**Efficacy and safety of fitusiran prophylaxis in people with haemophilia A or B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised Phase 3 trial**

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**Research in context**

**Evidence before this study:** Prophylaxis with haemostatic agent(s) is recommended as the standard of care for people with haemophilia. However, prophylaxis with clotting factor concentrates is limited by the need for frequent intravenous infusions, poor adherence to treatment, and breakthrough bleeding. The most frequent complication of prophylaxis with clotting factor concentrates is the development of inhibitory antibodies in approximately 30% of people with severe haemophilia A and 10% with haemophilia B, for whom treatment is complicated and disease burden is high. Immune tolerance induction (ITI) is the only current therapeutic strategy to eliminate inhibitors, but this approach is limited by a burdensome regimen, long-treatment duration, a success rate of 70–80% in haemophilia A and limited experience and efficacy in haemophilia B. Therefore, bypassing agents (BPAs), namely activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa), are broadly used either as prophylaxis or on-demand (episodic) treatment. However, such agents are limited by their variable efficacy and, when used as prophylaxis, impart a high treatment burden and extremely high cost. Emicizumab is an alternative non-factor treatment option only for people with haemophilia A, with and without inhibitors, which has been shown to provide effective bleed protection with a less burdensome regimen than prophylaxis with clotting factor concentrates or bypassing agents. However, gaps from clinical utility and access perspectives still exist, thus there remains a need for novel therapeutic strategies that aim to enhance thrombin generation, with the ultimate goal to prevent bleeding and enable all people with haemophilia to achieve quality of life comparable to the non-haemophilic population.

Fitusiran is an investigational, subcutaneously administered, prophylactic, small interfering RNA (siRNA) therapeutic, based on Nobel Prize-winning technology, that works through a novel mechanism in the haemophilia field to reduce antithrombin synthesis. Fitusiran targets antithrombin to enhance thrombin generation potential and rebalance haemostasis in people with haemophilia A or B, irrespective of inhibitor status. We searched for clinical trials published in English between April 2012 and April 2022 in PubMed using the terms “siRNA OR RNAi”, “haemophilia OR hemophilia”, and “clinical trial”; there were no trial results for siRNA molecules other than fitusiran in haemophilia. Early Phase 1/2 studies of fitusiran prophylaxis have demonstrated a dose‑dependent reduction of antithrombin levels and a corresponding dose‑dependent increase in thrombin generation, resulting in stable clot formation and improvement of bleeding phenotype in severe haemophilia A or B.

**Added value of the study:** The Phase 3 ATLAS-INH trial investigated fitusiran prophylaxis in participants with severe haemophilia A or B with inhibitory antibodies. Our findings demonstrated that once-monthly fitusiran prophylaxis resulted in statistically significant protection against bleeding compared with on-demand BPA therapy, improved quality of life, and reduced the overall treatment burden in those with inhibitors, expanding upon the positive outcomes reported in Phase 1 and 2 trials. In addition, fitusiran prophylaxis was generally well tolerated and reported treatment-emergent adverse events were consistent with the known risks of fitusiran or what is anticipated in an adult and adolescent population with severe haemophilia A or B.

**Implications of all the available evidence:** The evidence from available Phase 3 studies (NCT03417245 and NCT03417102) indicates that subcutaneous fitusiran has the potential to be the first prophylactic therapeutic option available for the management of people with both haemophilia A or B, irrespective of the presence of inhibitory antibodies. The positive trial results and convenient route of administration suggest that this prophylactic regimen will reduce overall treatment burden whilst preventing bleeds in all people with haemophilia, bringing them closer to a quality of life comparable to that of the non-­haemophilic population.

**Summary** (300/300 words)

**Background:** Fitusiran, a subcutaneous investigational siRNA therapeutic, targets antithrombin to rebalance haemostasis in people with haemophilia A or B, irrespective of inhibitor status. We evaluated the efficacy and safety of fitusiran prophylaxis in people with haemophilia with inhibitors.

**Methods:** This multicentre, randomised, open-label Phase 3 study was conducted at 26 sites in 12 countries. Males aged ≥12 years with severe haemophilia A or B with inhibitors previously treated with on-demand bypassing agents (BPAs) were randomised 2:1 to receive once-monthly 80 mg subcutaneous fitusiran prophylaxis or to continue with BPAs on-demand for 9 months. Primary endpoint was annualised bleeding rate (ABR) during the efficacy period. Safety and tolerability were assessed. This trial (clinicaltrials.gov: NCT03417102) has completed.

**Findings:** Between February 14, 2018, and June 23, 2021, 85 participants were screened and 57 were randomised to BPA on-demand (n=19) or fitusiran prophylaxis (n=38). Negative binomial model-based mean (95% CI) ABR was statistically significantly lower in the fitusiran prophylaxis group (1·7 [95% CI: 1·0–2·7]) versus BPA on-demand group (18·1 [95%CI: 10·6–30·8]), corresponding to a 90·8% (95% CI: 80·8–95·6%) reduction in ABR in favour of fitusiran prophylaxis (p<0·0001). Median (IQR) ABR was 0·0 (0–1·7) and 16·8 (6·7–23·5) in fitusiran prophylaxis and BPA on-demand groups, respectively. Twenty-five participants (65·8%) had zero treated bleeds in the fitusiran prophylaxis group versus one (5·3%) in the BPA on-demand group. The most frequent treatment-emergent adverse event in the fitusiran prophylaxis group was increased alanine aminotransferase in 13 (31·7%) participants. Suspected or confirmed thromboembolic events were reported in two (4·9%) participants. No deaths were reported.

**Interpretation:** Subcutaneous fitusiran prophylaxis resulted in statistically significant reductions in ABR in people with haemophilia A or B with inhibitors, with two-thirds of participants having zero bleeds. Reported treatment-emergent adverse events were generally consistent with the previously identified risks of fitusiran.

