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Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis (ATLAS-PPX)

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Abstract:
Fitusiran, a subcutaneous (SC) investigational siRNA therapeutic, targets antithrombin to rebalance hemostasis in people with hemophilia A or B (PwHA/B), irrespective of inhibitor status. This Phase 3, open-label study (NCT03549871) evaluated the efficacy and safety of fitusiran prophylaxis in males aged {greater than or equal to} 12 years with hemophilia A or B, with or without inhibitors, who received prior bypassing agent (BPA)/clotting factor concentrate (CFC) prophylaxis. Participants continued their prior BPA/CFC prophylaxis for 6 months before switching to once-monthly 80 mg fitusiran prophylaxis for 7 months (onset and efficacy periods). Primary endpoint was annualized bleeding rate (ABR) in the BPA/CFC prophylaxis and fitusiran efficacy period. Secondary endpoints included spontaneous ABR (AsBR) and joint ABR (AjBR). Safety and tolerability were assessed. Of 80 enrolled participants, 65 (inhibitor/non-inhibitor, n = 19/46) were eligible for ABR analyses. Observed median (IQR) ABRs were 6.5 (2.2, 19.6)/4.4 (2.2, 8.7) with BPA/CFC prophylaxis versus 0.0 (0.0, 0.0)/0.0 (0.0, 2.7) in the corresponding fitusiran efficacy period. Estimated mean ABRs were substantially reduced with fitusiran by 79.7% (P = 0.0021) and 46.4% (P = 0.0598) versus BPA/CFC prophylaxis, respectively. Forty-one participants (63.1%) experienced zero treated bleeds with fitusiran versus 11 (16.9%) with BPAs/CFCs. Median AsBR and AjBR were both 2.2 with BPA/CFC prophylaxis and 0.0 in the fitusiran efficacy period. Two participants (3.0%) experienced suspected or confirmed thromboembolic events with fitusiran. Once-monthly fitusiran prophylaxis significantly reduced bleeding events versus BPA/CFC prophylaxis in PwHA/B, with or without inhibitors and reported adverse events were generally consistent with previously identified risks of fitusiran.

Conflict of interest: COI declared - see note

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COI notes: B. Nolan has been a study investigator for Sobi, Biogen/Bioverativ, CSL, Bayer, and Sanofi; and received honoraria from Sobi (honoraria donated to Irish Haemophilia Society). B. Zulfikar has acted in advisory board and/or provided consultancy for Pfizer, Shire, Novo Nordisk, Roche, Sobi, Bayer, and BioMarin. B. Antmen has received honoraria and has acted in advisory board and/or provided consultancy for Pfizer, Takeda, NovoNordisk, Roche, Sobi, Bayer, and BioMarin. P. Kampmann has received honoraria as a member of an advisory board and/or speaker from BioMarin, Novo Nordisk, Roche, Takeda, AbbVie and CSL Behring. T. Matsushita has received honoraria from Bayer, Takeda/Shire, Novo Nordisk, Bioverative/Sanofi, CSL Behring, and Chugai. F. Peyvandi has received honoraria from Roche, Sanofi, Sobi, and Takeda; and is a member of advisory boards of Roche, Sanofi, Sobi, and Takeda. G. Kenet consults for Alnylam, Bayer, BioMarin Pharmaceutical, CSL, NovoNordisk, Opko Biologics, Pfizer, Takeda, Roche, Sanofi, and Uniquore. Receives research funding from Alnylam, Bayer, BPL, Opko Biologics, Pfizer, Roche, and Takeda. Has been involved with speaker bureaus for Bayer, Pfizer, CSL, Shire, Novo Nordisk, and Roche; and, has a membership on an entity's Board of Directors or advisory committees for Alnylam, Bayer, BioMarin Pharmaceutical, CSL, NovoNordisk, Opko Biologics, Pfizer, Takeda, Roche, Sanofi, and Uniquore. C. Negrier received honoraria/consultancy fees from Biomarin, Novo Nordisk, Roche, Sanofi, Sobi, Takeda, Pfizer, and Spark, Bayer; and grants from Novo Nordisk, Roche, Sanofi, and Sobi; has a membership on an entity's Board of Directors or advisory committees for Biomarin, Novo Nordisk, Roche, Sanofi, Takeda, Pfizer, Spark, Bayer, CSL Behring, and UniQure. G. Young has received grants from Genentech/Roche, Grifols, and Takeda; and speaking and consultancy fees from Apcintex, BioMarin, CSL Behring, Genentech/Roche, Grifols, Hema Biologics/LFB, Novo Nordisk, Pfizer, Sanofi, Spark and Takeda. J. Chi and B. Kittner are current employees of Sanofi. C. Sussebach is a current employee and stockholder in Sanofi. F. Shammas is a current employee in Sanofi and equity holder in Sanofi. S. Andersson is an employee and equity holder in Sanofi, and a member of the WEST advisory committee. B. Mei was an employee and equity holder in Sanofi at the time of the study, he also has divested equity in Sanofi in the past 24 months; he is an employee of Editas Medicine. K. Kavakli received honoraria from Pfizer, Bayer, Takeda, Roche, and Novo Nordisk, has attended speaker bureaus for Pfizer, Bayer, Takeda, Roche, and Novo Nordisk and has a membership on an entity's Board of Directors or advisory committees for Pfizer, Bayer, Takeda, Roche, and Novo Nordisk. CW. You, C. Bagot, A. Sharif, and K. Vilchevska have no disclosures to declare.

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Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis (ATLAS-PPX)

Running head: Fitusiran prophylaxis versus BPA/CFC prophylaxis

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Data sharing statement

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

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Key Points

- Fitusiran prophylaxis provided consistent protection against bleeding vs prior BPA/CFC prophylaxis in PwHA/B, with or without inhibitors.
- Fitusiran was well tolerated, and reported adverse events were consistent with previously identified risks of fitusiran.

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Abstract (249/250 words)

Fitusiran, a subcutaneous (SC) investigational siRNA therapeutic, targets antithrombin to rebalance hemostasis in people with hemophilia A or B (PwHA/B), irrespective of inhibitor status. This Phase 3, open-label study (NCT03549871) evaluated the efficacy and safety of fitusiran prophylaxis in males aged ≥ 12 years with hemophilia A or B, with or without inhibitors, who received prior bypassing agent (BPA)/clotting factor concentrate (CFC) prophylaxis. Participants continued their prior BPA/CFC prophylaxis for 6 months before switching to once-monthly 80 mg fitusiran prophylaxis for 7 months (onset and efficacy periods). Primary endpoint was annualized bleeding rate (ABR) in the BPA/CFC prophylaxis and fitusiran efficacy period. Secondary endpoints included spontaneous ABR (AsBR) and joint ABR (AjBR). Safety and tolerability were assessed. Of 80 enrolled participants, 65 (inhibitor/non-inhibitor, n = 19/46) were eligible for ABR analyses. Observed median (IQR) ABRs were 6.5 (2.2, 19.6)/4.4 (2.2, 8.7) with BPA/CFC prophylaxis versus 0.0 (0.0, 0.0)/0.0 (0.0, 2.7) in the corresponding fitusiran efficacy period. Estimated mean ABRs were substantially reduced with fitusiran by 79.7% (P = 0.0021) and 46.4% (P = 0.0598) versus BPA/CFC prophylaxis, respectively. Forty-one participants (63.1%) experienced zero treated bleeds with fitusiran versus 11 (16.9%) with BPAs/CFCs. Median AsBR and AjBR were both 2.2 with BPA/CFC prophylaxis and 0.0 in the fitusiran efficacy period. Two participants (3.0%) experienced suspected or confirmed thromboembolic events with fitusiran. Once-monthly fitusiran prophylaxis significantly reduced bleeding events versus BPA/CFC prophylaxis in PwHA/B, with or without inhibitors and reported adverse events were generally consistent with previously identified risks of fitusiran.

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Visual abstract legend

[a]A subgroup of Cohort A included participants with hemophilia B with inhibitors who were not responding adequately to BPA prophylaxis (historical ABR ≥ 20);

[b]Includes all participants who received BPA/CFC prophylaxis and at least one dose of fitusiran before dose resumption (after the Sponsor initiated dosing pause).

