STATISTICAL ANALYSIS PLAN

ATLAS-A/B: A Phase 3 study to evaluate the efficacy and safety of fitusiran in patients with hemophilia A or B, without inhibitory antibodies to Factor VIII or IX

Protocol Number:	ALN-AT3SC-004 (EFC14769)
Protocol Version and Date:	Original protocol: 19 May 2017 Amendment 1, 16 November 2017 Original protocol - United States: 19 May 2017 Amendment 1, 09 November 2017 Amendment 2, 27 June 2018
Name of Test Drug:	Fitusiran (ALN-AT3SC [SAR439774])
Phase:	Phase 3
Sponsor:	Genzyme Corporation 50 Binney Street Cambridge, MA 02142 USA Tel: +1 (617) 551-8200 Fax: +1 (617) 551-8101
Sanofi Statistician:	[redacted]
Analysis Plan Version and Date:	1, 06 March 2018 2, 06 August 2019 3, 22 July 2020

TABLE OF CONTENTS

Section **Page**

Section **Page**

ABBREVIATIONS

Abbreviation	Definition
ABR	annualized bleeding rate
AE	adverse event
ANCOVA	analysis of covariance
Anti-HCV Ab	anti–hepatitis C virus antibody
AT	antithrombin
ATC	anatomic therapeutic class
AUC	area under the concentration-time curve
BMI	body mass index
BPA	bypassing agent
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	Euro Quality of Life- 5 dimensions 5 levels
EU	European Union
HAL	haemophilia activities list
HJHS	hemophilia joint health score
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IRS	interactive response system
ISR	injection site reaction
IV	intravenous
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
PCSA	potentially clinically significant abnormalities

Abbreviation	Definition
MMRM	mixed model repeated measures
PD	pharmacodynamics
PedHAL	Pediatric HAL
PK	pharmacokinetics
Q1	first quartile
Q3	third quartile
QTc	Fridericia's corrected QT
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TP	treatment period
TSQM	treatment satisfaction questionnaire for medication
TSS	transformed scale score
VR	ventricular rate
WHO	World Health Organization

1 INTRODUCTION

Hemophilia A and hemophilia B are X-linked recessive inherited bleeding disorders, characterized by deficiency of coagulation factor (F) VIII or FIX, leading to a profound defect in the generation of thrombin leading to impaired hemostasis and increased risk of bleeding. Antithrombin (AT) is a natural anticoagulant expressed in the liver that plays a key role in inhibiting thrombin. Furthermore, AT acts as an inhibitor of FVIIa and FXa, which are typically at normal levels in patients with hemophilia A or B. Extensive preclinical in vitro and in vivo studies have described that a reduction of AT may be a potential safe and effective way to correct the generation of thrombin in both hemophilia A and B and control against microvascular and macrovascular traumatic bleeding episodes. Therefore, suppressing the production of AT is being investigated as a potential treatment for hemophilia.

Replacement with factor concentrates is the current standard of care for hemophilia patients without inhibitory antibodies to FVIII or FIX. While the current standard of care of factor substitution therapy, administered either episodically or as routine prophylaxis, is well established, safe, and efficacious, it is associated with high treatment burden due to requiring intravenous (IV) administration on a frequent schedule (2 to 3 times per week or more) to prophylactically maintain hemostasis. Factor concentrates also can be of limited availability in developing nations. In addition, patients receiving factor concentrates may develop an inhibitory antibody to factor, a result that carries a poorer prognosis and requires a change in treatment regimen to infusion with bypassing agents.

A fixed-dose subcutaneous therapy that can effectively and safely prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B, may reduce treatment burden, improve clinical outcomes and enhance quality of life.

Fitusiran is an investigational agent, comprising a synthetic siRNA covalently linked to a triantennary GalNAc ligand, designed to suppress liver production of AT as a strategy to rebalance the hemostatic system, thereby improving the generation of thrombin and hemostasis in individuals with hemophilia.

In the ATLAS-A/B study (ALN-AT3SC-004 [EFC14769]), fitusiran is evaluated as prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B without inhibitory antibodies to FVIII or FIX and who are being treated with on-demand factor concentrates. This statistical analysis plan (SAP) contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the clinical efficacy and safety of Study ALN-AT3SC-004 (EFC14769), original protocol amendment 1 (referred to as Global Protocol hereafter) dated 16 November 2016 and original protocol - United States amendment 1 (referred to as US Protocol hereafter), dated 09 November 2017, and protocol amendment 2 dated 27 June 2018. The contents of this SAP will apply to both versions of protocols amendment 1 and amendment 2 unless otherwise specified, where the methodologies for the two versions of protocol amendment 1 and amendment 2 are discussed separately. The data analyses will be used for the Clinical Study Report.