**Funding:** Sanofi.

**Introduction**

Haemostasis depends on balanced procoagulant and anticoagulant pathways that generate thrombin sufficient to control bleeding.1 Haemophilia A and B are the result of deficiencies of coagulation factors VIII (FVIII) or IX (FIX), respectively, resulting in insufficient thrombin generation.1,2 Prophylaxis is the standard of care for haemophilia management, defined as regular administration of haemostatic agents with the goal of preventing bleeding.2 Clotting factor concentrates are limited by the burden of intravenous infusions, difficulties with venous access, peak and trough factor levels, and breakthrough bleeding.2–4 Additionally, treatment with clotting factor concentrates is complicated by the development of inhibitory antibodies in approximately 30% of people with severe haemophilia A and 10% with haemophilia B, which render them ineffective.5,6 People with inhibitors experience greater disease burden, including heightened risk of bleeding complications and joint damage, compared with those without inhibitors.5,7 Immune tolerance induction, comprising regular high-dose FVIII/FIX infusions, is the only current therapeutic strategy to eliminate inhibitors.2 However, ITI is burdened by frequent intravenous injections, prolonged duration of treatment,8 and is ineffective in approximately 20 to 30% of people with haemophilia A with inhibitors, with a lower success rate in people with haemophilia B with inhibitors.2 People eligible for ITI may also require haemostatic intervention with intravenously administered BPAs, either as prophylaxis or on-demand (episodic) treatment with aPCC or rFVIIa for bleeding episodes. However, such agents are limited by their variable efficacy and the latter by its short half-life. When used for prophylaxis, both agents impart a high treatment burden and cost.9,10

Owing to the limitations of traditional management options, efforts have continued to develop novel products that can improve thrombin generation and rebalance haemostasis with the aim to further prevent bleeding, reduce joint damage, minimise treatment burden, and improve quality of life in people with haemophilia. One such therapeutic is emicizumab, a humanised bispecific monoclonal antibody that partially mimics FVIII function and is approved for the treatment of people with haemophilia A only, irrespective of inhibitor status.11,12 However, despite available treatment options, breakthrough bleeds still occur and additional therapeutic alternatives are needed for people with haemophilia A or B, irrespective of inhibitor status.13

It has been observed that people with severe haemophilia present with a mild clinical bleeding phenotype when coinherited with thrombophilic traits,14 suggesting rebalancing haemostasis may be an effective means to treat haemophilia. Fitusiran is an investigational, subcutaneously administered, prophylactic, small interfering RNA therapeutic that is designed to lower antithrombin with the goal of generating sufficient thrombin to rebalance haemostasis in people with haemophilia A or B, with or without inhibitors.15 Fitusiran works through a novel mechanism in the haemophilia field, whereby it leverages natural cellular RNA interference mechanisms to cleave and degrade antithrombin messenger RNA and reduce antithrombin synthesis.16 The siRNA technology utilised by fitusiran marks a major milestone in the management of human diseases and confers therapeutic effects with infrequent administration and subcutaneous delivery.17 In Phase 1/2 studies, fitusiran prophylaxis demonstrated a dose‑dependent reduction of antithrombin levels, resulting in a corresponding dose‑dependent increase in thrombin generation and enhanced clinical haemostasis.15,18

Here, we aimed to evaluate the efficacy and safety of fitusiran prophylaxis compared with episodic treatment with BPAs in people with haemophilia A or B with inhibitory antibodies.

**Methods**

**Study design**

This multicentre, multinational, open-label, randomised, Phase 3 trial was conducted at 26 sites across 12 countries (Supplementary Appendix, pp 3–4). The trial was conducted in accordance with the protocol and ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines for Good Clinical Practice. The study employed a Steering Committee composed of four experts in the field of haemophilia, some of whom were also study investigators, who advised the Sponsor on study design and conduct. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating centre (Supplementary Appendix, pp 5–7), and an independent external Data Monitoring Committee (IDMC) oversaw the safety and overall conduct of the trial and performed periodic reviews of data during the trial. The IDMC had an initial organisational meeting prior to start of study, followed by a meeting after around 10% of participants were enrolled in the ATLAS studies, and then every 6 months throughout the study; additional ad-hoc meetings were scheduled when needed.

**Participants**

Eligible participants were males aged ≥12 years with severe haemophilia A (a central laboratory measurement or documented medical record evidence of FVIII <1% at screening) or B (FIX ≤2%)19 and with inhibitory antibodies to FVIII or FIX (Nijmegen-modified Bethesda assay ≥0·6 Bethesda units/mL at screening) who had experienced ≥6 bleeding episodes requiring on-demand BPA treatment within 6 months prior to screening.

Participants were excluded if they had antithrombin activity <60% at screening as determined by central laboratory measurement or a history of arterial or venous thromboembolism, atrial fibrillation, significant valvular disease, myocardial infarction, angina, transient ischaemic attack, or stroke. Participants with a history of thrombosis associated with indwelling venous access were permitted to enrol. Full inclusion and exclusion criteria are detailed in the Supplementary Appendix (pp 8–9). Written informed consent was obtained prior to the conduct of any trial-related procedures.

**Randomisation and masking**

Eligible participants were randomised 2:1 to receive once-monthly 80-mg subcutaneously administered (0.8mL) fitusiran prophylaxis, with use of BPA on-demand for the treatment of breakthrough bleeds, or to continue with on-demand BPAs for the treatment of bleeding episodes (further information in the Supplementary Appendix, p 9). Participants were assigned to study groups by stratified permuted block randomisation (block size of 3). The system used for randomisation was provided by the external vendor Suvoda (under supervision of data management vendor SGS). On-demand use of BPAs was defined as the use of these agents, as needed, for episodic bleeding events (Supplementary Appendix, p 10, and Table S1, p 14). Randomisation was stratified by the number of bleeding episodes in the 6 months before screening (≤10 vs >10). Upon signing the informed consent form, each participant was assigned a unique identifier by an interactive response system. The investigator or his/her delegate contacted the interactive response system after confirming that the participant fulfilled all inclusion criteria. The trial was open‑label, with both participants and investigators aware of treatment assignment.

