

## ORIGINAL ARTICLE

# Targeting of antithrombin in hemophilia A or B with investigational siRNA therapeutic fitusiran—Results of the phase 1 inhibitor cohort

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## Abstract

**Background:** Fitusiran, an investigational small interfering RNA therapy, reduces antithrombin production to rebalance hemostasis in people with hemophilia A or B, with or without inhibitors.

**Objectives:** To evaluate the safety and efficacy of fitusiran treatment for people with moderate/severe hemophilia A or B with inhibitors.

**Patients/Methods:** In this open-label phase 1, part D study, 17 males with hemophilia A or B with inhibitors received three once-monthly subcutaneous injections of fitusiran 50 mg ( $n = 6$ ) or 80 mg ( $n = 11$ ); followed for up to 112 days. Endpoints

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included safety (primary), pharmacokinetics/pharmacodynamics (secondary), annualized bleeding rate, and patient-reported outcomes (exploratory).

**Results:** The most common adverse event was injection site erythema ( $n = 8$ ). No thrombotic events were reported. At nadir, mean (standard error of the mean [SEM]) antithrombin activity decreased from baseline by 82.0% (2.2) and 87.4% (0.7) in the 50 mg and 80 mg groups, respectively. Antithrombin reduction was associated with increased thrombin generation. 11/17 (64.7%) participants had no bleeds during the observation period (mean [standard deviation] 69.4 [16.3] days). Mean (SEM) changes from baseline in Haemophilia Quality of Life Questionnaire for Adults total (-9.2 [2.9]) and physical health (-12.3 [3.9]) domain scores suggested clinically meaningful improvement.

**Conclusions:** Monthly fitusiran was generally well tolerated, lowered antithrombin levels from baseline, and resulted in improved thrombin generation. These preliminary results suggest that monthly fitusiran treatment may reduce bleeding episodes and improve quality of life in participants with hemophilia A or B with inhibitors.

#### KEYWORDS

antithrombin, fitusiran, hemophilia, siRNA, inhibitors

#### Essentials

- Fitusiran is a synthetic siRNA targeting liver antithrombin (AT) to increase thrombin generation.
- Phase 1 study of monthly subcutaneous fitusiran for people with hemophilia A or B with inhibitors.
- Fitusiran reduced AT, increased thrombin generation, and reduced bleeding events in participants.
- Fitusiran treatment was well tolerated; no thrombotic events were reported.

## 1 | INTRODUCTION

Maintaining normal hemostasis relies on a regulated set of simultaneously occurring procoagulant and anticoagulant processes, in which thrombin generation has a central role.<sup>1</sup> Bleeding in hemophilia A and B arises from insufficient thrombin generation.<sup>1-3</sup> It is well recognized that, without effective treatment, people with hemophilia experience recurrent bleeding, which can be life-threatening and/or lead to major disability because of chronic hemarthropathy and significant pain.<sup>4</sup>

Significant unmet needs and management challenges continue to exist for all people with hemophilia despite treatment advances. Prophylaxis is considered the cornerstone of hemophilia management<sup>3,5,6</sup>; however, frequent intravenous injections of factor replacement for prophylaxis are not only burdensome,<sup>7,8</sup> but also a large proportion of the world hemophilia population is without prophylaxis because of the complexities of delivering factor replacement.<sup>9</sup> Additionally, the development of inhibitory alloantibodies to factor replacement remains one of the most serious complications of hemophilia treatment.<sup>10</sup> Compared with those patients without inhibitors, those with persistent inhibitors have a lower quality of life (QoL), greater joint disease, and higher mortality, including a higher

risk of death from hemophilia-related bleeding complications.<sup>10,11</sup> Current treatment strategies for these individuals, such as immune tolerance induction, prophylaxis, and bleeding treatment with bypassing agents (BPAs; ie, activated prothrombin complex concentrates [aPCC]; recombinant activated factor VII [rFVIIa]), have limited effectiveness.<sup>12-16</sup> The management of people with hemophilia B and inhibitors is further complicated by the occurrence of severe allergic/anaphylactic reactions and nephrotic syndrome, which can result from administration of FIX immune tolerance induction,<sup>17,18</sup> severely limiting safe treatment options.

Given these challenges and a clear need for improved management strategies, efforts have focused on the development of novel alternative therapies to factor replacement and can adequately provide prophylaxis in patients with inhibitors. These include bispecific antibodies that partially mimic VIII function or approaches that are designed to rebalance coagulation by targeted inhibition of natural anticoagulants (antithrombin [AT], tissue factor pathway inhibitor, protein S/activated protein C, protease nexin-1).<sup>19-29</sup>

Fitusiran is an investigational, subcutaneously administered small interfering RNA therapy that specifically targets AT messenger RNA to lower production of AT in the liver.<sup>28</sup> Fitusiran utilizes a <1 ml

fixed subcutaneous dose and has a prolonged pharmacodynamic effect, offering the potential for consistent hemostasis over time. In its role as an anticoagulant, AT regulates hemostasis by inhibiting thrombin and FXa.<sup>30</sup> Fitusiran-induced reduction of AT levels has the potential to promote hemostasis through increased thrombin generation and is intended as prophylactic therapy in individuals with hemophilia A or B, either with or without inhibitors. Preclinical studies with fitusiran have demonstrated proof of this concept.<sup>24</sup> In the phase 1 study in participants without inhibitors (parts B and C), fitusiran was well tolerated, and dose-dependent reduction of AT levels was demonstrated that correlated with increased thrombin generation. Further, an exploratory analysis of bleeding events suggested a decrease in bleeding episodes.<sup>28</sup>

Based on its mechanism of action, it was hypothesized that fitusiran treatment may be beneficial in individuals with hemophilia A or B with or without inhibitors. Given its safety and tolerability in dose-escalation studies in individuals with hemophilia *without* inhibitors reported previously,<sup>28</sup> the phase 1 study was extended to study safety, pharmacokinetic/pharmacodynamic (PK/PD) characteristics, and exploratory efficacy as measured by bleeding frequency in individuals with hemophilia A or B *with* inhibitors, which we report here.

## 2 | METHODS

### 2.1 | Study oversight

This was the part D cohort of a multicenter, international, open-label study in subjects with hemophilia A or hemophilia B and inhibitors. Full methodology and results of parts A through C were previously published.<sup>28</sup> The full list of clinical sites that participated in the phase 1 study are provided in Table S1 in the Supplementary Appendix. This part of the study (part D) was initiated in November 2015 and was conducted according to the International Conference on Harmonization for Good Clinical Practice, the Declaration of Helsinki, and the 1996 Health Insurance Portability and Accountability Act. The study protocol was approved by the institutional review board or ethics committee at each participating center. The study data were periodically reviewed by the Safety Review Committee. All study participants provided written informed consent. The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier: NCT02035605).