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Introduction

Hemostasis results from balanced procoagulant and anticoagulant pathways that generate sufficient thrombin to control bleeding.[1] Hemophilia A and hemophilia B arise from FVIII or FIX deficiencies, respectively, resulting in insufficient thrombin generation (TG), disrupting hemostasis.[2-4] Prophylaxis, the regular administration of hemostatic agents with the goal of preventing bleeding, is recommended for hemophilia management.[3] However, prophylaxis with clotting factor concentrates (CFC) can be burdensome due to frequent intravenous infusions and venous access difficulties.[3,5,6] CFCs may be also limited by development of inhibitory antibodies in approximately 30% and 10% of people with hemophilia A and B (PwHA/B), respectively, which render treatment ineffective.[3,7,8] Although current prophylactic options are effective, they do not satisfy needs of all PwH;[9,10] options for people with inhibitors are limited,[5,11,12] and despite all available therapeutics for people without inhibitors, PwH continue to experience breakthrough bleeds,[1,5,13] which leads to joint damage[10,14] and reduced quality of life.[15,16] Efforts have focused on developing effective treatments for people with inhibitors, and therapies that aim to further prevent bleeding while reducing the treatment burden for PwH.[3,5,17] One such option is subcutaneous (SC) emicizumab prophylaxis, indicated for PwHA, irrespective of inhibitor status.[18-20] Currently, no such SC option is available for hemophilia B.[21] However, breakthrough bleeds and pain on injection may still occur with emicizumab prophylaxis, and neutralizing antidrug antibodies (ADAs) may develop.[18,22-25] Novel therapeutics are needed to address ongoing unmet needs of prophylaxis and achieve health equity among all PwH.[1,3,5,17]

Fitusiran is an investigational SC prophylactic small interfering RNA (siRNA) therapeutic designed to lower antithrombin (AT) with the goal of restoring sufficient TG to rebalance hemostasis in PwHA/B, with or without inhibitors.[26-28] In previous Phase 3 trials (ATLAS-A/B [NCT03417245], ATLAS-INH [NCT03417102]), once-monthly (QM) 80 mg fitusiran prophylaxis significantly reduced annualized bleeding rate (ABR) in PwHA/B, with or without inhibitors versus on-demand treatment.[29,30] This Phase 3 trial evaluated the efficacy and safety of fitusiran prophylaxis versus prior BPA/CFC prophylaxis in PwHA/B, with or without inhibitors.

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Methods

Study design

This Phase 3, multicenter, multinational, open-label trial (ATLAS-PPX, NCT03549871) was conducted at 35 sites in 15 countries. The trial was conducted in accordance with the protocol and ethical principles derived from international guidelines including the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. Informed participant consent/assent was obtained prior to study conduct; the consent form was modified according to local regulations and requirements whenever applicable. The study protocol was approved by the Independent Ethics Committees or Institutional Review Boards, and an independent Data Monitoring Committee oversaw the safety and conduct of the trial and performed periodic data reviews during the trial.

Participants

Eligible participants included males aged ≥ 12 years with severe hemophilia A or B (FVIII < 1% or FIX ≤ 2% at screening or documented by medical record evidence), with or without inhibitors, who were receiving BPA (Cohort A; people with inhibitors [Nijmegen-modified Bethesda [NBA] assay ≥0.6 Bethesda units/mL at screening], with ≥ 2 BPA-treated bleeding events in the past 6 months) or CFC prophylaxis (Cohort B; people without inhibitors [NBA assay < 0.6 Bethesda units/mL at screening], with ≥ 1 CFC-treated bleeding event in the last 12 months). A subgroup of Cohort A included PwHB with inhibitors who were not responding adequately to BPA prophylaxis prior to enrolment (historical ABR ≥ 20). Full inclusion/exclusion criteria are available in supplemental methods.

Procedures

The trial consisted of a 6-month BPA/CFC prophylaxis period during which participants continued their prior prophylaxis regimen **(Table S1)**; a 1-month onset period in which participants received the first fitusiran dose, while allowed to continue BPA/CFC prophylaxis for up to 7 days, and when fitusiran gradually reached the target pharmacodynamic effect of AT lowering; and a 6-month fitusiran efficacy period in which participants received fitusiran prophylaxis. The subgroup of Cohort A (non-responders to BPA prophylaxis) started fitusiran prophylaxis directly after the screening period. Fitusiran treatment (prophylaxis) period included both the onset and fitusiran efficacy periods. Participants initially received fitusiran 80 mg QM; following implementation of the fitusiran revised AT-based dosing regimen, two participants started with 50 mg once every 2 months (Q2M). The AT follow-up period lasted approximately 6 months post-final fitusiran dose, until AT levels returned to approximately

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60% or until enrolment into an open-label extension study (ATLAS-OLE, NCT03754790; **Figure S1**).

During fitusiran treatment, participants could receive on-demand BPAs/CFCs to treat breakthrough bleeds in accordance with specific breakthrough bleed management guidelines (BBMG) (**Table S2**).

Participants were to record all bleeding events and all doses of BPAs/CFCs administered during the trial in an eDiary (**supplemental methods**). A treated bleeding episode was defined as any occurrence of hemorrhage requiring BPAs/CFC administration. The definitions of bleeding episode types were according to the recommendations of the International Society on Thrombosis and Hemostasis (**supplemental methods**).[31]

Health-related quality of life (HRQoL) was assessed at Month -6, Day 1, and Month 7 in participants aged ≥ 17 years using the validated Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) instrument (**supplemental methods**).[32]

Safety assessments included adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESIs), and laboratory tests, including markers of coagulation. AESIs were pre-defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations > 3× upper limit of normal (ULN), suspected or confirmed thrombosis, severe or serious injection site reactions (ISR), systemic injection-associated reactions (IAR), cholecystitis, and cholelithiasis (**supplemental methods**).

For pharmacodynamic assessments, AT levels and peak TG were measured from blood samples, and monitored, initially after two weeks from baseline, and then monthly. ADAs to fitusiran were measured from serum blood samples using a validated enzyme-linked immunosorbent assay method (**supplemental methods)**.

Endpoints

The primary endpoint was ABR in the BPA/CFC prophylaxis and fitusiran efficacy periods. Secondary endpoints included spontaneous ABR (AsBR) and joint ABR (AjBR) in the BPA/CFC prophylaxis and fitusiran efficacy periods; change in Haem-A-QoL physical health score and total score in the fitusiran treatment and BPA/CFC prophylaxis periods;[32] ABR in the onset and treatment periods; and annualized weight-adjusted BPA/CFC consumption.

Subgroup analysis included hemophilia type (hemophilia A or B), age category (< 18 years, 18–64 years, and ≥ 65 years) and number of bleeding episodes within 6 or 12 months prior to screening (≤ 10 or > 10). Exploratory endpoints included number of treated target joint

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bleeds; change in AT levels and peak TG over time; and incidence and titer of ADAs (**supplemental methods**).

Safety and tolerability endpoints included incidence, severity, seriousness, and relatedness of AEs.

Statistical analysis

Sample size determination is described in the supplemental methods. Population analysis sets included the safety analysis sets (SAS), efficacy analysis sets (EAS), per protocol analysis set and COVID-19 unaffected set (**supplemental methods**). The primary endpoint was based on bleeding episodes in the BPA/CFC prophylaxis (Day -168 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190). Primary analyses were performed on EAS 1 which included all participants who received BPA/CFC prophylaxis and at least one dose of 80 mg QM fitusiran. Safety summaries were performed on SAS 1 which included all participants who enrolled and then received at least one dose of 80 mg QM fitusiran before dose resumption.

To avoid confounding the treatment effect, bleeding data from the intercurrent events (premature discontinuation, surgeries, and ATIII concentrate treatment) were excluded from the primary analysis. The number of bleeding episodes was analyzed using a repeated measures negative binomial model with fixed effect of treatment period. The logarithm number of days that each participant spent in the respective period matching the analyzed bleeding episode data was included as an offset variable to account for unequal follow-up time due to early withdrawal or surgery. In addition, a Bayesian analysis was performed to provide the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. Summary statistics for observed ABR, including median and interquartile range (IQR), were also calculated for each study period. The observed ABR was calculated as total number of qualifying bleeding episodes divided by total number of days in the respective period multiplied by 365.25.

Bleeding episodes in the treatment (Day 1 to Day 190) and onset period, and AsBR and AjBR in the fitusiran efficacy and BPA/CFC prophylaxis period were analyzed and compared using the same negative binomial model as the primary analysis. Change from baseline in Haem-A-QoL physical health score and total score (in participants aged ≥ 17 years) in the BPA/CFC prophylaxis and fitusiran treatment period were analyzed using a mixed model for repeated measure analysis (MMRM) with robust sandwich covariance matrix, with fixed effects of study period, baseline Haem-A-QoL physical health score and total score for each study period as covariates. Safety, pharmacodynamic, and immunogenicity results were summarized descriptively. Safety endpoints were analyzed for the BPA/CFC prophylaxis and

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the fitusiran prophylaxis period (comprising the fitusiran treatment and AT follow-up period). All statistical analyses were performed separately for Cohort A and Cohort B. Pooled analyses were performed after all participants in the two cohorts had either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study.