**Procedures**

The trial consisted of several periods (Figure S1, p 21): the onset period, from Days 1 to 28, during which fitusiran gradually reached the target pharmacodynamic effect of antithrombin lowering;15 the efficacy period, from Day 29 up to Day 246; and the treatment period that consisted of both the onset and efficacy periods. The follow-up period lasted from 1 to 6 months, until antithrombin levels returned to approximately 60% following the final dose or until enrolment into an open-label extension study.

Participants recorded all bleeding episodes, doses of BPAs, and reasons for doses administered during the conduct of the trial in an eDiary (Supplementary Appendix, p 10). A treated bleeding episode was defined as any occurrence of haemorrhage that required administration of BPAs. The definitions of bleeding episode types were according to the recommendations of the International Society on Thrombosis and Hemostasis (Table S2, p 15).

Health-related quality of life (HRQoL) was assessed at Day 1 and end of the treatment period in adults aged 17 years or older using the validated Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) instrument (Supplementary Appendix, p 10).20

Safety assessments consisted of treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs) and treatment-emergent adverse events of special interest (TEAESIs); physical examinations, including vital signs and electrocardiograms; and laboratory tests, including markers of coagulation (results reported in Supplementary Appendix, p 13).

For pharmacodynamic assessments, antithrombin activity levels were measured from blood samples collected within 4 hours before dosing and monitored at monthly intervals from Day 1 until returning to an approximate activity level of 60% after the final fitusiran dose (unless participants opted to continue fitusiran in an open-label extension study). Thrombin generation was also assessed at monthly intervals. Antidrug antibodies (ADA) to fitusiran were measured from serum blood samples collected within 4 hours of treatment administration on Day 1, Months 1 and 3, and at end of treatment using a validated enzyme‑linked immunosorbent assay method.

**Outcomes**

The primary efficacy endpoint was ABR in the efficacy period. ABR was defined as the number of qualifying bleeding episodes divided by the total number of days in the efficacy period multiplied by 365·25. Pre-specified subgroup analyses of the primary endpoint were performed according to haemophilia type (Type A vs B), number of bleeding episodes during the 6 months prior to study (<=10 vs >10) and age group (<18, 18–64, ≥65 years) in the efficacy period. Secondary endpoints included ABR in the treatment period, annualised spontaneous bleeding rate (AsBR) in the efficacy period, and annualised joint bleeding rate (AjBR) in the efficacy period. Change from baseline in Haem-A-QoL physical health domain and total score in the treatment period were also assessed as a secondary endpoint.

Safety and tolerability endpoints included incidence, severity, seriousness, and relatedness of adverse events. TEAESIs were pre-defined as alanine aminotransferase (ALT) or aspartate aminotransferase elevations (AST) >3× upper limit of normal (ULN), suspected or confirmed thrombosis, severe or serious injection site reactions, and systemic injection-associated reactions (further details in Supplementary Appendix, p 11).

Pre-specified exploratory endpoints included number of target joint bleeding episodes in the efficacy period, pharmacokinetic and pharmacodynamic effects of fitusiran (including antithrombin activity and thrombin generation), and incidence and titre of ADA in the fitusiran prophylaxis group. There was no allowance for multiplicity for the exploratory outcomes.

**Determination of sample size**

Using a negative binomial regression model with a two-sided type I error rate of 0·05, an estimated sample size of 14 participants in the BPA on-demand group (assuming mean [SD] ABR of 18 [14]) and 28 participants in the fitusiran prophylaxis group (assuming mean [SD] ABR of 4 [6]) was projected to provide >90% power for detecting treatment difference in the primary endpoint. The planned sample size was 54 randomised participants assuming a 20% drop-out rate.

**Statistical analysis**

All statistical analyses were performed using SAS statistical software Version 9·4. The primary analyses were performed on the intent-to-treat analysis set (all randomised participants). As per the requirement from China’s health authority, three sentinel Chinese participants were not randomised as they represented a sentinel cohort and needed to be treated with a single 50 mg dose before any other Chinese participants could be randomised to receive 80 mg subcutaneously administered fitusiran prophylaxis. This requirement was included in the study protocol. These participants were not included in the intent-to-treat population but were included in the safety set (further details in Supplementary Appendix, p 9).

The number of bleeding episodes in the efficacy period were analysed using a negative binomial model with fixed effects of treatment group and the number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10). The logarithm number of days that each participant spent in the efficacy period matching the bleeding episode data being analysed was included as an offset variable to account for unequal follow-up time due to early withdrawal, surgery, etc. The estimated mean ABR in both treatment groups along with their 95% confidence intervals (CIs) were presented from this model. Summary statistics for ABR, including median and IQR, were also calculated for each group. Sensitivity analyses were performed for the efficacy outcomes (Supplementary Appendix, p 11).

AsBR and AjBR were analysed using the same methodology as the primary analysis. Least square (LS) mean change from baseline in physical health score and total score of Haem-A-QoL were analysed using an analysis of covariance model with fixed effects of treatment group, baseline Haem-A-QoL physical health score and total score, and number of bleeding episodes 6 months before enrolment (≤10 vs >10). To control for the familywise error rate in the testing of primary and secondary endpoints, a hierarchical testing approach was used (Supplementary Appendix, p 11).

Safety, pharmacokinetic, pharmacodynamic, and immunogenicity results were summarised descriptively. In the safety population, all participants received at least one dose of fitusiran or were randomised to the on-demand group; all by-treatment analyses based on the safety analysis set were according to the actual treatment received. The study protocol is available from <https://clinicaltrials.gov/ProvidedDocs/02/NCT03417102/Prot_000.pdf>.

The trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (identifier: NCT03417102).

**Role of the funding source**

The funder was involved in the study design, data collection, data analysis and interpretation, and drafting of the report. The funder was not involved in the decision to submit, submission was at the discretion of the authors.

**Results**

Between February 14, 2018, and June 23, 2021, a total of 85 participants were screened, 25 of whom failed screening and three of whom were not randomised, and 57 participants were randomised to the BPA on-demand group (n=19) and the fitusiran prophylaxis group (n=38; Figure 1). All randomised participants completed the study. Baseline demographics and clinical characteristics were similar between both groups in the safety set (Table 1); most participants had haemophilia A (n=48, 80%) and target joints present at baseline (67% of participants had ≥1 target joint). Information regarding medical history at baseline and most frequently used concomitant medications are reported in the Supplementary Appendix (Table S3 and S4). Numbers of participants randomised and treated at each site are provided for both groups in the Supplementary Appendix (Table S5). The median duration of fitusiran exposure was 252·0 days (minimum 203 days; maximum 271 days).

Mean ABR estimated by the negative binomial model in the efficacy period was statistically significantly lower in the fitusiran prophylaxis group (1·7 [95% CI: 1·0, 2·7]) compared with the BPA on-demand group (18·1 [95% CI: 10·6, 30·8]; Table 2, Figure S2), corresponding to a statistically and clinically significant reduction in bleeding rate of 90·8% (95% CI: 80·8, 95·6%) in favour of fitusiran prophylaxis (p<0·0001). Median ABRs were consistent with these findings: 0·0 (IQR: 0·0, 1·7) in the fitusiran prophylaxis group and 16·8 (IQR: 6·7, 23·5) in the BPA on-demand group (Table 2, Figure S2). In the efficacy period, 25 participants (66%) had zero treated bleeds in the fitusiran prophylaxis group versus one (5%) in the BPA on-demand group. In the fitusiran arm, 13 participants experienced a treated bleed, two of whom received aPCC and 11 received rFVIIa. In the BPA on demand group, 18 participants experienced a treated bleed, nine of whom received aPCC and 13 received rFVIIa (n=4 received both). Annualised bleeding rate in the treatment period demonstrated similar results to the primary endpoint (see Supplementary Appendix, p 13). When analysed by haemophilia subtypes, median ABRs in the efficacy period were lower in the fitusiran prophylaxis group compared with BPA on‑demand group in both haemophilia A (0·0 [IQR: 0·0, 0·0] versus 15·9 [IQR: 6·7, 23·5], respectively) and haemophilia B (1·7 [IQR: 0·0, 5·0] versus 18·4 [IQR: 5·1, 23·5], respectively) (Table S6).

Subgroup analyses confirmed the primary endpoint. In all subgroups, estimated ABR results favoured fitusiran prophylaxis (Figure 2, Table S6). The results of the sensitivity analyses supported the primary efficacy outcomes and are reported in the Supplementary Appendix (Table S7).

In the efficacy period, median AsBRs were 0·0 (IQR: 0·0, 0·0) and 13·4 (IQR: 3·4, 21·8) in the fitusiran prophylaxis and BPA on-demand groups, respectively. A greater proportion of participants in the fitusiran prophylaxis group had zero spontaneous bleeds (76%) versus the BPA on-demand group (11%). Median AjBRs were 0·0 (IQR: 0·0, 1·7) and 11·7 (IQR: 3·4, 16·8) in the fitusiran prophylaxis and BPA on-demand groups, respectively. In the fitusiran prophylaxis group, 11 (29%) participants had ≥1 joint bleed, compared with 18 (95%) participants in the BPA on-demand group; two (5%) and 13 (68%) participants, respectively, had >3 joint bleeds. In participants with ≥1 target joint identified at baseline, 4/26 (15%) and 12/12 (100%) participants in the fitusiran prophylaxis and BPA on-demand groups, respectively, had a treated spontaneous target joint bleeding event during the efficacy period. Most participants (85%) in the fitusiran prophylaxis group had zero target joint bleeding events compared with none (0%) of the BPA on-demand group (Table S8).

The percentage of participants with major protocol deviations identified during the study was similar between treatment arms, 76·3% (n=29) in the fitusiran prophylaxis arm, and 68·4% (n=13) in the BPA on-demand group (Table S9).

There were statistically significant reductions (improvements) in LS mean (95% CI) Haem-A-QoL transformed physical health domain score relative to baseline in the fitusiran prophylaxis group (-30·7 [-36·9, -24·4]) compared with the BPA on-demand group (-1·9 [-10·3, 6·4]), with a LS mean difference of -28·7 (-39·1, -18·4) in favour of fitusiran prophylaxis (p<0·0001) (Figure S3). A statistically significant reduction was also observed in the Haem-A-QoL transformed total score in the fitusiran prophylaxis group (-15·3 [-19·3, -11·2]) compared with the BPA on-demand group (-0·4 [-5·7, 4·8]), with a LS mean difference of -14·9 (-21·4, -8·3) in favour of fitusiran prophylaxis (p<0·0001) (Figure S3).

Overall, 38 (93%) participants in the fitusiran prophylaxis group and 11 (58%) participants in the BPA on-demand group experienced at least one TEAE; the most common TEAEs (reported in >5% of participants in the fitusiran prophylaxis group) are summarised in Table 3. TESAEs were reported in seven participants (17%) in the fitusiran prophylaxis group and five participants (26%) in the BPA on-demand group. In the fitusiran prophylaxis group, one participant (2%) experienced two TESAEs that were assessed by the investigator as possibly related to fitusiran and that resulted in study drug discontinuation (spinal vascular disorder and thrombosis [suspected spinal vessel thrombosis]). There were no TEAEs that resulted in study withdrawal and no TEAEs leading to death.