### 2.2 | Study design and population

Eligible participants were male and aged 18 to 65 years (inclusive), with moderate or severe hemophilia A or hemophilia B (FVIII or FIX  $\leq 5\%$ ) with inhibitors (Bethesda inhibitor assay  $>0.6$  BU/ml). Participants had received on-demand treatment or, if previously on prophylactic therapy, they were willing to discontinue prophylaxis for at least 5 days before BPA administration or initiation of study drug.

Key exclusion criteria included a history of venous thromboembolism, a known coexisting thrombophilic disorder, D-dimer  $>3.0 \times$  upper limit of normal (ULN) at screening, AT activity  $<60\%$  at screening, liver dysfunction, HIV positive with a CD4 count  $<200$  cells/ $\mu\text{L}$ , or an estimated glomerular filtration rate  $\leq 45$  ml/min/ $1.73$  m<sup>2</sup> (using the Modification of Diet in Renal Disease formula).<sup>31</sup>

Participants received three once-monthly fixed subcutaneous doses of fitusiran at 50 mg or 80 mg and were followed for up to 112 days (or up to 84 days for those who transitioned from the phase 1 study to the open-label extension study [ALN-AT3SC-002]) or until AT levels returned to  $\geq 80\%$  of the baseline value, whichever period was longer. Bleeding episodes were managed during the study with rFVIIa or aPCC therapy.

### 2.3 | Study assessments

The primary objective of part D was to evaluate the safety of fitusiran in participants with hemophilia A or B with inhibitors. Secondary objectives were to characterize the PK of fitusiran and assess the PD effects of fitusiran on AT activity and thrombin generation. Exploratory objectives included assessment of the effect of fitusiran on annualized bleeding rates (ABRs) and patient-reported outcomes.

Safety assessments included adverse event (AE) monitoring, clinical laboratory assessments (eg, hematological; biochemical, including liver function tests; coagulation measurements, including activated partial thromboplastin time [aPTT], prothrombin time [PT], international normalized ratio, platelets, D-dimer, fibrinogen; antidrug antibody formation using a validated human enzyme-linked immunosorbent assay), vital signs, and 12-lead electrocardiography. AEs and serious AEs (SAEs) were assessed throughout the study and coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 16.0). AEs were graded based on their severity (mild, moderate, or severe) and the causal relationship to study drug or premedication recorded.

For PK/PD analyses, AT activity was measured in human plasma using a validated chromogenic assay for the quantification of functionally active AT calibrated against the AT activity of the World Health Organization reference plasma standard (lower limit of quantitation of 5% AT activity). A calibrated automated thrombogram assay (Thromboscope BV, Maastricht, the Netherlands), with an affinity fluorogenic substrate triggered by tissue factor, was used for real-time analysis of thrombin generation. The fluorescence was read with a Thermo Scientific Fluoroskan (Thermo Fisher Scientific) and reported as peak height. Fitusiran PK parameters were calculated from plasma concentration–time data using noncompartmental analysis and Phoenix WinNonlin (Certara) software.

To assess the effect of fitusiran on ABR, detailed hemophilia and bleeding history was collected and used to determine participants' historical ABR based on a 6-month period. During the study,

all participants had a study-specific diary in which all episodes of bleeding, administration of BPA, and response to BPA treatment were recorded. Based on fitusiran's mechanism of action, the expected onset period to reach AT reduction of  $\geq 75\%$  is approximately 28 days. Onset period bleeding episodes were those that occurred from the first dose date and time of the study drug to day 28 (inclusive). Observation period bleeding episodes were those that occurred from 4 weeks after the first dose (first dose date +29 days) until 8 weeks after the last dose of fitusiran (last dose date +56 days), or the last visit date in study, whichever was earlier. Causes and locations of bleeding episodes, and dose of BPA treatments for each bleed were captured. Patient-reported outcomes were collected using the EuroQol 5-Dimensions questionnaire<sup>32</sup> and the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL).<sup>33</sup>

## 2.4 | Statistical analyses

The safety analysis population included all the participants who had received at least one dose of fitusiran and was the primary population for the analysis of safety and exploratory endpoints. The PK/PD population included all participants who had received at least one dose of fitusiran and had at least one plasma sample that could be evaluated. Statistical analyses were primarily descriptive and performed using SAS software, version 9.2 (SAS Institute) or higher. Descriptive statistics were presented for continuous variables, and frequencies and percentages for categorical and ordinal variables. Percentages were based on the number of nonmissing values. The ABR in each period was calculated as the number of bleeds in the period divided by the number of days in that period, multiplied by 365.25.

**TABLE 1** Baseline demographics and clinical characteristics of the patient population

Characteristic	50 mg (n = 6)	80 mg (n = 11)	All Treated (n = 17)
Mean (SEM) age, y	32.3 (2.9)	35.8 (3.6)	34.6 (2.5)
Mean (SEM) weight, kg	72.9 (7.0)	74.7 (5.0)	74.0 (4.0)
Type of hemophilia, n			
A	5	10	15
B	1	1	2
Baseline disease severity, n (%)			
Severe (<1% factor activity)	6 (100)	11 (100)	17 (100)
Mean (SEM) time since diagnosis, y	26.2 (4.8)	35.4 (3.7)	32.1 (3.0)
Mean historical ABR (SEM)	35.7 (11.6)	32.0 (5.2)	33.3 (5.1)
History of HCV, n (%)	3 (50.0)	9 (81.8)	12 (70.6)

Abbreviations: ABR, annualized bleeding rate; HCV, hepatitis C virus; SEM, standard error of the mean.

## 3 | RESULTS

### 3.1 | Study population and baseline characteristics

A total of 17 males with hemophilia (hemophilia A [n = 15]; hemophilia B [n = 2]) and inhibitors were enrolled. Three fixed once-monthly injections of fitusiran were given to participants; six received 50 mg (single injection of 0.5 ml) and 11 received 80 mg (single injection of 0.8 ml). All participants completed the study (Figure S1).

Baseline demographics and clinical characteristics of the study population are shown in Table 1. All participants had severe hemophilia (<1% factor level). One participant in each dose group had hemophilia B and the remainder had hemophilia A. Age, weight, and number of bleeding episodes per year were broadly similar in both dose groups. A history of hepatitis C was reported in 12/17 participants, but no participants were receiving ribavirin, interferon, or other antiviral therapy. Additionally, participants who had significant liver disease, including clinically significant cirrhosis per medical history or alanine/aspartate aminotransferase (ALT/AST)  $> 3 \times$  ULN at screening, were excluded.