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Results

Study population

Between July 25, 2018 and March 25, 2022, 99 participants were screened and 80 were enrolled into the study (Cohort A, n = 30; Cohort B, n = 50). Seventy-eight participants entered the BPA/CFC prophylaxis period and two participants started directly with fitusiran 80 mg QM (subgroup of Cohort A; excluded from EAS1). Of the 67 participants who completed the BPA/CFC prophylaxis period, 65 initiated fitusiran 80 mg QM and two, excluded from this analysis, fitusiran 50 mg Q2M. Fifty-four participants completed 80 mg fitusiran treatment; 13 participants discontinued treatment (due to dosing pause, n = 9; AEs, n = 2; withdrawn consent, n = 2) but 9 remained in the study. Sixty-four participants (80.0%) completed the study (**Figure 1**). Efficacy and safety results are presented for EAS 1 (n = 65) and SAS 1 (n = 67), respectively. In EAS 1, 50 participants had hemophilia A and 15 had hemophilia B; 19 and 46 participants were with and without inhibitors, respectively (**Table 1**).

Efficacy

Observed median ABR (IQR) was 0.0 (0.0, 2.3) in the fitusiran efficacy and 4.4 (2.2, 10.9) in the BPA/CFC prophylaxis period. Estimated mean ABR was 2.9 (95% CI: 1.7, 4.9) in the fitusiran efficacy period, which was significantly lower than the estimated ABR of 7.5 (95% CI: 5.5, 10.1) in the BPA/CFC prophylaxis period, corresponding to a significant 61.1% reduction in bleeding rate (95% CI: 32.5, 77.6, P = 0.0008). With BPA/CFC prophylaxis, 11/65 participants (16.9%) had zero treated bleeds and 43/65 (66.2%) had ≤ 3 treated bleeds versus 41/65 participants (63.1%) and 58/65 (89.2%) in the fitusiran efficacy period, respectively. In people with inhibitors, median ABR (IQR) was 6.5 (2.2, 19.6) in the BPA prophylaxis and 0.0 (0.0, 0.0) in the fitusiran efficacy period; in people without inhibitors, median ABR (IQR) was 4.4 (2.2, 8.7) in the CFC prophylaxis and 0.0 (0.0, 2.7) in the fitusiran efficacy period (**Figure 2; Table 2)**.

ABRs in the onset and treatment periods demonstrated similar results to the primary endpoint (**supplemental results**). Median AsBR (IQR) was 2.2 (0.0, 6.5) and 0.0 (0.0, 2.3) in the BPA/CFC prophylaxis and fitusiran efficacy period, respectively. Median AjBR (IQR) was 2.2 (0.0, 6.5) and 0.0 (0.0, 2.3) in the BPA/CFC prophylaxis and fitusiran efficacy period, respectively.

In participants with ≥ 1 target joint identified at baseline, 5/14 participants (35.7%) in the BPA/CFC period had zero treated target joint bleeds versus 10/14 (71.4%) participants in the fitusiran efficacy period.

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Subgroup analyses demonstrated a consistent effect in favor of fitusiran prophylaxis versus BPA/CFC prophylaxis (**Table S3**). Sensitivity analyses of the per-protocol analysis set and the COVID-19 unaffected set were consistent with the primary analysis (**Table S4**). There was no notable impact on the primary analysis due to the COVID-19 pandemic.

Annualized weight-adjusted consumption of BPA/CFC

Annualized mean weight-adjusted consumption, total number of injections, and mean total weight-adjusted dose per bleed of CFCs/BPAs were markedly reduced in the fitusiran treatment versus BPA/CFC prophylaxis period (**Table 3**). In the fitusiran treatment period, 21/22 (95.5%) and 60/61 bleeds (98.4%) in participants with and without inhibitors, respectively, were treated in compliance with the single- and repeat-dose BBMG (**Table S5**).

Health-related quality of life

There was an improvement in the Haem-A-QoL transformed physical health score from Month -6 with fitusiran (-9.6 [95% CI: -15.4, -3.8]) versus BPA/CFC prophylaxis (-6.0 [95% CI: -10.2, -1.8]), with a least squares (LS) mean difference of -3.6 (95% CI: -10.5, 3.3; P = 0.3008). For the Haem-A-QoL transformed total score relative to Month -6, there was a significant improvement in HRQoL with fitusiran (-7.6 [95% CI: -10.3, -5.0]) versus BPA/CFC prophylaxis (-3.1 [95% CI: -5.6, -0.6]), with an LS mean difference of -4.6 (95% CI: -7.6, -1.5; P < 0.01) (**Figure S2**).

Safety

Overall, 22/65 participants (33.8%) with BPA/CFC prophylaxis and 48/67 (71.6%) with fitusiran prophylaxis experienced ≥ 1 AE. The most common AEs with fitusiran prophylaxis (> 5% of participants) are summarized in **Table 4**. With BPA/CFC prophylaxis, five SAEs were reported in 5/65 participants (7.7%); 13 SAEs were reported in 9/67 participants (13.4%) with fitusiran prophylaxis (three SAEs in 3/67 participants were assessed by the investigator as related to fitusiran). With fitusiran prophylaxis, 2/67 participants (3.0%) experienced AEs that resulted in fitusiran discontinuation and study withdrawal (cerebrovascular accident, and abdominal discomfort classified by the investigator as not related to fitusiran, in a participant with reported gastroesophageal reflux disease). There were no AEs leading to death.

AESI of ‘any suspected or confirmed thromboembolic events’ were reported in 2/67 participants (3.0%) receiving fitusiran prophylaxis. These events were cerebrovascular accident (CVA) and thrombosis (suspected thrombosis on papilla of left eye; onset reported 87 days post-final fitusiran dose). The participant with CVA was a 37-year-old male with a history of right lower extremity deep vein thrombosis not known by the investigator at the

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time of enrolment (exclusion criterion), and several risk factors including diabetes and possible hypertension and hyperlipidemia around the time of the event. This participant experienced complete left sided weakness and then likely developed right middle cerebral artery territory infarct hemorrhagic with transformation and subsequent subarachnoid bleed. On two consecutive days before the CVA onset, the participant was treated with recombinant FVIII (rFVIII) for a spontaneous bleed. The AT values range prior to the event onset was 9%–13%. The participant recovered from the event with sequelae 28 days after the onset. The CVA was classified by the investigator as serious and possibly related to fitusiran, resulting in fitusiran discontinuation and study withdrawal. The participant with thrombosis was a 56-year-old male, with papilledema of both eyes 10 days before the event onset. He experienced pain in eye with the thrombosis onset. No bleeds were reported immediately prior to the thrombosis and the participant did not use CFCs or BPAs. It was suspected that there was obstruction in the capillary vessels in the eyes. The investigator considered it possible that the observed papilledema was secondary to a thrombotic event in a capillary that supplies the optic nerve. A brain MRI revealed inflammatory changes in the maxillary sinus and normal orbital structures; magnetic resonance venography was unremarkable. The AT values range before the thrombosis onset was 9%–11%. The thrombosis on papilla was classified as non-serious and assessed by the investigator as possibly related to fitusiran. The participant was in the follow-up period when the event occurred and therefore no action with fitusiran was applicable. There were no AESIs of 'suspected or confirmed thromboembolic events' reported with BPA/CFC prophylaxis.

AESIs of 'any ALT/AST elevations > 3 x ULN' were reported in 17/67 participants (25.4%) receiving fitusiran prophylaxis. The participants had no medical history relevant to the events, and their cases varied and included positive antibodies to hepatitis A and C, Epstein-Barr virus, and human herpes virus, among others, and concomitant use of hepatoxic medications could not be ruled out. The highest mean (SD) of ALT/AST values was 4.8 (1.3) x ULN; their mean (SD) duration was 41.1 (36.9) days. The majority of ALT/AST elevations occurred within 90 and 135 days of fitusiran initiation, respectively. All events were classified by the investigator as non-serious and the majority as mild-to-moderate in severity. The majority (14/20) of liver enzyme elevations were reported by the investigator as recovered or resolved within 2–3 months of onset. AESIs of increased ALT resulted in interruption of fitusiran in 6/67 participants (9.0%), all of which resumed fitusiran prophylaxis thereafter; one participant had recurring ALT elevation after fitusiran interruption. Non-symptomatic laboratory abnormalities consistent with Hy's Law[33] were identified in one participant during the last study visit, with resolution following the final fitusiran dose. Additional doses were not

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administered and all abnormalities resolved by the following month. AESIs of ‘any ALT/AST elevations > 3 x ULN’ were reported in 2/65 participants (3.1%) with BPA/CFC prophylaxis.