In the fitusiran prophylaxis group, TEAESIs of ‘any ALT or AST elevations >3× ULN’ were reported in ten (24%) participants (Table 3). For most participants, event onset occurred within 60 days of fitusiran initiation. All events were classified by the investigator as non-serious and mild-to-moderate in severity. These events resulted in interruption of fitusiran prophylaxis in three (7%) participants, which was required due to ALT or AST elevations >5× ULN, and in discontinuation of fitusiran prophylaxis in no participants. In all three participants with an interruption in fitusiran prophylaxis, the events were reported by the Investigator as recovered or resolved; median time to event resolution was 42 days (minimum 5 days; maximum 50 days). Recurrent elevations >3× ULN were reported in one of these participants. Of the seven participants who continued on fitusiran prophylaxis, the events were reported by the Investigator as recovered or resolved in four participants; median time to event resolution was 76.5 days (minimum 24 days; maximum 148 days). Recurrent elevations >3× ULN were reported in one of these participants. Laboratory abnormalities consistent with Hy’s Law were not identified. There were no reports of ‘any ALT or AST elevations >3× ULN’ in the BPA on-demand group.

In the fitusiran prophylaxis group, four TEAESIs of ‘suspected or confirmed thromboembolic events’ were reported in two (5%) participants (Table 3). These events were deep vein thrombosis (non-serious), subclavian vein thrombosis (serious), and superficial thrombophlebitis (non-serious) involving the upper extremities in a single participant in the setting of central venous access and associated complications. All three of these events resulted in interruption of fitusiran and were assessed by the investigator as unlikely related to the study drug. The antithrombin value in this participant prior to onset of these events was 11.9%. In a second participant, an event of thrombosis (suspected spinal vessel thrombosis) was assessed by the investigator as serious and possibly related to the study drug, resulting in discontinuation of fitusiran prophylaxis. Steady state antithrombin values in this participant prior to event onset ranged from 7.8% to 11.6%. There were no TEAESIs of ‘any suspected or confirmed thromboembolic events’ reported in the BPA on-demand group.

There were no TEAESIs of severe or serious injection site reactions or systemic injection associated reactions reported.

In the fitusiran group, six participants experienced TEAEs of cholecystitis and/or cholelithiasis. Of those six participants, cholecystitis and cholelithiasis were reported concomitantly in three participants, acalculous cholecystitis was reported in one participant, and cholelithiasis alone was reported in two participants. Events of cholecystitis and/or cholelithiasis were managed via cholecystectomy in one participant. There were no events of cholecystitis or cholelithiasis reported in the BPA on-demand group.

Once-monthly dosing with fitusiran prophylaxis resulted in a sustained lowering of antithrombin activity levels from mean 104% (SD: 10.5) at baseline, with a 77% mean reduction (SD: 8·6) from baseline by Day 15, and an 84% mean reduction (SD: 7·2) by Day 29 (Figure S4A). Antithrombin levels remained reduced by 84 to 90% from Day 29 to trial end. At study endpoint, mean AT levels were 11% (SD: 2.9). As expected, treatment with BPA had no effect on antithrombin levels. There was a mean (SD) increase in peak thrombin generation of 21·9 nM (16·4) from baseline in the fitusiran group on Day 15, increasing to a peak mean thrombin generation of 40·3 nM (17·9) on Day 29 and 46·7 nM (23·0) by Day 43 (corresponding to a 540% change from baseline) that remained elevated during the trial in the fitusiran prophylaxis group (Figure S4B).

Overall, one (3%) participant in the fitusiran prophylaxis group was confirmed ADA positive at Day 29, at a low ADA titre of 50 (equivalent to minimum required dilution of the assay); this was transient, and the participant was negative at subsequent assessments in Month 3 and 8.

**Discussion**

In people with haemophilia A or B with inhibitors, once-monthly, 80 mg subcutaneous, prophylactic fitusiran resulted in a median ABR of zero, a high rate (65·8%) of participants with zero bleeds, and improvements in quality of life, thereby meeting the primary endpoint of the study. These results demonstrate the efficacy of fitusiran prophylaxis in providing consistent protection against bleeding in those with inhibitors, confirming the findings of previous Phase 1 and 2 studies, and suggest fitusiran may be the first drug to help address unmet needs for all people with haemophilia receiving prophylactic treatment.18,21

These findings were supported by substantially lower rates of other bleeding-related end points, including events of spontaneous bleeding and joint bleeding. Despite most participants presenting with target joints at baseline, only 29% of participants reported one or more treated target joint bleeds while receiving fitusiran prophylaxis. However, there was an imbalance between groups for the number of target joints at baseline; 25% of the BPA on-demand group had ≥3 target joints, while 25% of those in the fitusiran prophylaxis arm had ≥2 target joints. Combined with clinically meaningful improvements in HRQoL, particularly in aspects of physical health (painful swelling, joint pain, pain with movement, difficulty walking, time to get ready), these results suggest fitusiran prophylaxis may provide protection against recurrent joint bleeds and development of arthropathy, a leading cause of morbidity in haemophilia.2 Subgroup analyses also demonstrated that fitusiran prophylaxis offers protection against bleeding episodes in both people with haemophilia A or B with inhibitors. While the population of this study was predominantly Asian or Caucasian, taken with the results of previous studies of fitusiran18,21,22 it is not expected that there will be a difference in outcomes in those of Hispanic, African and Japanese descent. Analysis of pharmacodynamic endpoints confirmed that fitusiran achieved sustained reductions in antithrombin levels and increased peak thrombin generation by Day 29, consistent with its pharmacokinetics.15,16,18 Fitusiran demonstrated a consistent effect of antithrombin lowering (84–90% reduction from baseline) during the efficacy period. As previously reported, thrombin generation values associated with lowering in antithrombin levels >75% from baseline are consistent with those reported for mild haemophilia.15,23 These pharmacodynamic effects were consistent throughout the duration of the trial, establishing the potential of fitusiran to rebalance haemostasis, improve overall bleeding phenotype and provide consistent protection from bleeding.