### 3.2 | Safety

There were no fitusiran treatment discontinuations during the study, no thrombosis events, and no SAEs considered related to fitusiran. There were no instances of drug-induced antidrug antibody formation. Overall, AEs were reported by 17 (100%) participants in part D (Table 2), which had the maximum severity of mild or moderate in

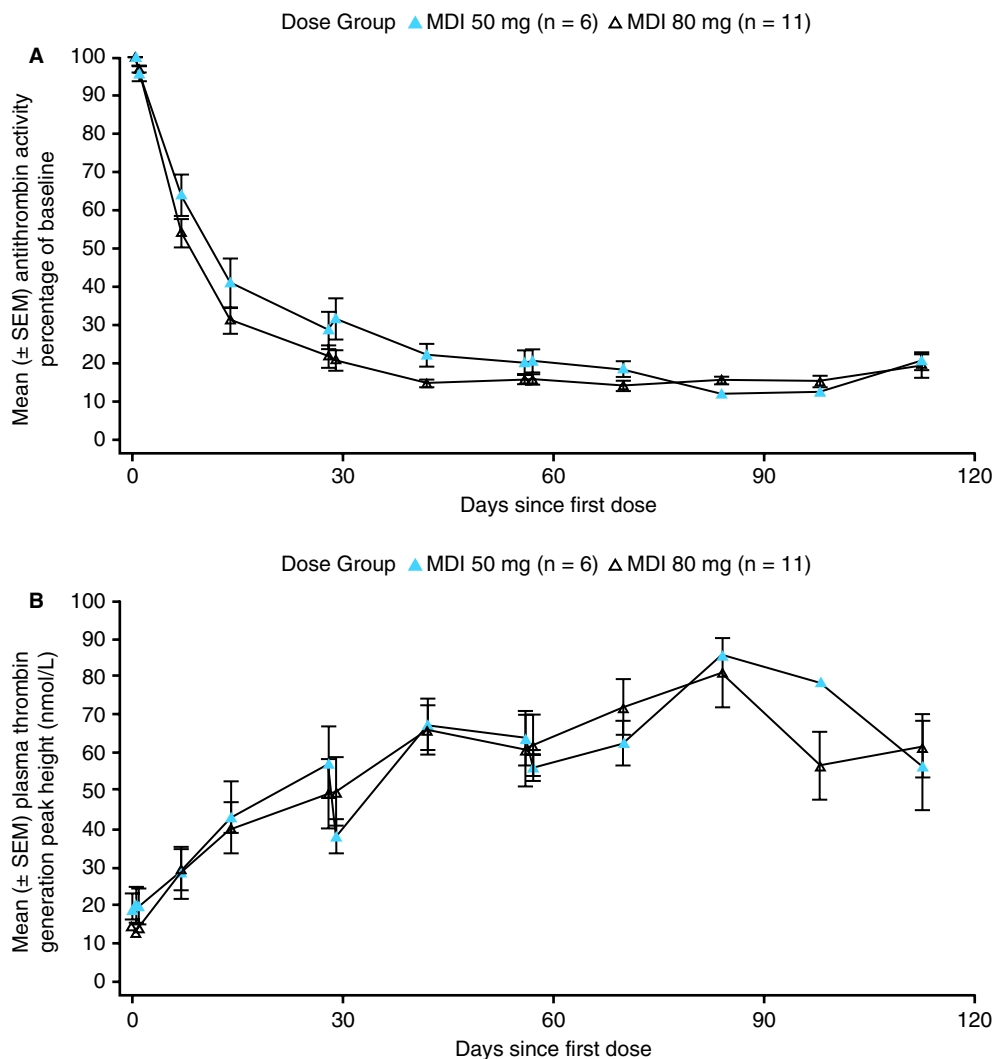
**TABLE 2** Adverse events in the safety population (all patients who received at least a single dose of fitusiran)

n (%)	50 mg (n = 6)	80 mg (n = 11)	All Treated (n = 17)
Any AE	6	11	17 (100)
Any drug-related <sup>a</sup> AE	5	7	12 (71)
Serious AE	0	1	1
Serious drug-related AE	0	0	0
AE leading to discontinuation	0	0	0
Most common drug-related AEs <sup>b</sup>			
Injection site erythema	3	5	8 (47)
Alanine aminotransferase increase	1	2	3 (18)
Aspartate aminotransferase increase	1	2	3
Fibrin D-dimer increase	1	1	2 (12)
Injection site pain	2	0	2 (12)

Abbreviation: AE, adverse event.

<sup>a</sup>Any AE that was considered by the investigator to be possibly or definitely related to the study drug.

<sup>b</sup>All the listed events were reported during the study period in at least two participants.



**FIGURE 1** (A) Effect of fitusiran on AT activity. Mean ( $\pm$  SEM) percentage of AT activity relative to baseline<sup>a</sup> in participants with hemophilia A or B with inhibitors receiving fitusiran once monthly. (B) Mean ( $\pm$  SEM) plasma thrombin generation peak height (nmol/L) over time by fitusiran dose group. <sup>a</sup>As baseline AT levels may vary between individuals, percentage of AT activity for each participant was calculated relative to individual participant baseline measurements. Baseline measurements are the average of all predose measurements within 60 days of first dose excluding optional predose PK visits. The mean of these individual AT activity measurements is presented. Abbreviations: AT, antithrombin; MDI, multiple dose with inhibitors; PK, pharmacodynamics; SEM, standard error of the mean

all cases. The most common AE was injection site erythema ( $n = 8$ ; 47%). The most common study drug-related AEs (occurring in  $\geq 2$  patients) were injection site erythema ( $n = 8$ ; 47%), ALT/AST increase, hepatic enzyme increase (alkaline phosphatase, bilirubin), or transaminases increase ( $n = 5$ ; 29%), fibrin D-dimer increase ( $n = 2$ ; 12%), and injection site pain ( $n = 2$ ; 12%). Injection site reactions were all mild and transient, and none required medical intervention. ALT elevations were generally mild and transient (four participants with peak ALT  $\leq 3 \times$  ULN, one participant with ALT  $\geq 5 \times$  ULN). There were no associated elevations in bilirubin greater than  $2 \times$  ULN (reference range 3.4–20.5  $\mu\text{mol/L}$ ), and no severe liver function impairment meeting Hy's Law criteria, which is predictive of drug-induced liver injury.<sup>34</sup> Three of the five participants with reported ALT elevations had a history of hepatitis C virus (HCV) infection. The one case of ALT increase  $>3 \times$  ULN on day 42 ( $5.1 \times$  ULN; 254.9 U/L) occurred

in a participant (80 mg) with a history of HCV and was reported as moderate in intensity by the investigator; fitusiran dosing continued with subsequent ALT decrease to  $<3 \times$  ULN by day 98 and resolved at the end of the study. The remaining four cases of ALT elevations ( $<3 \times$  ULN) were resolved ( $n = 1$ ) or resolving ( $n = 3$ ) at the end of the study. The elevations in liver enzymes considered related to fitusiran were all asymptomatic, were assessed as mild or moderate by the investigator, and did not require fitusiran dosing suspensions or interruptions. Overall, generally mild and transient ALT/AST elevations (mostly  $<3 \times$  ULN) were frequently observed in both dose cohorts and appeared to be more pronounced in participants receiving the 80 mg fitusiran dose (Figure S2).