AESIs of ‘cholecystitis’ and/or ‘cholelithiasis’ were reported in eight participants receiving fitusiran prophylaxis (cholecystitis and cholelithiasis reported concomitantly, n = 2; acalculous cholecystitis, n = 3 cholelithiasis, n = 3; chronic cholecystitis, n = 1)**.** Four participants with cholecystitis and/or cholelithiasis had ALT/AST elevations > 3 x ULN. In cases of concomitant cholecystitis/cholelithiasis, biliary sludge was noted with associated biliary wall thickening. None of the participants had significant risk factors commonly associated with cholelithiasis/cholecystitis. Hepatic steatosis was noted in five cases (two of which were related to concomitant cholelithiasis/cholecystitis), with one additional case of a biliary polyp, but no association was made with cholelithiasis/cholecystitis or transaminase elevations. These events were not reported with BPA/CFC prophylaxis.

There were no AESIs of severe or serious ISRs or systemic IARs with fitusiran prophylaxis. Clinical laboratory assessments of coagulation markers showed a trend toward increased D-dimer and prothrombin fragments 1+2 values and decreased fibrinogen values with fitusiran versus BPA/CFC prophylaxis (**Figure S3**).

Pharmacodynamics and immunogenicity

With fitusiran prophylaxis, mean AT activity level was 101.6% (SD: 8.6) at baseline and 18.2% (SD: 7.5) at end of onset period; mean AT levels were maintained at 10.6–13.4% from Day 43 onwards. On Day 29, there was a mean decrease of 83.4% (SD: 11.5) from baseline in AT levels, maintained at 88.3–90.6% from Day 43 onwards. Mean peak thrombin values of 50.7 nM were reported on Day 29 and maintained at 47.6 nM–62.6 nM from Day 43 onwards. AT levels and TG results were similar in participants with and without inhibitors (**Figure 3**).

Overall, 2/67 participants (3%) who received fitusiran had one confirmed ADA positive sample each at Month 1, both with a titer of 50 (equivalent to the minimum required dilution of the assay); however, these had no effect on AT reduction in these participants. No participants had confirmed ADA samples at baseline.

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Discussion

Once-monthly 80 mg SC fitusiran prophylaxis resulted in a median ABR of zero and 63.1% of participants with zero bleeds during the fitusiran efficacy period, demonstrating that fitusiran prophylaxis provided significant and consistent protection against bleeding in PwHA/B, with or without inhibitors who switched from prior BPA/CFC prophylaxis. Primary efficacy endpoint results were supported by subgroup and sensitivity analyses and clinically meaningful reductions in spontaneous and joint bleeding events. These outcomes confirm and extend the findings from previous fitusiran studies,[27,29,30,34,35] and suggest fitusiran may provide an effective, SC, prophylactic option in PwHA/B, irrespective of inhibitor status.

Currently, management of people with inhibitors may be complex, as a response to ITI or BPAs may not be optimal, which can result in frequent hospitalizations, high treatment burden, morbidity, and costs.[3,11,12] Fitusiran may provide an additional prophylactic option for all PwH. In this study, fitusiran prophylaxis significantly reduced mean ABR by 79.7% in people with inhibitors versus BPA prophylaxis. Fitusiran may also improve prophylaxis outcomes for people without inhibitors receiving CFC prophylaxis as the 46.4% mean ABR reduction in the fitusiran versus CFC prophylaxis period was clinically meaningful. The difference in reduction rates may be due to a higher variability in efficacy of BPAs versus CFCs.[11]

Prevention of spontaneous and joint bleeds is a reliable indicator of a significant level of protection and efficient prophylaxis in severe hemophilia. Joint bleeds can lead to joint damage, which ultimately results in arthropathy, one of the leading causes of morbidity in hemophilia.[36] Quality of life of PwH is considerably impaired, mainly due to the pain and disability associated with joint bleeds and resulting complications.[14,16,36-38] Current prophylactic regimens are insufficient to completely protect joints over time, despite early prophylaxis.[10,14] Fitusiran prophylaxis resulted in significantly lower rates of spontaneous and joint bleeds, as well as reduction in target joint bleeds versus BPA/CFC prophylaxis; this led to meaningful improvements in HRQoL as measured by Haem-A-QoL scores, fewer intravenous infusions, and lower consumption of BPAs/CFCs. These results suggest fitusiran prophylaxis may provide significant protection against bleeding while reducing the overall treatment and disease burden. Despite advances in prophylactic treatments, some PwH still experience bleeds as the current therapeutic landscape does not cater to everyone or satisfy all medical needs of people requiring consistent protection or different management approaches.[5,10,39] Fitusiran might help address unmet needs of achieving consistent bleed protection, less burdensome prophylaxis with a convenient dosing regimen and improved quality of life in PwH.

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Fitusiran prophylaxis was well tolerated and reported AEs were generally consistent with previously identified risks of fitusiran including increased liver transaminases, thrombosis, cholecystitis, and symptomatic cholelithiasis.[27,29,30,34] Transaminase elevations were defined as AESI because of liver-targeted delivery; these have been also reported with approved siRNA therapies for conditions other than hemophilia.[40,41] Participants with transaminase elevations and cholelithiasis/cholecystitis had no relevant risk factors and their cases varied. The underlying pathophysiology for the development of transaminase elevations, cholecystitis, and cholelithiasis is unknown; these events remain under investigation in ongoing trials. Risk mitigation strategies for hepatotoxicity included transaminase monitoring, guidelines for withholding and permanent discontinuation of fitusiran, and restricted alcohol consumption. Thrombotic events with the original dose regimen (80 mg QM) have been reported in six participants in completed Phase 2 and 3 studies, including this study.[42] In previous completed Phase 3 fitusiran trials, thrombotic events were reported in two participants with inhibitors (ATLAS-INH[30]) and in none of the participants without inhibitors (ATLAS-A/B[29]). In this study, thrombotic events were reported in two participants with fitusiran prophylaxis. These events were CVA (the participant should have been excluded as per exclusion criteria) and thrombosis on papilla of left eye, both events assessed as possibly related to fitusiran. In both participants AT levels were low prior to the onset of events. The participant with the CVA had a history of thrombosis risk factors and was treated with rFVIII just before the event onset. Thrombosis was associated with papilledema of both eyes and suspicion of obstruction in the capillary vessels in the eyes.

Thrombosis is a potential adverse event of clinical interest for therapies aiming to restore TG; thrombotic events have been reported with emicizumab, BPAs, CFCs, concizumab and investigational anti-tissue factor pathway inhibitor therapies.[3,43-47] Initial risk mitigation for thrombosis included screening and exclusion of participants with thrombophilia or certain thrombotic risk factors, and the provision of BBMG to enable treatment of bleeds during fitusiran prophylaxis. Compliance to BBMG demonstrated their effectiveness in managing episodic bleeds. After the voluntary pause in dosing initiated by the sponsor in response to reports of non-fatal vascular events in a separate fitusiran trial, AT levels were evaluated as a potential modifiable target for risk mitigation, and additional risk mitigation measures including a revised AT-based dosing regimen have been implemented. The revised dosing regimen was designed to target AT activity levels of 15–35%, beginning with 50 mg Q2M and escalating or de-escalating dose/frequency based on individual participant response, as determined by measurements of AT activity levels. Due to the study progress at the time, only two participants started with 50 mg Q2M; both participants discontinued fitusiran prematurely due to AT levels < 15% and withdrawal of consent. All reported AESIs in the

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current study occurred with the original dose regimen (80 mg QM). Additional risk mitigation measures are currently being evaluated in ongoing Phase 3 trials (ATLAS-OLE, NCT03754790; ATLAS-NEO, NCT05662319).[48] Observations of increased coagulation markers, D-dimers and prothrombin fragments 1+2 during fitusiran versus BPA/CFC prophylaxis may be secondary to prophylaxis with procoagulant therapies and generally are not associated with reported clinical outcomes.