The results of this trial complement those from the ATLAS-A/B trial of fitusiran prophylaxis in people with haemophilia A or B without inhibitors, which showed a statistically significant reduction in ABR with fitusiran prophylaxis compared with on‑demand factor replacement therapy.22 Overall, clinical trial results indicate that fitusiran prophylaxis is an efficacious, subcutaneously administered, prophylactic option for people with haemophilia, irrespective of haemophilia subtype or inhibitor status.

Fitusiran prophylaxis was generally well tolerated and reported TEAEs were consistent with previously identified risks of fitusiran including hepatoxicity, vascular thrombosis, cholecystitis, and symptomatic cholelithiasis. The occurrence of such TEAEs is comparable to safety data from other fitusiran studies.15,18,22,24,25 The underlying pathophysiology for the development of transaminase elevations, cholecystitis and cholelithiasis is unknown and these risks remain under investigation in ongoing trials. Risk mitigation strategies for hepatotoxicity are implemented in ongoing clinical studies and include transaminase monitoring and guidelines for the withholding and permanent discontinuation of fitusiran. Transaminase elevations have also been reported with approved siRNA therapies for other indications.26,27

Thrombotic events were reported in two participants in the fitusiran prophylaxis group; in one participant these events occurred in the setting of central venous access and associated complications, and in the other participant the event involved a suspected spinal vessel thrombosis, for which further evaluation was not feasible. There were no unique findings in antithrombin values or other coagulation parameters in these participants. Real-world variability between local assays was observed in this study; the acceptable limit of measurement for antithrombin local assays will be further investigated. Thrombosis is a potential adverse event of clinical interest for all haemostasis products.13,28 Thrombotic microangiopathy and thromboembolic events have been reported with concomitant use of prophylactic emicizumab and aPCC; thromboembolic events have also been reported with use of prophylactic emicizumab alone.2,29 Thrombotic events have similarly been reported with use of rFVIIa and aPCC alone,30 and in ongoing anti-tissue factor pathway inhibitor clinical programmes.2 Risk mitigation strategies, including a revised fitusiran dose and regimen aimed at enhancing the benefit/risk profile of fitusiran, are being evaluated in ongoing clinical studies.24,25 The potential for personalisation and optimisation of fitusiran therapy based on an individual’s response is currently under investigation.31

A limitation of this study was that the comparator group received on-demand (episodic) BPA therapy rather than prophylaxis. However, it should be noted that, at the time of design and planning of this study, emicizumab was not yet available and the only approved drugs for prophylaxis in people with haemophilia and inhibitors were aPCC (FEIBA, Takeda, Cambridge, MA) and rFVIIa (Novoseven, Bagsvaerd, Denmark), both of which are limited by variable efficacy, high treatment burden and considerable costs.9,10 Furthermore, in previous trials of new haemophilia therapies, it has been standard practice to use an on-demand group as the initial comparator rather than a prophylaxis group as it would be uncommon for people responding to prophylaxis to switch to an investigational agent. Though relative reduction in ABR may be expected in such a comparison, this study also employed zero bleed rates and number of people with ABR <3 as parameters to demonstrate high levels of haemostatic efficacy, both of which are the new benchmarks for efficacy assessment in haemophilia being the best predictors of long-term outcomes. While a comparison with prophylaxis is warranted and is part of the wider fitusiran ATLAS Phase 3 programme (NCT03549871; participants will continue their BPA/factor prophylaxis regimen for 6 months before receiving fitusiran; intra-individual comparison will be included), these parameters suggest that the haemostatic efficacy of fitusiran compares well with currently available haemostatic therapies. The open‑label nature of this study could also be considered as a limitation due to potential biases, particularly in patient-reported outcomes; however, this design was consistent with previous trials for haemophilia. Additionally, at the time of enrolment, participants were required to have had ≥6 bleeding episodes during the previous 6 months requiring episodic treatment with BPAs. Thus, eligible participants could potentially show a more substantial decrease in bleeding events over the course of the trial compared with ineligible participants with lower pre-trial bleeding rates. However, randomisation was stratified by the number of bleeds reported in the 6 months prior to enrolment to mitigate this potential bias (≤10 bleeds and >10 bleeds). The trial was also limited by the relatively small number of participants, particularly those with haemophilia B. However, this is reflective of the lower prevalence of haemophilia B.1 Furthermore, it should be noted that even though the sample size was small (e.g., 12 participants without previously subcutaneously administered haemostatic agent; nine received fitusiran as per the protocol making up nearly a quarter of the recruited patients on the investigational agent), this cohort is one of the largest treated successfully with a single drug described in the literature for this rare condition.

To conclude, in the ATLAS-INH study, once-monthly 80 mg subcutaneously administered fitusiran prophylaxis resulted in a low median ABR in people with haemophilia A or B with inhibitors, and meaningfully improved HRQoL, compared with people with haemophilia A or B receiving on-demand BPAs. Reported TEAEs were generally consistent with previously identified risks of fitusiran or what is anticipated in an adult and adolescent population with severe haemophilia. Fitusiran prophylaxis may demonstrate haemostatic efficacy in people with haemophilia A or B with inhibitors and therefore has the potential to improve the management of people with haemophilia.

**Contributions**

SA, KK, SK, BM, ZQ, SR, CR, AS, C-WY, and GY contributed to the design of the trial. SA, KK, BM, SR, CR, JS, AS, JSun, HT, RW, C-WY, and GY contributed to the data acquisition. SA, KK, SK, BM, SP, ZQ, SR, CR, AS, HT, RW, C-WY, and GY contributed to data analysis or interpretation of data.

All authors critically revised the manuscript for important intellectual content, approved the final version submitted, had full access to all the data, and agreed to be accountable for all aspects of the work.