The majority of participants did not exhibit any shifts from baseline in coagulation parameters (eg, PT, aPTT, D-dimer, fibrinogen). There were no shifts in PT or aPTT that were reported as

clinically significant by the investigators. Elevated D-dimer levels were seen in a proportion of the cohort and observed elevations appeared to be more frequent and greater with the 80 mg fitusiran dose (6/11 participants [55%]) compared with the 50 mg fitusiran dose (2/6 participants [33%]) (Figure S3). An increased D-dimer was reported as an AE in three participants: two as possibly related and one as unlikely related to the study drug (plots for the individuals with D-dimer reported as an AE showing D-dimer levels over time are shown in Figure S4). All elevations in D-dimer were considered mild in intensity by the investigator and were transient. None of the elevations in D-dimer were associated with laboratory signs of pathological clot formation (changes in platelets, fibrinogen, and/or PT/international normalized ratio). One participant (50 mg) experienced D-dimer increase (412  $\mu\text{g/L}$  on day 29 to 1349  $\mu\text{g/L}$  on day 42; reference range 0-130  $\mu\text{g/L}$ ) that was considered possibly related to treatment. This was mild in intensity and was resolving at the end of the study (526  $\mu\text{g/L}$ ) (Figure S3A and Figure S4A). The participant had increased D-dimer (231  $\mu\text{g/L}$ ) before receiving fitusiran and the event occurred simultaneously with an AE reported of moderate gastritis and mild ALT increase ( $<3 \times \text{ULN}$ ). Another participant (80 mg) experienced D-dimer increase (2480  $\mu\text{g/L}$  on day 42; reference range 0-590  $\mu\text{g/L}$ ) that was judged as possibly related to treatment and was mild in intensity (Figure S3B and Figure S4C). The participant remained on a monthly fixed dose of fitusiran and was subsequently enrolled in the open-label extension study in which the participant continued to receive fitusiran treatment with D-dimer levels measured. A D-dimer increase occurred (2090  $\mu\text{g/L}$  on day 42; reference range 0-590  $\mu\text{g/L}$ ) in another participant (80 mg) that was judged as unlikely related to fitusiran (Figure S3B and Figure S4B). This participant had a baseline elevation in D-dimer (690  $\mu\text{g/L}$ ) before receiving fitusiran and a history of HCV with mild elevation in ALT ( $<3 \times \text{ULN}$ ) reported as an AE on day 29. Fitusiran dosing was continued and the D-dimer AE was resolved by the end of the study (450  $\mu\text{g/L}$ ). For all participants, including those with D-dimer elevations as AEs, an association was not observed between D-dimer elevations and bleeding events or concomitant treatment with BPA during fitusiran treatment.

A total of four SAEs were reported. One participant (18%) reported two SAEs of pneumonia and hamartoma, one had duodenal ulcer bleeding, and one had muscle hemorrhage. None of the SAEs were considered related to the study drug, and all the SAEs resolved.

### 3.3 | Pharmacokinetics

Following the administration of single 50 and 80 mg doses of fitusiran, mean peak plasma levels of the drug (maximum plasma concentration,  $C_{\text{max}}$ ) were 85.4 and 142.9 ng/ml on day 0, and 96.5 and 157.1 ng/ml on day 56 (after 3 monthly doses), respectively. In both dose groups, maximum plasma concentration was achieved approximately 4 hours postdose (time to maximum plasma concentration,

$T_{\text{max}}$ ) for both assessment days (days 0 and 56). Fitusiran levels decreased rapidly in plasma; the mean elimination half-life ranged from 3.4 to 5.2 hours, which was similar to results previously observed in part C.<sup>28</sup> Fitusiran PK parameters were similar in hemophilia patients with or without inhibitors. Further details of PK parameters are provided in Table S2 in the Supplementary Appendix.

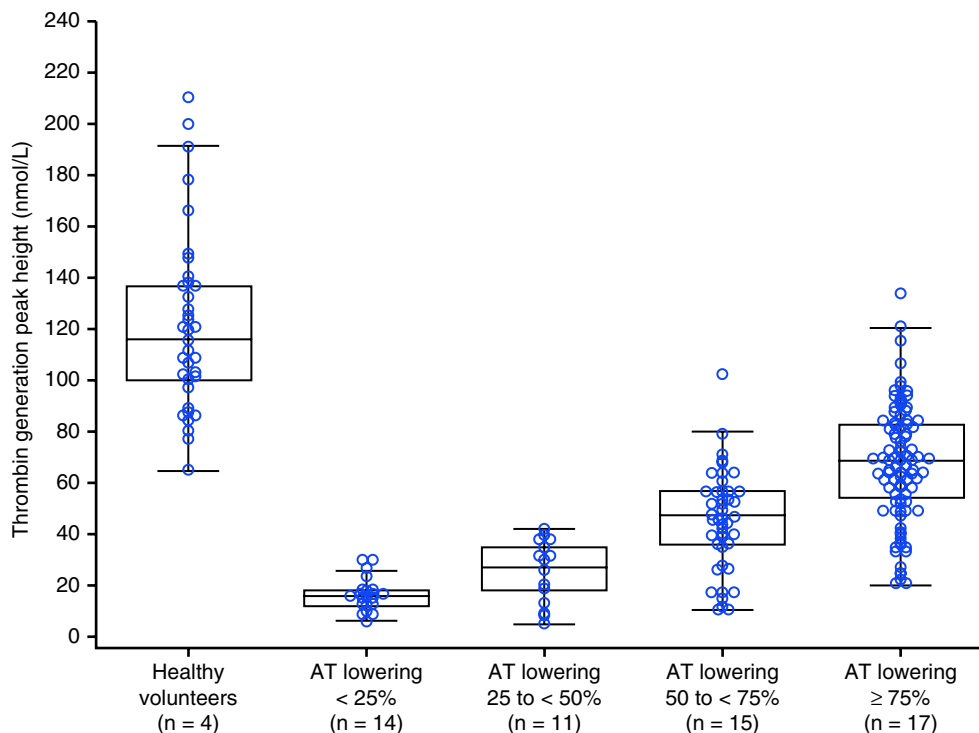
### 3.4 | Pharmacodynamics

AT activity is measured in percent (normal range is approximately 80%-120% activity). In part D, the mean (standard error of the mean [SEM]) baseline AT activity was 109.5% (4.4) and 100.2% (4.8) in the fitusiran 50 mg and 80 mg dose groups, respectively. Because baseline levels may vary between individuals, we evaluated AT reduction based on percentage of AT activity relative to individual participant baseline. There was consistent reduction in AT activity with fitusiran treatment, evident initially at day 7 and progressing to maximal effect after day 28. The mean nadir AT activity was similar between the two dose groups, specifically, 18.0% in the 50 mg dose group and 12.6% in the 80 mg dose group, corresponding to an 82.0% and 87.4% reduction from baseline, respectively. The minimum residual postdose AT level was 9.8%, observed in the 80 mg dose group. Mean (SEM) percentages of AT activity from baseline over time are shown in Figure 1A.