The pharmacokinetic profile of fitusiran has been presented.[27,34] Pharmacodynamic analysis confirmed that fitusiran achieved sustained reductions in AT levels and increased peak TG by Day 29 (onset period) and during the efficacy period, consistent with its pharmacokinetics.[27,28,34] TG values associated with lowering in AT levels > 75% from baseline were close to the lower range of normal peak TG previously observed in healthy volunteers (64–210 nM).[27,49] Together, these sustained pharmacodynamic effects and a low ABR suggest fitusiran has the potential to rebalance hemostasis and improve bleeding phenotype in PwH.

The open-label nature of this study could be a limitation as a result of potential bias, particularly in patient-reported outcomes; however, this design was consistent with previous fitusiran trials, and justified, as hemophilia is a rare disease with a wealth of data regarding expected bleeding outcomes with BPA/CFC prophylaxis. The sample size was based on clinical considerations and was expected to provide reasonable precision around the bleeding rate with fitusiran versus BPA/CFC prophylaxis. Given a low ABR with CFC prophylaxis and a relatively small number of participants among subgroups, the study was not powered to show statistically significant differences among subpopulations. A lack of participants with prior emicizumab prophylaxis could be considered a limitation; however, at the time of this study, emicizumab was an investigational therapy.

In conclusion, once-monthly SC fitusiran prophylaxis resulted in a significant reduction in ABR versus BPA/CFC prophylaxis with a median ABR of zero in PwHA/B, with or without inhibitors, resulting in a meaningful improvement in HRQoL. Fitusiran was well tolerated and reported AEs were generally consistent with previously identified risks of fitusiran; the currently evaluated fitusiran revised AT-based dosing regimen aims to further enhance its benefit-risk profile. Fitusiran prophylaxis may provide effective and consistent bleeding protection reducing overall treatment and disease burden; therefore, it has the potential to address the unmet needs of PwHA/B, with or without inhibitors, with a favorable benefit-risk profile.

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Conflict-of-interest disclosure:

B. Nolan has been a study investigator for Sobi, Biogen/Bioverativ, CSL, Bayer, and Sanofi; and received honoraria from Sobi (honoraria donated to Irish Haemophilia Society).

B. Zulfikar has acted in advisory board and/or provided consultancy for Pfizer, Shire, Novo Nordisk, Roche, Sobi, Bayer, and BioMarin.

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S. Andersson is an employee and equity holder in Sanofi, and a member of the WEST advisory committee.

B. Mei was an employee and equity holder in Sanofi at the time of the study, he also has divested equity in Sanofi in the past 24 months; he is an employee of Editas Medicine.

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CW. You, C. Bagot, A. Sharif, and K. Vilchevska have no disclosures to declare.

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Tables

Table 1. Demographics and baseline characteristics (EAS 1*)

Characteristic	Participants with inhibitors (n = 19)	Participants without inhibitors (n = 46)	All (N = 65)
Age at baseline, years			
Mean (SD)	27.8 (17.1)	23.5 (7.3)	24.8 (11.2)
Median (IQR)	23 (15.0; 30.0)	23 (17.0; 29.0)	23 (16.0; 29.0)
Age group at baseline, n (%)			
12–17 years	7 (36.8)	12 (26.1)	19 (29.2)
18–64 years	11 (57.9)	34 (73.9)	45 (69.2)
≥ 65 years	1 (5.3)	0	1 (1.5)
Sex, n (%)			
Male	19 (100)	46 (100)	65 (100)
Hemophilia type, n (%)			
Hemophilia A	14 (73.7)	36 (78.3)	50 (76.9)
Hemophilia B	5 (26.3)	10 21.7)	15 (23.1)
Weight, kg, mean (SD)	68.2 (16.2)	71.7 (15.3)	70.7 (15.5)
BMI, kg/m^2, mean (SD)	23.7 (4.6)	23.6 (4.1)	23.6 (4.2)
Race, n (%)			
White	15 (78.9)	27 (58.7)	42 (64.6)
Asian	3 (15.8)	17 (37.0)	20 (30.8)
Black or African American	1 (5.3)	0	1 (1.5)
Other	0	2 (4.3)	2 (3.1)
Region, n (%)			
North America	0	0	0
Europe	15 (78.9)	28 (60.9)	43 (66.2)
Asia	3 (15.8)	17 (37.0)	20 (30.8)
Other	1 (5.3)	1 (2.2)	2 (3.1)
Number of bleeding episodes in the last 6 months prior to screening, mean (SD)[†]	4.6 (2.6)	NR	NR
Number of bleeding episodes in the last 12 months prior to screening, mean (SD)[†]	NR	4.0 (5.2)	NR
Inhibitor type, n (%)			
Highest historical inhibitor titre result[‡]			
< 5 BU/mL	1 (5.3)	N/A	1 (1.5)
≥ 5 BU/mL	18 (94.7)	N/A	18 (27.7)
Number of target joints[§], median (IQR)	0.0 (0.0; 1.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)

BMI, body mass index; BU, Bethesda unit; EAS 1, efficacy analysis set 1; IQR, interquartile range; SD, standard deviation; N/A, not applicable; NR, not reported.

*Includes all participants who received BPA/CFC prophylaxis and at least one dose of 80 mg fitusiran before dose resumption (after the Sponsor initiated pause in dosing).

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[†]Number of bleeding episodes in the last 6 months was only reported for participants with inhibitors and in the last 12 months only for participants without inhibitors.

[‡]Bethesda assay.

[§]A target joint is defined as a joint where 3 or more spontaneous bleeding episodes in a single joint within a consecutive 6-month period has occurred; where there have been ≤ 2 bleeding episodes in the joint within a consecutive 12-month period, the joint is no longer considered a target joint.

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Table 2. Bleeding events in the fitusiran and BPA/CFC prophylaxis period* (EAS 1†)

	Inhibitor			Non-inhibitor			Overall		
Event	**BPA PPX (n = 19)**	**Fitusiran 80 mg PPX (n = 19)**	***P*‡**	**CFC PPX (n = 46)**	**Fitusiran 80 mg PPX (n = 46)**	***P*‡**	**BPA/CFC PPX (N = 65)**	**Fitusiran 80 mg PPX (N = 65)**	***P*‡**
Any treated bleeding event									
Estimated ABR (95% CI)	11.4 (7.4, 17.7)	2.3 (0.8, 6.6)		5.9 (4.0, 8.7)	3.2 (1.7, 5.8)		7.5 (5.5, 10.1)	2.9 (1.7, 4.9)	
% ABR reduction		79.7	0.0021		46.4	0.0598		61.1	0.0008
Median ABR (IQR)	6.5 (2.2; 19.6)	0.0 (0.0; 0.0)		4.4 (2.2; 8.7)	0.0 (0.0; 2.7)		4.4 (2.2; 10.9)	0.0 (0.0; 2.3)	
Participants with zero treated bleeds, n (%)	1 (5.3)	15 (78.9)		10 (21.7)	26 (56.5)		11 (16.9)	41 (63.1)	
Treated spontaneous bleeds									
Estimated AsBR (95% CI)	7.2 (4.4, 11.8)	1.9 (0.7, 5.7)		4.1 (2.4, 7.0)	2.4 (1.1, 5.1)		5.0 (3.4, 7.3)	2.2 (1.2, 4.2)	
% AsBR reduction		73.2	0.0100		42.3	0.1842		55.6	0.0129
Median AsBR (IQR)	4.4 (2.2; 15.2)	0.0 (0.0; 0.0)		2.2 (0.0; 4.4)	0.0 (0.0; 2.3)		2.2 (0.0; 6.5)	0.0 (0.0; 2.3)	
Participants with zero spontaneous treated bleeds, n (%)	3 (15.8)	15 (78.9)		20 (43.5)	31 (67.4)		23 (35.4)	46 (70.8)	
Treated joint bleeds									
Estimated AjBR (95% CI)	7.9 (4.7, 13.0)	2.1 (0.7, 5.8)		4.2 (2.5, 7.1)	2.8 (1.4, 5.5)		5.3 (3.6, 7.7)	2.6 (1.4, 4.6)	
% AjBR reduction		73.6	0.0207		34.4	0.2681		51.5	0.0242
Median AjBR (IQR)	4.4 (0.0; 15.2)	0.0 (0.0; 0.0)		2.2 (0.0; 4.4)	0.0 (0.0; 2.3)		2.2 (0.0; 6.5)	0.0 (0.0; 2.3)	
Participants with zero joint treated bleeds, n (%)	5 (26.3)	15 (78.9)		17 (37.0)	29 (63.0)		22 (33.8)	44 (67.7)	

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ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; AsBR, annualized spontaneous bleeding rate; BPA, bypassing agent; CFC, clotting factor concentrate; CI, confidence interval; IQR, interquartile range; PPX, prophylaxis; SD, standard deviation.