S. Rangarajan and G. Young directly accessed and verified the underlying data reported in the manuscript.

**Declaration of interests**

G. Young has received grants from Genentech/Roche, Grifols, and Takeda; and speaking and consultancy fees from Apcintex, BioMarin, Genentech/Roche, Grifols, Hema Biologics/LFB, Novo Nordisk, Pfizer, Rani, Sanofi, Spark, Takeda, and UniQure. A. Srivastava has membership on advisory committees/grant review committees for Sanofi, Takeda, Novo Nordisk, Roche, Pfizer and Bayer Healthcare and received research funding from Roche, Novo Nordisk, Sanofi and Pfizer. K. Kavakli has received grants and consultancy fees from Novo Nordisk, Roche, and Takeda. C. Ross has nothing to disclose. J. Sathar is the president of the Malaysian Society of Patient Blood Management. C.W. You has nothing to disclose. H. Tran has received grants or honorarium from Sanofi, Takeda, Roche and CSL Behring. J. Sun has nothing to disclose. R. Wu has nothing to disclose. S. Poloskey, Z. Qui and S. Kichou are employees and equity holders in Sanofi. 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. S. Andersson is an employee and equity holder in Sanofi, and a member of the WEST advisory committee. S. Rangarajan has received consultancy fees from Reliance Life Sciences, grants for conference attendance from Takeda, and fees for attendance at advisory board meetings from Pfizer, Sanofi, Sigilon, and Takeda.

Data were presented in part at the 63rd American Society of Hematology (ASH) Annual Meeting and Exposition, December 11–14, 2021

**Data sharing**

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 anonymised 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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**Tables**

**Table 1. Demographics and baseline characteristics – Safety set**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **BPA on-demand(N=19)** | **Fitusiran 80 mgprophylaxis(N=41)†** | **All(N=60)** |
| **Age, years, median (IQR)** | 28·0 (23·0; 36·0) | 26·0 (17·0; 32·0) | 27·0 (19·5; 33·5) |
| **Weight, kg, mean (SD)** | 70·2 (17·6) | 66·1 (18·5) | 67·4 (18·2) |
| **BMI, kg/m2, mean (SD)** | 25·2 (5·8) | 23·5 (5·5) | 24·1 (5·6) |
| **Race, n (%)** |  |  |  |
| White | 6 (31·6) | 10 (24·4) | 16 (26·7) |
| Asian | 13 (68·4) | 29 (70·7) | 42 (70·0) |
| Other | 0 | 1 (2·4) | 1 (1·7) |
| Multiple | 0 | 1 (2·4) | 1 (1·7) |
| **Region, n (%)** |  |  |  |
| North America | 0 | 6 (14·6) | 6 (10·0) |
| Europe | 4 (21·1) | 7 (17·1) | 11 (18·3) |
| Asia | 13 (68·4) | 28 (68·3) | 41 (68·3) |
| Other | 2 (10·5) | 0 | 2 (3·3) |
| **Number of bleeding episodes in the last 6 months prior to screening, median (IQR)**  | 10·0 (7·0; 15·0)  | 10·0 (7·0; 16·0) | 10·0 (7·0; 16·0) |
| **Haemophilia type, n (%)** |  |  |  |
| Haemophilia A | 16 (84·2) | 32 (78·0) | 48 (80·0) |
| Haemophilia B | 3 (15·8) | 9 (22·0) | 12 (20·0) |
| **Inhibitor titre (highest historical inhibitor titre result\*), n (%)** |  |  |  |
|  |  |  |  |
| <5 BU/mL | 1 (5·3) | 6 (14·6) | 7 (11·7) |
| Haemophilia A | 1 (5·3) | 3 (7·3) | 4 (6·7) |
| Haemophilia B | 0 | 3 (7·3) | 3 (5·0) |
| ≥5 BU/mL | 18 (94·7) | 35 (85·4) | 53 (88·3) |
| Haemophilia A | 15 (78·9) | 29 (70·7) | 44 (73·3) |
| Haemophilia B | 3 (15·8) | 6 (14·6) | 9 (15·0) |
| **Number of target joints, median (IQR)** | 1·0 (0·0; 3·0) | 1.0 (0·0; 2·0) | 1·0 (0·0; 2·0) |

\*Bethesda assay

†Three participants in China were treated but not randomised; participants were enrolled into a China-specific non-randomised fitusiran group to receive subcutaneous fitusiran prophylaxis every 4 weeks, with initial starting dose of 50 mg.

One participant had a reported medical history of thrombosis associated with indwelling venous access. This participant did not experience a TEAESI of ‘suspected or confirmed thrombosis’ while enrolled in the study.
BMI, body mass index; BPA, bypassing agent; BU, Bethesda unit; IQR, interquartile range; ITT, intent-to-treat; rFVIIa, recombinant activated factor VII; SD, standard deviation