Reduced AT levels were associated with increased thrombin generation (Figure 1B). Consistent with results from parts A through C of this study, thrombin peak height was associated with the degree of AT reduction in both dose groups and AT reduction by  $\geq 75\%$  from baseline resulted in a median peak thrombin height of 68.05 nM, which falls in the lower range previously observed in healthy volunteers (64-210 nM) (Figure 2).<sup>28</sup>

### 3.5 | Exploratory efficacy

Figure 3 shows prestudy ABRs and observation period ABRs for individual participants receiving monthly fitusiran treatment in part D. The median (range) ABR across all 17 participants in part D was 0.0 (0.0-45.7). Overall, 11/17 (65%) participants recorded no bleeding events while on fitusiran treatment and had an ABR of zero during the observation period (mean [standard deviation] 69.4 [16.3] days). Bleeds treated with BPA were successfully managed as assessed by the number of injections per bleed and based on participant perception of the amount of BPA needed to control bleeds compared with bleeds before using fitusiran in the same location. When AT reduction was  $\geq 75\%$ , there were six bleeds that were treated with aPCC and 13 with rFVIIa. Overall, 83.3% (5/6) of the bleeds treated with aPCC were reported to use less aPCC than normal and 61.5% (8/13) of the bleeds treated with rFVIIa were reported to use less rFVIIa than normal to control the bleeding event. BPA injection doses ranged from 93 to 133  $\mu\text{g/kg}$  for rFVIIa (median 108.6  $\mu\text{g/kg}$ ) and 14 to 75 U/kg for aPCC (median 28.6 U/kg).



**FIGURE 2** Post hoc analysis of thrombin generation associated with AT reduction in patients with hemophilia A or B with inhibitors. For all patients, at each time point an AT level and a corresponding thrombin generation measurement were recorded. All available thrombin generation values were associated with an AT activity level relative to baseline and were binned into AT lowering quartiles. Boxes denote median and interquartile ranges. Middle line in the boxes denote median values and top and bottom of the boxes represent the interquartile ranges. Minimum and maximum values are shown by the bars (excluding outliers). Healthy volunteer data were previously presented in Pasi et al.<sup>28</sup> Abbreviation: AT, antithrombin

### 3.6 | Patient-reported outcomes

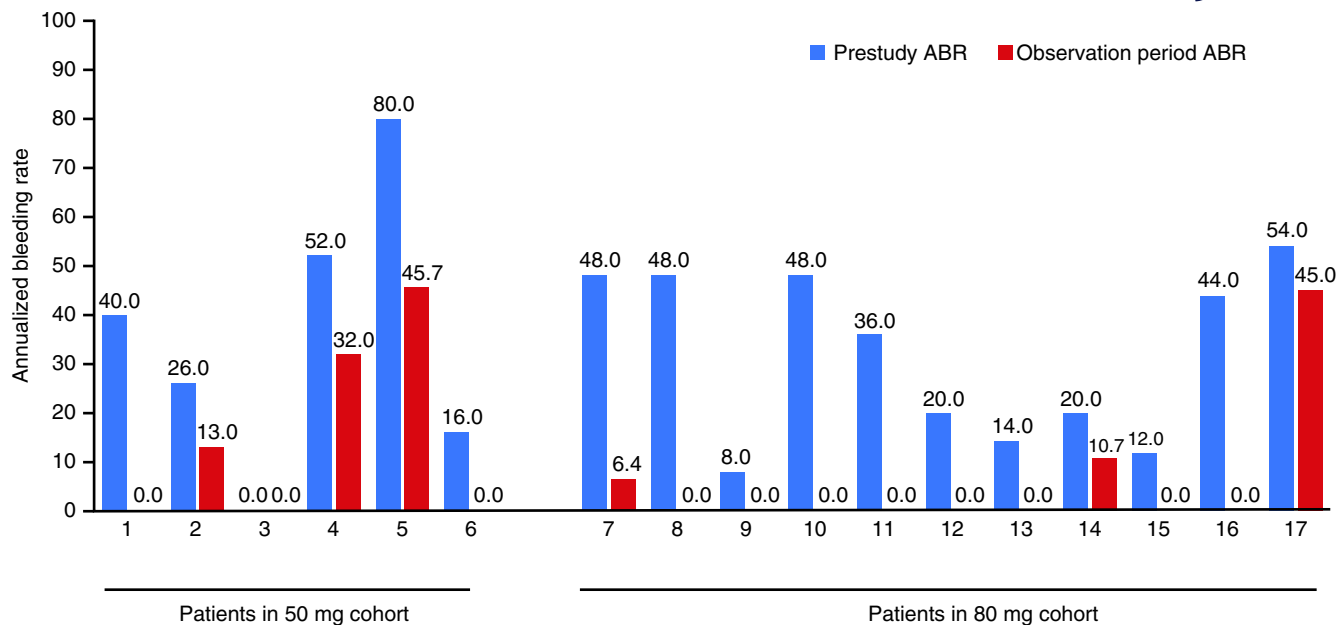
Mean (SEM) changes from baseline to end of study (day 112) in Haem-A-QoL total (-9.2 [2.9]) and physical health (-12.3 [3.9]) domain scores (lower scores indicate better health-related QoL) suggest clinically meaningful improvements based on published thresholds (Table 3).<sup>35</sup> In addition, in the overall population, all domain scores improved with treatment as demonstrated by mean changes from baseline scores (Table 3).

## 4 | DISCUSSION

The therapeutic hypothesis of fitusiran in individuals with hemophilia A or B, with or without inhibitors, is that inhibiting AT production will increase thrombin generation resulting in reduced bleeding events. Consistent with the therapeutic hypothesis, this study extends the findings from the first-in-human study conducted in participants with hemophilia without inhibitors,<sup>28</sup> and demonstrated that fixed monthly subcutaneous doses of fitusiran (50 mg or 80 mg) were safe and well tolerated, reduced AT levels, and increased thrombin generation from baseline in participants with hemophilia A or B with inhibitors. Analysis of exploratory endpoints indicated an observed reduction in bleeding events and an improvement in QoL over the short duration of this study. These preliminary findings

will be further evaluated over a longer exposure time in the ongoing phase 3 studies.