*Fitusiran efficacy period (fitusiran prophylaxis) was defined as starting on Day 29 after the first dose of fitusiran up to Day 190, or the last day of bleeding follow-up, whichever was the earliest. The BPA/CFC prophylaxis period was defined as starting on Day -168 to Day -1, or the last day of bleeding follow-up, whichever was the earliest.

†Includes all participants who received BPA/CFC prophylaxis and at least one dose of 80 mg fitusiran before dose resumption (after the Sponsor initiated pause in dosing).

‡P-value from a negative binomial regression model with study period (fitusiran efficacy period or BPA/CFC prophylaxis period) as a fixed effect and a robust sandwich covariance matrix constructed to account for the within subject dependence, the logarithm of the duration (in years) that each participant spends in each study period matching the bleeding episode data being analyzed as an offset variable (p-value versus null hypothesis of ratio = 1).

The analysis is based on an on-treatment strategy, which included all treated bleeding events in the fitusiran efficacy period and the BPA/CFC prophylaxis period and excluded any bleeding events in the period of intercurrent events.

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Table 3. Consumption of BPA/CFC for treatment of breakthrough bleeds (EAS 1*)

	Inhibitor				Non-inhibitor			
	BPA prophylaxis (n = 19)		Fitusiran 80 mg prophylaxis (n = 19)		CFC prophylaxis (n = 46)		Fitusiran 80 mg prophylaxis (n = 46)	
Event	**aPCC (U/kg)**	**rFVIIa (µg/kg)**	**aPCC (U/kg)**	**rFVIIa (µg/kg)**	**FVIII (IU/kg)†**	**FIX (IU/kg)‡**	**FVIII (IU/kg)†**	**FIX (IU/kg)‡**
Mean annualized weigh-adjusted consumption, unit (SD)	2353.0 (4317.0)	7468.7 (5756.6)	25.6 (82.6)	236.4 (327.0)	294.5 (366.6)	288.6 (402.9)	60.7 (148.3)	17.8 (56.1)
Mean total weight-adjusted dose per bleed, unit (SD)	199.8 (366.1)	709.9 (1163.8)	34.1 (16.1)	38.2 (17.0)	45.3 (41.8)	73.6 (54.7)	13.4 (5.5)	26.2 (0.0)
Total number of injections, n	260	159	7	19	159	30	56	3
Total number of treated bleeds, n	77	24	5	13	108	18	51	3

aPCC, prothrombin complex concentrate; BPA, bypassing agent; CFC, clotting factor concentrate; EAS 1, efficacy analysis set 1; EHL, extended half-life; rFVIIa, recombinant activated factor VII; SD, standard deviation; SHL, standard half-life.

*Includes all participants who received BPA/CFC prophylaxis and at least one dose of 80 mg fitusiran before dose resumption (after the Sponsor initiated pause in dosing); †SHL products ; ‡Due to the very limited number of participants with FIX EHL product consumption for treatment of breakthrough bleeds (only 1 participant received FIX EHL), a further distinction between SHL and EHL product consumption for breakthrough bleeds treatment was not feasible in this study.

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Table 4. Summary of adverse events (SAS 1*)

Event, n (%)	BPA/CFC prophylaxis (N = 65)	Fitusiran 80 mg prophylaxis (N = 67*)
Participants with any AE	22 (33.8)	48 (71.6)
Most common AEs in fitusiran group (in > 5% of participants)		
ALT increased	1 (1.5)	18 (26.9)
Nasopharyngitis	1 (1.5)	8 (11.9)
Upper respiratory tract infection	4 (6.2)	6 (9.0)
Arthralgia	4 (6.2)	5 (7.5)
Cholelithiasis	0	5 (7.5)
Fibrin D dimer increased	0	5 (7.5)
Injection site pain	0	5 (7.5)
AST increased	1 (1.5)	4 (6.0)
Cholecystitis	0	4 (6.0)
Cough	0	4 (6.0)
Participants with any SAE	5 (7.7)	9 (13.4)
SAEs assessed as related to fitusiran†	N/A	3 (4.5)
Cerebrovascular accident	N/A	1 (1.5)
Pancreatitis acute	N/A	1 (1.5)
Cholelithiasis	N/A	1 (1.5)
Most common SAEs‡		
Hemophilic arthropathy§	2 (3.1)	2 (3.0)
Participants with any AESI	2 (3.1)	22 (32.8)
Any suspected or confirmed thromboembolic events¶	0	2 (3.0)
Any ALT or AST elevations > 3 x ULN**	2 (3.1)	17 (25.4)
Cholecystitis††	0	5 (7.5)
Cholelithiasis	0	5 (7.5)
Participants with any AE leading to fitusiran discontinuation‡‡	N/A	2 (3.0)
Participants with any AE leading to study withdrawal‡‡	0	2 (3.0)
Participants with any AE leading to death	0	0

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate transaminase; N/A, not applicable; SAE, serious adverse event;
SAS 1, safety analysis set 1; ULN, upper limit of normal.

*Includes all participants who enrolled and then received at least one dose of fitusiran before dose resumption (after the Sponsor initiated pause in dosing).

†The participant with cerebrovascular accident recovered from the event with sequelae 28 days after the onset. This event resulted in fitusiran discontinuation and study withdrawal. Pancreatitis acute and cholelithiasis were assessed as serious due to the need for hospitalization; both of these events were resolved by the end of the study.

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‡In the BPA/CFC prophylaxis period, additional SAEs included gastroenteritis, hemarthrosis, and muscle hemorrhage (1 [1.5%] participant each). In the fitusiran prophylaxis period, additional SAEs included vascular device infection, biliary neoplasm, cerebrovascular accident, asthma late onset, pancreatitis acute, cholelithiasis, Stevens-Johnson syndrome (occurred 62 days after the last dose of fitusiran prophylaxis; the event was due to allergic reaction to concomitant medications and was assessed by the investigator as not related to fitusiran prophylaxis), C-reactive protein increased, fall, femur fracture, and central venous catheter removal (1 [1.5%] participant each).

§Reported as worsening of hemophilic arthropathy. Both participants with events of worsening of hemophilic arthropathy during fitusiran prophylaxis had the history of hemophilic arthropathy ongoing before the study entry. These events were due to traumatic joint bleeds and participants recovered from these events within 2–3 days of onset. None of the events were assessed by the investigator as related to fitusiran prophylaxis.

¶Includes AEs of cerebrovascular accident and thrombosis (suspected thrombosis on papilla of left eye). The participant with cerebrovascular accident had a history of right lower extremity deep vein thrombosis not known by the investigator at the time of enrolment (exclusion criterion).

**Laboratory abnormalities consistent with Hy's Law were identified in 1 of these participants at the end of study visit. Additional doses of fitusiran were not administered and all abnormalities resolved.

††Includes one AE of chronic cholecystitis.

‡‡Includes AEs of cerebrovascular accident and abdominal discomfort.

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Figure legend

Figure 1. Participant disposition

BPA, bypassing agent; CFC, clotting factor concentrate; PwHB, people with hemophilia B; QM, every month; Q2M, once every other month.

*Among the 19 screen failures, the main reasons for screen failure were exclusion criterion of the co-existing thrombophilic disorder (7 [7.1%] of the overall participants screened, 2 [5.7%] in Cohort A and 5 [7.8%] in Cohort B) or withdrawn consent (7 [7.1%] of the overall participants screened, 1 [2.9%] in Cohort A and 6 [9.4%] in Cohort B).

†A subgroup of Cohort A included PwHB with inhibitors who were not responding adequately to BPA prophylaxis prior to enrolment (historical ABR ≥ 20).

‡After Sponsor initiated pause in dosing and subsequent protocol amendment.

§Nine participants with fitusiran 80 mg prophylaxis who discontinued therapy remained in the study to complete study assessments and follow-up to allow for the best study integrity and interpretation.

¶One participant with fitusiran 50 mg prophylaxis who discontinued therapy remained in the study to complete study assessments and follow-up to allow for the best study integrity and interpretation.