**Table 2. Primary and secondary efficacy outcomes – ITT set**

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **BPA on-demand (N=19)** | **Fitusiran 80 mg prophylaxis (N=38)** | **P-value** |
| **Primary efficacy outcome** |
| **All treated bleeds (efficacy period)**  |  |  |  |
| Mean ABR estimated by negative binomial model (95% CI)\* | 18·1 (10·6; 30·8) | 1·7 (1·0; 2·7) | p<0·0001 |
| Observed median ABR (IQR)  | 16·8 (6·7; 23·5) | 0·0 (0·0; 1·7) |  |
| Participants with zero bleeds, n (%)  | 1 (5·3) | 25 (65·8) |  |
| **Secondary efficacy outcomes** |
| **All treated bleeds (treatment period)** |  |  |  |
| Mean ABR estimated by negative binomial model (95% CI)\* | 18·8 (11·5; 30·7) | 2·0 (1·3; 3·1) | p<0·0001 |
| Observed median ABR (IQR)  | 16·3 (5·9; 23·8) | 0·0 (0·0; 1·6) |  |
| Participants with zero bleeds, n (%)  | 1 (5·3) | 20 (52·6) |  |
| **Treated spontaneous bleeds (efficacy period)**  |  |  |  |
| Mean AsBR estimated by negative binomial model (95% CI)\* | 15·7 (9·3, 26·5) | 0·9 (0·5, 1·6) | p<0·0001 |
| Observed median AsBR (IQR)  | 13·4 (3·4; 21·8) | 0·0 (0·0; 0·0) |  |
| Participants with zero bleeds, n (%)  | 2 (10·5) | 29 (76·3) |  |
| **Treated joint bleeds (efficacy period)**  |  |  |  |
| Mean AjBR estimated by negative binomial model (95% CI)\* | 13·8 (8·0; 23·8) | 1·3 (0·8; 2·3) | p<0·0001 |
| Observed median AjBR (IQR)  | 11·7 (3·4; 16·8) | 0·0 (0·0; 1·7) |  |
| Participants with zero bleeds, n (%)  | 1 (5·3) | 27 (71·1) |  |
| **Change in Haem-A-QoL20 transformed scores in the treatment period**  |  |  |  |
| Physical health score LS Mean (95% CI) | -1·9 (-10·3; 6·4) | -30·7 (-36·9; -24·4) | p<0·0001 |
| Total scoreLS mean (95% CI)  | -0·42 (-5·7; 4·8) | -15·3 (-19·3; -11·2) | p<0·0001 |

\*Negative binomial regression model includes treatment group, randomisation strata of number of bleeds in the 6 months prior to study (≤10, >10) as fixed effects, and the logarithm of the duration that each participant spent in the efficacy period matching the bleeding episode being analysed as an offset variable.
ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; AsBR, annualised spontaneous bleed rate; BPA, bypassing agent; CI, confidence interval; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; IQR, interquartile range; LS, least-squares.

**Table 3. Summary of treatment-emergent adverse events – Safety Set**

|  |  |  |
| --- | --- | --- |
| **n (%)** | **BPA on-demand(N=19)** | **Fitusiran 80 mgprophylaxis(N=41)\*** |
| **Participants with any TEAE** | 11 (57·9) | 38 (92·7) |
| **Most frequent (>5%) TEAEs in fitusiran group** |  |  |
| ALT increased | 0 | 13 (31·7) |
| AST increased | 0 | 8 (19·5) |
| Upper respiratory tract infection | 1 (5·3) | 6 (14·6) |
| Headache | 1 (5·3) | 6 (14·6) |
| Abdominal pain upper | 0 | 6 (14·6) |
| Gamma-glutamyl transferase increased | 0 | 6 (14·6) |
| Arthralgia  | 0 | 5 (12·2) |
| Blood alkaline phosphatase increased | 0 | 5 (12·2) |
| Transaminases increased  | 0 | 5 (12·2) |
| Influenza | 0 | 3 (7·3) |
| Nasopharyngitis | 0 | 3 (7·3) |
| Pyrexia | 0 | 3 (7·3) |
| Fibrin D dimer increased | 0 | 3 (7·3) |
| Prothrombin fragment 1·2 increased | 0 | 3 (7·3) |
| **Participants with any TEAE leading to study drug discontinuation†** | 0 | 1 (2·4) |
| **Participants with any TESAE‡** | 5 (26·3) | 7 (17·1) |
| **Participants with any TEAE leading to study withdrawal** | 0 | 0 |
| **Participants with any TEAE leading to death** | 0 | 0 |
| **Participants with any TEAESI**  |  |  |
| ALT or AST elevations >3× ULN | 0 | 10 (24·4) |
| Suspected or confirmed thromboembolic events  | 0 | 2 (4·9) |
| Severe or serious injection site reactions  | 0 | 0 |
| Systemic injection-associated reactions | 0 | 0 |

\*Three participants in China were treated but not randomised; participants were enrolled into a China-specific non-randomised fitusiran group to receive subcutaneous fitusiran prophylaxis every 4 weeks, with initial starting dose of 50 mg.

†In the fitusiran 80 mg prophylaxis group, one (2·4%) participant experienced two TEAEs that resulted in study drug discontinuation (spinal vascular disorder and thrombosis [suspected spinal vessel thrombosis]).
‡TESAEs were reported in seven participants in the fitusiran prophylaxis group (asymptomatic COVID-19, device-related infection, haematoma infection, vascular device infection, anaemia, spinal vascular disorder, subclavian vein thrombosis, thrombosis, biliary colic, acute cholecystitis, chronic cholecystitis, and haematuria [all n=1]). In the BPA on-demand group, TESAEs were reported in five participants (haemorrhage, haemarthrosis, muscle haemorrhage, haematuria, tooth fracture, and traumatic haemorrhage [all n=1]).
ALT, alanine transaminase; AST, aspartate aminotransferase; BPA, bypassing agent; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TEAESI, adverse event of special interest; ULN, upper limit of normal.

**Figures**

**Figure 1. Trial profile**



Diagnosis of severe haemophilia A or B was based on a central laboratory measurement or documented medical record evidence of FVIII level <1% or FIX level ≤2% at screening. \*Three participants in China were treated but not randomised; participants were enrolled into a China-specific non-randomised fitusiran group to receive subcutaneous fitusiran prophylaxis every 4 weeks, with initial starting dose of 50 mg.

BPA, bypassing agent; FIX, factor IX; FVIII, factor VIII

**Figure 2: Forest plot of estimated annualised bleeding rate ratio for treated bleeds in the efficacy period based on on-treatment strategy using negative binomial model by baseline factor - ITT Set**



For haemophilia B subgroup, negative binomial model convergence is questionable due to limited sample size. The efficacy period is from Day 29 to Day 246, or the last day of bleeding follow up, whichever is the earliest. The analysis is based on on-treatment strategy which excluded any bleeding events in the period of intercurrent events.

BPA, bypassing agent; ITT, intent-to-treat; NA, not available; RR, rate ratio.