Treatment with fitusiran was generally safe and well tolerated. Mild injection site reactions were the most common AEs reported and none required medical intervention. There were no deaths or drug-related SAEs in part D. Reduction in AT levels has been associated with a risk of thrombosis in people without hemophilia.<sup>36,37</sup> It has been reported that people with both hemophilia and AT deficiency have an ameliorated bleeding phenotype<sup>38,39</sup>; however, the risk of thrombosis in people with hemophilia and with lowered AT is currently unknown. In this study, which had a relatively short observation period and limited sample size, there were no thrombotic events. Overall, transient D-dimer elevations were frequently observed (8/17 participants [47%]) and appeared to occur more often with the 80 mg fitusiran dose. In 3/17 participants (18%), D-dimer elevations were reported as AEs and were transient, mild in intensity, asymptomatic, and were not accompanied by clinically significant changes in other coagulation parameters. Further observations are needed to understand the clinical significance of these findings. These findings were consistent with previous clinical experience with fitusiran across a wider dosing range.<sup>28</sup> Although D-dimer assays are often used in combination with clinical symptoms to assess the potential for thrombosis, they are nonspecific and may be elevated as an acute phase reaction in many situations, such as infection, stress, neoplasia, and



**FIGURE 3** ABR during monthly fitusiran treatment in individual participants with hemophilia A or B with inhibitors. Prestudy ABR was calculated as the occurrence of clinically significant bleeds based on 6-month history multiplied by 2. Observation period ABR was estimated by the number of poststudy drug treatment bleeding episodes that occurred from day 29 until 8 weeks after the last dose of fitusiran. Abbreviation: ABR, annualized bleeding rate

inflammation, and, further, baseline levels in people with hemophilia have not been established.<sup>40</sup> However, thrombosis is an AE of important clinical interest and is being monitored in phase 3 trials of fitusiran in people with hemophilia.

Given the liver-targeted mechanism of action of fitusiran, the occurrence of hepatic AEs in the participants of this study are of particular interest. Many participants in this study have hepatitis C, which can complicate the assessment of the impact of fitusiran on the liver. Reversible increases in ALT levels were observed in some participants with inhibitors in part D. None of these liver enzyme elevations was associated with increases in total bilirubin or clinical symptoms and there was no evidence of severe drug-induced liver function impairment.<sup>34</sup> Liver enzyme elevations were also reported as AEs in two participants who had D-dimer elevations. Although a relationship is not entirely clear, an association is confounded in this small subset by history of HCV in one case and in the other case in the setting of gastritis. Overall, elevations in liver enzyme levels, although mostly mild and transient, were frequently observed with fitusiran treatment in this study, and appeared to be more frequent and pronounced in the higher dose cohort. The clinical relevance of such elevations is unclear from this small phase 1 study; however, this will be further evaluated in the ongoing phase 2 open-label extension study and phase 3 studies.

As a small interfering RNA approach that lowers AT messenger RNA, it was hypothesized that the PK/PD of fitusiran would not be altered by the presence of a preexisting inhibitor to FVIII or FIX coagulation proteins. As anticipated, the PK/PD data in participants with inhibitors were generally similar to those obtained in noninhibitor participants,<sup>28</sup> indicating that the presence of an inhibitor does not affect fitusiran PK/PD characteristics.

In the current part D of this phase 1 study, monthly subcutaneous fitusiran injections at a fixed dose resulted in robust and sustained AT reduction and decreased the median ABR in participants with inhibitors, consistent with previous observations in participants without inhibitors (parts B through C).<sup>28</sup> The reductions in AT activity were also associated with increased thrombin generation; in participants with  $\geq 75\%$  AT reduction, peak thrombin generation values were within the low normal range of healthy volunteers.<sup>28</sup> Although these results are encouraging, it is recognized that the coagulation pathway is a dynamic and complex system and many endogenous pro- and anticoagulants have been identified that impact the rate, peak, and amount of total thrombin generated in *in vitro* models.<sup>41,42</sup> The fixed monthly 80 mg dose was associated with the least amount of variability in AT reduction compared with the other doses (0.015-0.075 mg/kg weekly, 0.225-1.8 mg/kg monthly, 50 mg monthly) investigated in patients with hemophilia across the whole phase 1 program.<sup>28</sup>

Participants reported overall that, while on fitusiran, less aPCC was required to successfully treat bleeding events than that required before receiving the study drug. The median aPCC dose used to treat bleeding events was 28.6 U/kg, representing a 43% to 71% reduced dose compared with the recommended range for aPCC of 50 to 100 U/kg for mild or moderate bleeds.<sup>43</sup> *In vitro* data have shown an additive effect of AT reduction and BPA on thrombin generation in plasma from people with hemophilia, suggesting that reduced doses of rFVIIa and aPCC may potentially be used with AT reduction to confer sufficient hemostasis in the case of breakthrough bleeds.<sup>44</sup> Thus, this study suggests that people with hemophilia treated with fitusiran require less aPCC to treat breakthrough bleeds. Although other hemostatic agents (eg, BPAs) have a known risk for thrombosis,<sup>43,45</sup> there were no thrombotic events observed in this phase 1 study. However,



**TABLE 3** Change from baseline in Haem-A-QoL domains (negative values indicate improvement in HRQoL)

Haem-A-QoL Domains	50 mg (n = 6)	80 mg (n = 11)	Overall (n = 17)
<b>Total score</b>			
Mean (SEM)	-5.4 (3.9)	-10.5 (3.7)	-9.2 (2.9)
Median	-2.4	-10.3	-8.6
n	4	11	15
<b>Sports and leisure</b>			
Mean (SEM)	-5.4 (5.3)	1.9 (7.0)	-0.2 (5.5)
Median	-8.8	5.0	5
n	3	10	13
<b>Family planning</b>			
Mean (SEM)	0.7 (0.7)	-9.0 (5.4)	-6.6 (4.2)
Median	0.0	-6.3	-3.1
n	3	9	12
<b>Feeling</b>			
Mean (SEM)	6.3 (7.7)	-20.5 (8.0)	-13.3 (6.9)
Median	6.3	-18.8	-12.5
n	4	11	15
<b>Future</b>			
Mean (SEM)	-8.8 (9.7)	-12.7 (4.3)	-11.7 (3.9)
Median	-5.0	-10.0	-10.0
n	4	11	15
<b>Dealing with hemophilia</b>			
Mean (SEM)	0.0 (3.4)	-8.3 (5.7)	-6.1 (4.3)
Median	0.0	-8.3	0.0
n	4	11	15
<b>Partnership and sexuality</b>			
Mean (SEM)	0.0 (0.0)	-9.8 (4.9)	-7.2 (3.7)
Median	0.0	-16.7	-8.3
n	4	11	15
<b>Physical health</b>			
Mean (SEM)	-5.0 (3.5)	-15.0 (5.1)	-12.3 (3.9)
Median	-7.5	-15.0	-10.0
n	4	11	15
<b>Work and school</b>			
Mean (SEM)	-9.4 (5.4)	-16.3 (6.7)	-14.3 (5.0)
Median	-6.3	-12.5	-12.5
n	4	10	14
<b>Treatment</b>			
Mean (SEM)	-10.2 (6.0)	-12.5 (5.3)	-11.9 (4.1)
Median	-10.9	-15.6	-15.6
n	4	11	15
<b>View of self</b>			
Mean (SEM)	-11.3 (4.3)	-6.8 (4.2)	-8.0 (3.3)
Median	-12.5	0.0	0.0
n	4	11	15

