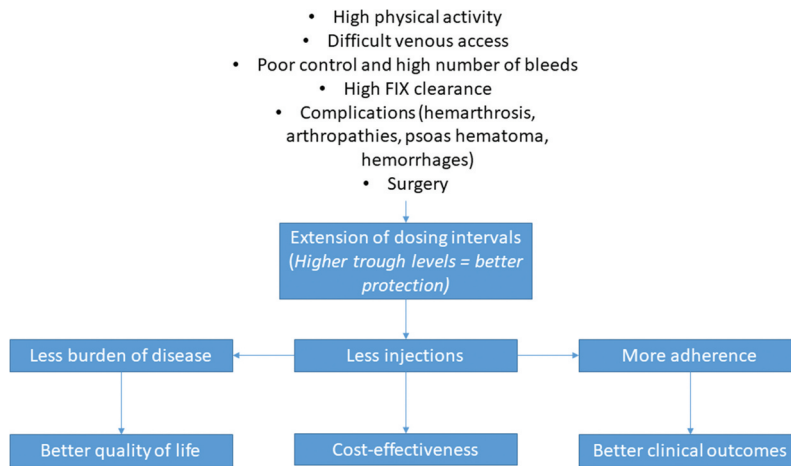


Figure 1. Characteristics of patients who may especially benefit from prophylactic treatment with rIX-FP and potential advantages.

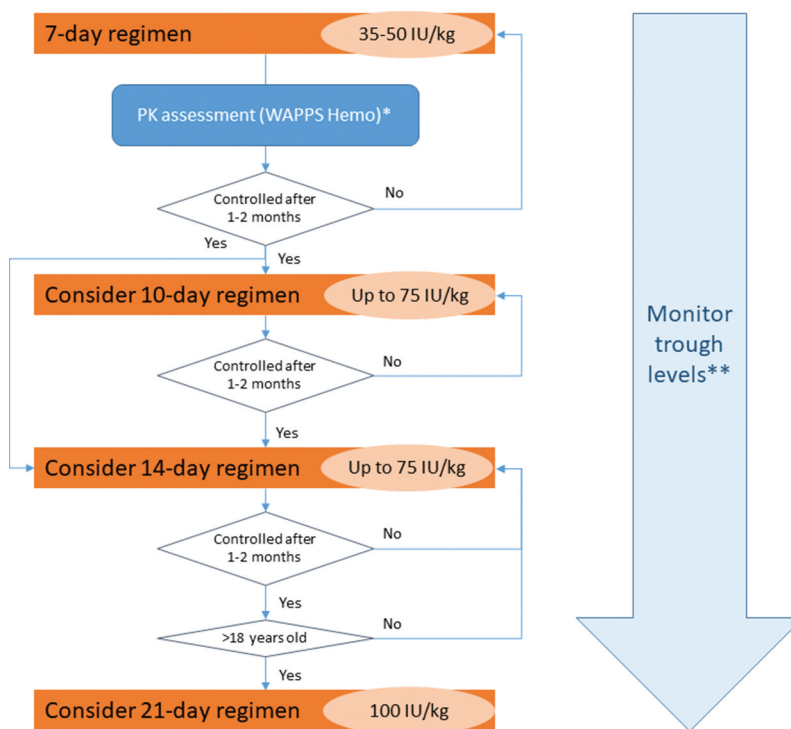


Figure 2. Algorithm for switching patients from FIX products to rIX-FP.

PK, Pharmacokinetics\*PK assessment to be performed before switching, to estimate the dose and frequency of infusion for maintaining appropriate trough levels; or two weeks after switching, to assess whether the dose and frequency of infusion are adequate.\*\* At the discretion of the clinician.

useful and reliable to confirm that adequate rIX-FP levels have been achieved and maintained. However, it should be considered that some activated partial thromboplastin time (aPTT) reagents, such as actin FS or kaolin-based aPTT reagents could lead to an underestimation of the activity of up to 50% [15,54]. Therefore, FIX activity was measured in clinical trials evaluating rFIX-FP with silica activator aPTT reagent [55,56].

### Acknowledgments

The authors want to thank Ampersand Consulting and CSL Behring, respectively, for organizing and supporting the virtual meeting to review the available evidence.

### Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

## Declaration of interest

María Teresa Álvarez Román has participated as speaker, in advisory boards and sponsored symposia with Novo Nordisk, Bayer, Takeda, Roche, Pfizer, Octapharma, Amgen, Novartis, CSL Behring and Sobi. Olga Benítez has participated as consultant, speaker or has received medical grants from Bayer, CSL Behring, Pfizer, Sobi, Roche and Takeda. Francisco J. López Jaime has participated as consultant or speaker for CSL Behring, Novo Nordisk, Roche, Sobi and Takeda. José Mateo Arranz has participated as speaker or consultant for CSL-Behring, Bayer-AG, Sobi, Roche, Octapharma, Grifols, Takeda, Novo Nordisk. Ramiro Núñez has received fees from Novo Nordisk, Takeda, Grifols, Roche, Pfizer, Octapharma, CSL Behring and Sobi. Víctor Jiménez Yuste has received grants, travel or research support from Pfizer, Grifols, Shire, Novo Nordisk, Sobi and Octapharma, and has participated in scientific advisory boards for CSL Behring, Sobi, Octapharma, Grifols, Pfizer, Shire, Novo Nordisk, Roche, Biomarin and Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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## Funding

This work was supported by CSL Behring.

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