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Figure 2. Bleeding events in the fitusiran efficacy and BPA/CFC prophylaxis period (EAS 1*): A) Annualized bleeding rates for treated bleeds (estimated by negative binomial model), B) Annualized bleeding rates for treated bleeds by inhibitor status (estimated by negative binomial model), C) Number of treated bleeds

ABR, annualized bleeding rate; BPA, bypassing agent; CFC, clotting factor concentrate; CI, confidence interval; IQR, interquartile range.

*Includes all participants who received BPA/CFC prophylaxis and at least one dose of 80 mg fitusiran before dose resumption (after the Sponsor initiated pause in dosing)

†P-value from a negative binomial regression model with study period (fitusiran efficacy period or BPA/CFC prophylaxis period) as a fixed effect and a robust sandwich covariance matrix constructed to account for the within subject dependence, the logarithm of the duration (in years) that each participant spends in each study period matching the bleeding episode data being analyzed as an offset variable (p-value versus null hypothesis of ratio = 1).

‡The BPA/CFC prophylaxis period was defined as starting on Day -168 to Day -1, or the last day of bleeding follow-up, whichever was the earliest.

§Fitusiran efficacy period was defined as starting on Day 29 after the first dose of fitusiran up to Day 197, or the last day of bleeding follow-up, whichever was the earliest.

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Figure 3. Pharmacodynamic outcomes: A) Mean change in antithrombin levels from baseline B) Mean peak thrombin generation

BL, baseline; BPA, bypassing agent; SE, standard error.

Measurements after fitusiran discontinuation +28 days were excluded. Measurements from start date of heparin, antithrombin concentrate and Factor Xa inhibitor to the final date on which those products were administered plus 5 half-lives of that specific product were excluded. Measurements in the period of missing at least two consecutive fitusiran doses were excluded. Only central laboratory assessments were taken into account.

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Fitusiran prophylaxis in people with hemophilia A or B, with or without inhibitors who switched from prior BPA/CFC prophylaxis: A Phase 3 study (ATLAS-PPX, NCT03549871)

Study Design

Males with hemophilia A or B aged ≥ 12 who had prior BPA/CFC prophylaxis

- **Cohort A:** participants with inhibitors
- **Subgroup[a]**
- **Cohort B:** participants without inhibitors

n = 78

Continuation of BPA/CFC prophylaxis — **6 months**

n = 65

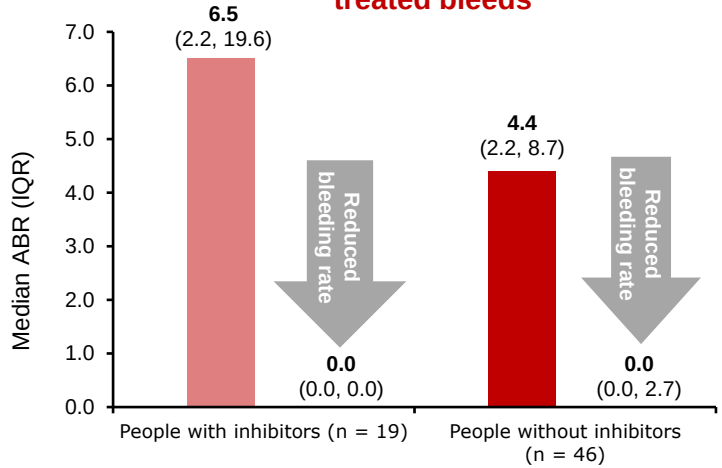
Fitusiran 80mg QM SC prophylaxis
- **Onset period** 1 month
- **Efficacy period** 6 months

Treatment period

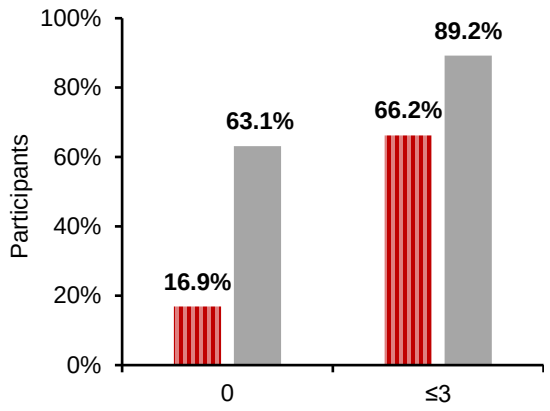
Extension study or follow up for 6 months

Results

Observed median ABR for all treated bleeds



Number of treated bleeds

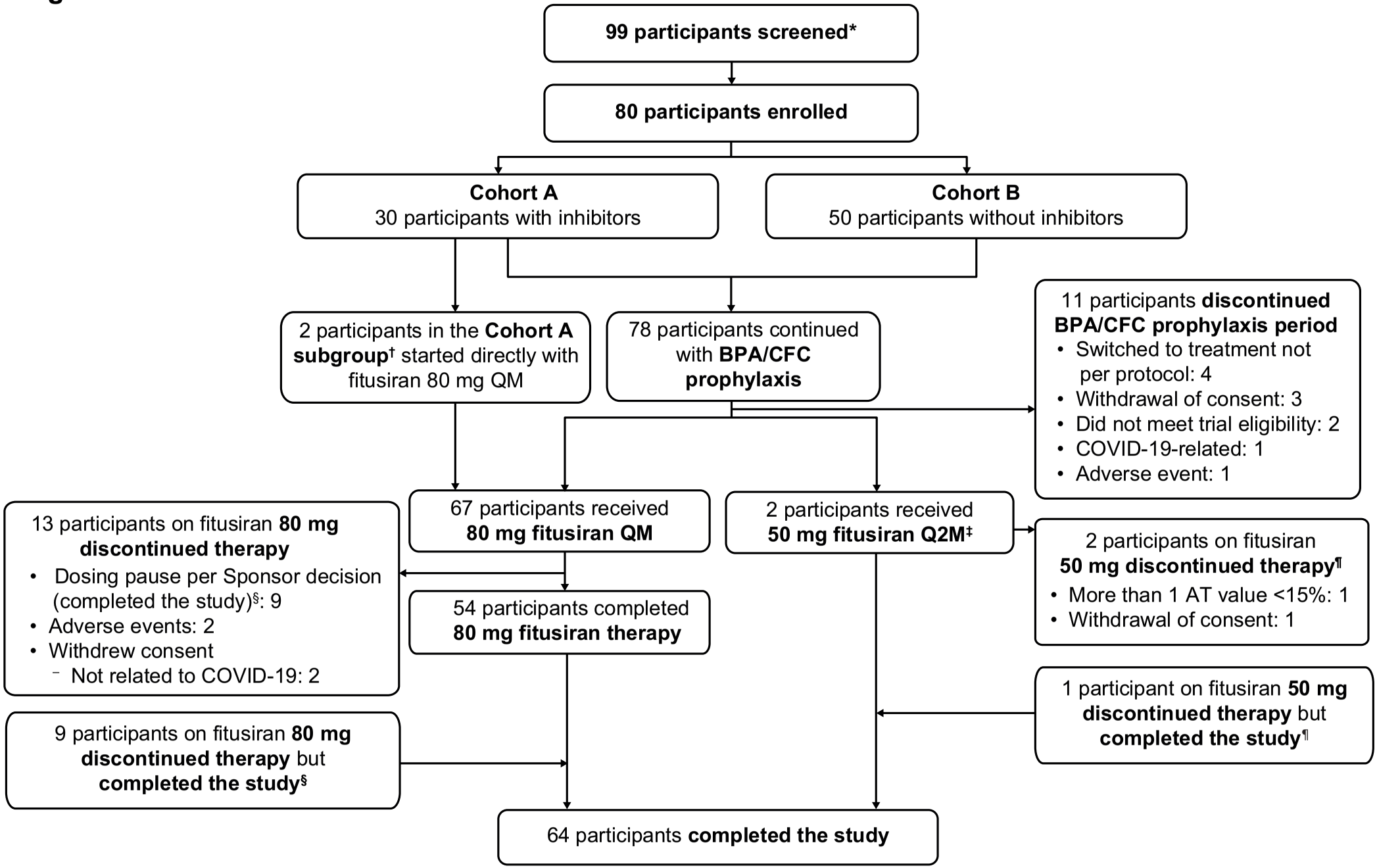


- Fitusiran resulted in observed median **ABR of zero** in PwHA/B, with or without inhibitors
- Once-monthly 80 mg fitusiran prophylaxis substantially **reduced bleeding events by 79.7% and 46.4%** versus BPA and CFC prophylaxis, respectively
- Reported adverse events were **generally consistent** with previously identified risks of fitusiran

[a]A subgroup of Cohort A included participants with hemophilia B with inhibitors who were not responding adequately to BPA prophylaxis (historical ABR ≥ 20);
[b]Includes all participants who received BPA/CFC prophylaxis and at least one dose of fitusiran before dose resumption (after the Sponsor initiated dosing pause).