Abbreviations: Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; HRQoL, health-related quality of life; SEM, standard error of the mean.

the risk of thrombosis with fitusiran alone, or in combination with BPA, is being investigated further in the phase 2 open-label extension study<sup>46</sup> and phase 3 ATLAS studies.<sup>47-50</sup>

Finally, clinically meaningful improvements in the physical health domain and total score of the Haem-A-QoL were observed based on published thresholds (10- and 7-unit reduction for physical health domain and total score, respectively).<sup>35</sup> Of note, the physical health domain that, including items related to painful swelling, joint pain, restriction of motion from pain, difficulty walking, and time to get ready, has been shown to be most responsive to change with effective prophylactic treatment in people with hemophilia.<sup>35</sup> All other domains of the Haem-A-QoL demonstrated a numeric reduction (ie, improvement). These results suggest that fitusiran may have a positive impact in people with hemophilia and on their QoL, including joint health. Further studies are planned to assess these initial observations in larger clinical trials with longer follow-up.

Effective prophylactic treatment options for individuals with hemophilia with inhibitors remain limited. A major challenge of prophylaxis with bypass therapy is the need for frequent infusions, which is limited by difficulties with venous access and risk of infections.<sup>51,52</sup> This study suggests that fitusiran may offer individuals with either hemophilia A or B with inhibitors effective prophylaxis delivered via a monthly, low-volume, fixed-dose, subcutaneous administration. The first-in-human study of fitusiran in people with hemophilia without inhibitors demonstrated this same profile.<sup>28</sup> In addition, fitusiran may also be a feasible option for people with hemophilia in parts of the world where access to refrigeration is a challenge because it has exhibited a robust stability profile, with stability at room temperature and resistance to thermal stress and cyclic temperature fluctuations.<sup>53</sup>

Limitations of the phase 1, part D, study include its open-label design, absence of a control group, limited study population, and limited duration. Further studies are planned to confirm that changes based on patient-reported outcomes are not attributable to the placebo effect.<sup>54</sup>

An open-label extension study (NCT02554773) and two open-label, randomized, active-controlled phase 3 studies in people with hemophilia A or hemophilia B with inhibitors (NCT03417102), without inhibitors (NCT03417245), a one-way crossover study (NCT03549871), and one open-label pediatric study (NCT03974113) have been designed to provide further information on the efficacy and safety and QoL benefits of fitusiran prophylaxis in these populations.

In conclusion, monthly, fixed-dose, subcutaneous injections of fitusiran were generally well tolerated and consistently reduced AT levels from baseline, resulting in improved thrombin generation and fewer bleeding episodes in participants with hemophilia A or B with inhibitors.

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#### CONFLICT OF INTEREST

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#### AUTHOR CONTRIBUTIONS

K. John Pasi, Kate Madigan, Huy Van Nguyen, Qifeng Yu, Baisong Mei, and Margaret V. Ragni made substantial contributions to the conception and design of the work. K. John Pasi, Toshko Lissitchkov, Vasily Mamonov, Tim Mant, Margarita Timofeeva, Catherine Bagot, Pratima Chowdary, Pencho Georgiev, Liana Gercheva-Kyuchukova, Qifeng Yu, and Margaret V. Ragni made substantial contributions to the acquisition of data for the submitted work. All authors made substantial contributions to the analysis and interpretation of data for the work, critically revised the manuscript for important intellectual content, approved the final version submitted, and agreed to be accountable for all aspects of the work.

#### REFERENCES

1. Monroe DM, Hoffman M. What does it take to make the perfect clot? *Arterioscler Thromb Vasc Biol.* 2006;26:41-48.
2. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet.* 2003;361:1801-1809.
3. Peyvandi F, Garagiola I, Young G. The past and future of haemophilia: diagnosis, treatments, and its complications. *Lancet.* 2016;388:187-197.
4. Pipe SW, Valentino LA. Optimizing outcomes for patients with severe haemophilia a. *Haemophilia.* 2007;13(Suppl 4):1-16.quiz 13 p following 16.
5. Ljung R, Gretenkort AN. The current status of prophylactic replacement therapy in children and adults with haemophilia. *Br J Haematol.* 2015;169:777-786.
6. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia.* 2013;19:e1-e47.
7. Bauer KA. Current challenges in the management of hemophilia. *Am J Manag Care.* 2015;21:S112-S122.
8. Mannucci PM, Franchini M. Present and future challenges in the treatment of haemophilia: a clinician's perspective. *Blood Transfus.* 2013;11(Suppl 4):s77-s81.
9. World Federation of Hemophilia. Treatment safety and supply. 2020. Available from: <https://www.wfh.org/en/our-work-treatment/treatment-safety-supply>. Last accessed 4 Mar 2020.
10. Morfini M, Haya S, Tagariello G, et al. European study on orthopaedic status of haemophilia patients with inhibitors. *Haemophilia.* 2007;13:606-612.
11. Oladapo AO, Lu M, Walsh S, O'Hara J, Kauf TL. Inhibitor clinical burden of disease: a comparative analysis of the CHES data. *Orphanet J Rare Dis.* 2018;13:198.
12. Benson G, Auerswald G, Elezovic I, et al. Immune tolerance induction in patients with severe hemophilia with inhibitors: expert panel views and recommendations for clinical practice. *Eur J Haematol.* 2012;88:371-379.
13. Collins PW, Chalmers E, Hart DP, et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia (4th edition). *Br J Haematol.* 2013;160(2):153-170. <https://doi.org/10.1111/bjh.12091>
14. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. *Blood.* 2014;124:3365-3372.
15. Astermark J, Rocino A, Von Depka M, et al. Current use of bypassing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors. *Haemophilia.* 2007;13:38-45.
16. Eichinger S, Lubczyk B, Kollars M, et al. Thrombin generation in haemophilia a patients with factor VIII inhibitors after infusion of recombinant factor VIIIa. *Eur J Clin Invest.* 2009;39:707-713.
17. Goodeve AC. Hemophilia B: molecular pathogenesis and mutation analysis. *J Thromb Haemost.* 2015;13:1184-1195.
18. Mauro M, Bonetti E, Balter R, Poli G, Cesaro S. Recurrent episodes of anaphylaxis in a patient with haemophilia B: a case report. *Blood Transfus.* 2016;14:582-584.
19. Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *J Thromb Haemost.* 2015;13:743-754.
20. Hartmann J, Croteau SE. 2017 Clinical trials update: innovations in hemophilia therapy. *Am J Hematol.* 2016;91:1252-1260.
21. Waters EK, Genga RM, Schwartz MC, et al. Aptamer ARC19499 mediates a procoagulant hemostatic effect by inhibiting tissue factor pathway inhibitor. *Blood.* 2011;117:5514-5522.
22. Gissel M, Orfeo T, Foley JH, Butenas S. Effect of BAX499 aptamer on tissue factor pathway inhibitor function and thrombin generation in models of hemophilia. *Thromb Res.* 2012;130:948-955.
23. Polderdijk SG, Adams TE, Ivanciu L, Camire RM, Baglin TP, Huntington JA. Design and characterization of an APC-specific serpin for the treatment of hemophilia. *Blood.* 2017;129:105-113.

24. Sehgal A, Barros S, Ivanciu L, et al. An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia. *Nat Med*. 2015;21:492-497.
25. Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med*. 2016;374:2044-2053.
26. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377:809-818.
27. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123:317-325.
28. Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. *N Engl J Med*. 2017;377:819-828.
29. Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? *Blood*. 2017;130:2463-2468.
30. Walker CP, Royston D. Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. *Br J Anaesth*. 2002;88:848-863.
31. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247-254.
32. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199-208.
33. von Mackensen S, Gringeri A, Ravera S, et al. Validation of the haemophilia-specific quality of life questionnaire for adult patients with haemophilia (HAEM-A-QOL). *Haematologica*. 2005;90:115-116.
34. Katarey D, Verma S. Drug-induced liver injury. *Clin Med (Lond)*. 2016;16:s104-s109.
35. Wyrwich KW, Krishnan S, Poon JL, et al. Interpreting important health-related quality of life change using the Haem-a-QoL. *Haemophilia*. 2015;21:578-584.
36. Sokol J, Timp JF, le Cessie S, et al. Mild antithrombin deficiency and risk of recurrent venous thromboembolism: results from the mega follow-up study. *J Thromb Haemost*. 2018;16:680-688.
37. de la Morena-Barrio B, Orlando C, de la Morena-Barrio ME, Vicente V, Jochmans K, Corral J. Incidence and features of thrombosis in children with inherited antithrombin deficiency. *Haematologica*. 2019;104:2512-2518.
38. Escuriola Eittingshausen C, Halimeh S, Kurnik K, et al. Symptomatic onset of severe hemophilia a in childhood is dependent on the presence of prothrombotic risk factors. *Thromb Haemost*. 2001;85:218-220.
39. Shetty S, Vora S, Kulkarni B, et al. Contribution of natural anticoagulant and fibrinolytic factors in modulating the clinical severity of haemophilia patients. *Br J Haematol*. 2007;138:541-544.
40. Riley RS, Gilbert AR, Dalton JB, Pai S, McPherson RA. Widely used types and clinical applications of D-dimer assay. *Lab Med*. 2016;47:90-102.
41. Butenas S, van't Veer C, Mann KG. "Normal" thrombin generation. *Blood*. 1999;94:2169-2178.
42. Machlus KR, Colby EA, Wu JR, Koch GG, Key NS, Wolberg AS. Effects of tissue factor, thrombomodulin and elevated clotting factor levels on thrombin generation in the calibrated automated thrombogram. *Thromb Haemost*. 2009;102:936-944.
43. FDA. Feiba US prescribing information. Available from: <https://www.fda.gov/media/78852/download>. Last accessed 4 Mar 2020.
44. Qian K, Huang S, Akinc A, Liu J. Thrombin generation response with the addition of bypassing agents in plasma of patients treated with fitusiran, an investigational RNAi therapeutic targeting antithrombin for the treatment of hemophilia. WFH 2018 World Congress. 2018;M-P-219 (141).
45. Nordisk N. US prescribing information: Novoseven®, coagulation factor VIIa (recombinant), for intravenous use only. 2006. Available from: <https://www.fda.gov/media/70435/download>. Last accessed 27 August 2020.
46. Sanofi. An open-label extension study of an investigational drug, fitusiran, in patients with moderate or severe hemophilia a or b. ClinicalTrials.gov NCT02554773, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT02554773>. Last accessed 27 August 2020.
47. Sanofi. A study of fitusiran (ALN-AT3SC) in severe hemophilia a and b patients with inhibitors (ATLAS-INH). ClinicalTrials.gov NCT03417102, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT03417102>. Last accessed 27 August 2020.
48. Sanofi. A study of fitusiran (ALN-AT3SC) in severe hemophilia a and b patients without inhibitors. ClinicalTrials.gov NCT03417245, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT03417245>. Last accessed 27 August 2020.
49. Sanofi. A study of fitusiran in severe hemophilia a and b patients previously receiving factor or bypassing agent prophylaxis (ATLAS-PPX). ClinicalTrials.gov NCT03549871, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT03549871>. Last accessed 27 August 2020.
50. Sanofi. Fitusiran prophylaxis in male pediatric subjects aged 1 to less than 12 years with hemophilia a or b (ATLAS-PEDS). ClinicalTrials.gov NCT03974113, 2020. Available from: <https://clinicaltrials.gov/ct2/show/NCT03974113>. Last accessed 27 August 2020.
51. Valentino LA, Kawji M, Grygotis M. Venous access in the management of hemophilia. *Blood Rev*. 2011;25:11-15.
52. Fischer K, Valentino L, Ljung R, Blanchette V. Prophylaxis for severe haemophilia: clinical challenges in the absence as well as in the presence of inhibitors. *Haemophilia*. 2008;14(Suppl 3):196-201.
53. McKinney E, Deshpande A, Verrilli B, et al. Evaluation of room temperature and accelerated stability data for fitusiran, an investigational RNAi therapeutic targeting antithrombin for treatment of hemophilia and rare bleeding disorders: European Association for Haemophilia and Allied Disorders (EAHAD); 2017.
54. Frendl DM, Strom M, Ware J. Placebo effect sizes for patient reported outcomes in well-controlled drug trials: a 12-year systematic review. *Value Health*. 2013;16(3):A38. Abstract PRM138.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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