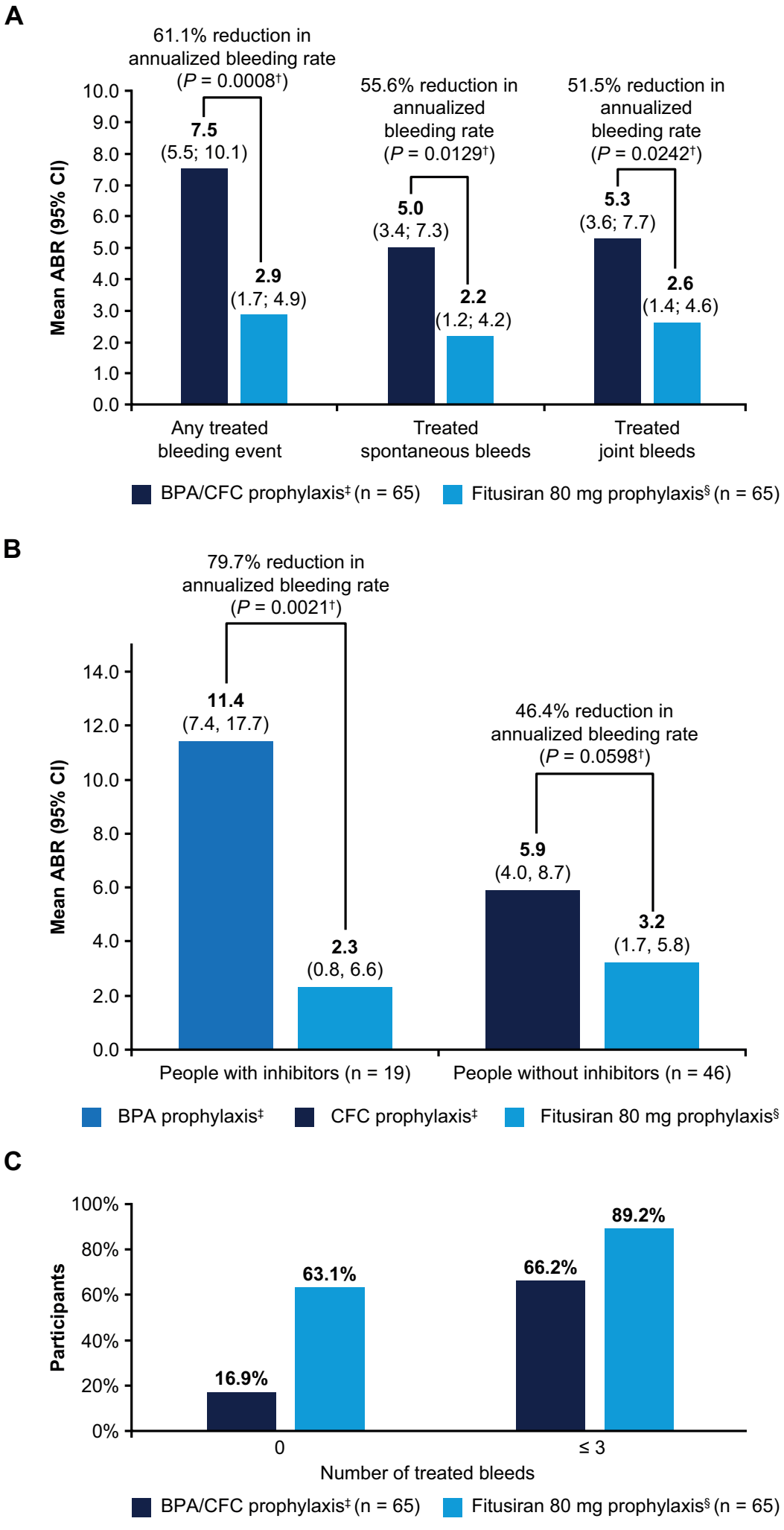
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Figure 1



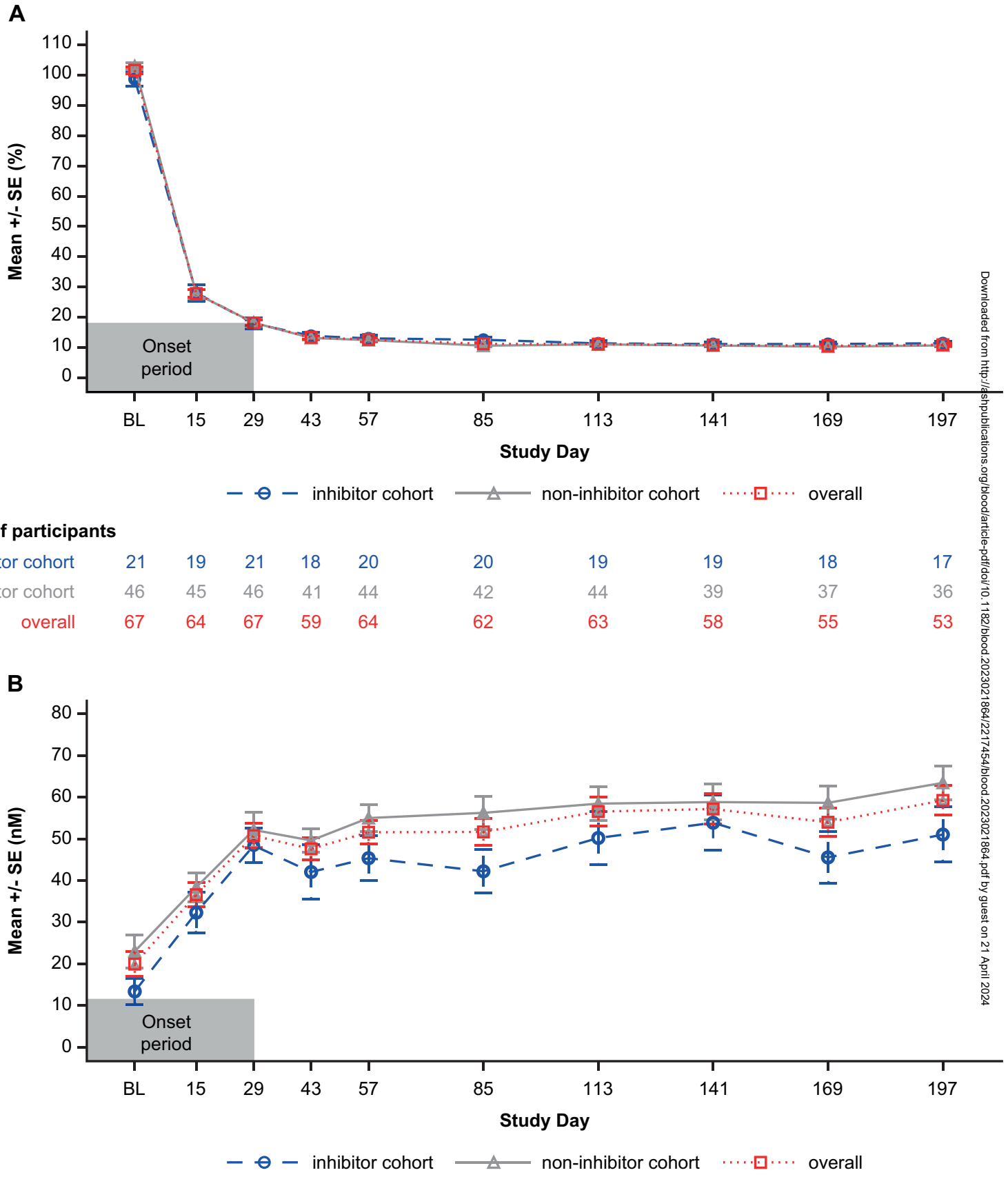
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Figure 2



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Figure 3



Number of participants

	BL	15	29	43	57	85	113	141	169	197
inhibitor cohort	21	19	21	18	20	20	19	19	18	17
non-inhibitor cohort	46	45	46	41	44	42	44	39	37	36
overall	67	64	67	59	64	62	63	58	55	53

Number of participants

	BL	15	29	43	57	85	113	141	169	197
inhibitor cohort	21	18	21	12	17	16	13	16	16	16
non-inhibitor cohort	45	43	36	33	31	33	43	32	29	31
overall	66	61	57	45	48	49	56	48	45	47

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