2 STUDY OVERVIEW

2.1 Synopsis of study design

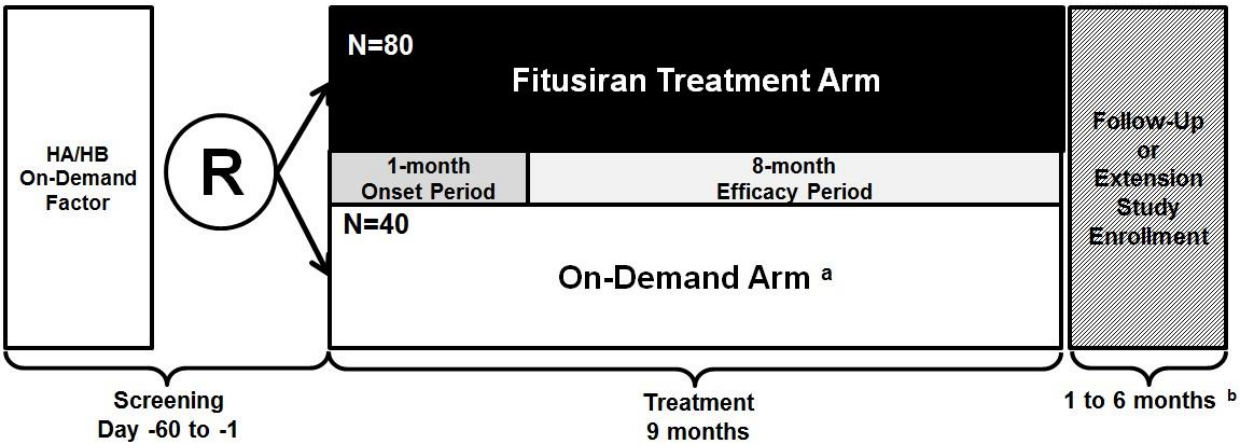
ALN-AT3SC-004 (EFC14769) is a multicenter, multinational, randomized, open-label Phase 3 study designed to evaluate the efficacy and safety of fitusiran in male patients aged ≥12 years with hemophilia A or B, without inhibitory antibodies to FVIII or FIX, who are not receiving prophylactic therapy.

Eligible patients will be randomized in a 2:1 ratio to:

- **Fitusiran treatment arm**: Fitusiran 80 mg administered SC as prophylaxis once monthly, with use of on-demand factor concentrates of breakthrough bleeding episodes
- **On-demand arm**: On-demand factor concentrates for treatment of breakthrough bleeding episodes

The study design schema is presented in Figure 1.

Figure 1 - Study design



Abbreviations: HA/HB = hemophilia Type A/hemophilia Type B; R = randomized

a On-demand factor concentrates as routinely prescribed by physician per local standard practice.

b Fitusiran treatment arm patients who do not enroll in the extension study: AT activity level will be monitored at monthly intervals following the final fitusiran dose until returning to activity levels return to approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

2.2 Randomization methodology

Patients are randomized 2:1 to the fitusiran treatment arm and the on-demand arm. Randomization is stratified by the number of bleeding episodes in the 6 months prior to Screening (≤10 vs >10) and hemophilia type (hemophilia A or B).

2.3 Unblinding

Although this is an open-label study, Sponsor personnel will not have access to efficacy summaries by treatment arms prior to conducting the formal reporting of the study.

2.4 Study procedures

The schedule of assessments is described in the study protocol (Table 1).

2.5 Modifications to the statistical section of the protocol

This section summarizes major changes to the protocol statistical section. These changes are made before the first patient is randomized. The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the protocol statistical section.

The first patient was enrolled on March 1, 2018. There are no planned interim analyses.

Protocol Amendment statistical changes

Amendment number	Date approved	Rationale	Description of statistical changes
1	16-Nov-2017	Revised the definition of efficacy period based on on-treatment strategy for the primary analysis of primary endpoint in assessing the primary objective of the study (ICH E9 (R1)).	Efficacy period (Day 29 to Day 246) defined in the protocol is changed to (Day 29, earliest of (Day 246, or the last day of bleeding follow up) excluding the period for each intercurrent event.
1	16-Nov-2017	Added exclusion periods due to fitusiran treatment discontinuation, major or minor surgery, prophylactic treatment with emicizumab or factor since including bleeding events in these periods in the primary analysis would bias fitusiran treatment effect.	Exclusion period for each intercurrent event is described in details in Section 6.3

2.6 Statistical modifications made in the statistical analysis plan

This section summarizes major changes in statistical analysis features made in approved SAP versions from statistical considerations in protocol or previous SAP versions, with emphasis on changes after study start (after the first patient was enrolled). These changes are made before database lock.

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	06-Aug-2019	[redacted]	The sensitivity analysis to include all bleeding events was added in Section 6.3.1.2.
2	06-Aug-2019		The summary statistics for number of patients who lost-to-follow-up and who had each intercurrent event is added in Section 6.3
2	06-Aug-2019		A summary of missing data pattern by treatment arm for patient who doesn't have bleeding data after Day 28 is added in Section 6.3.1.1. A sensitivity analysis based on imputed bleeding data in the efficacy period using multiple imputation (MI) method is added in Section 6.3.1.1.
2	06-Aug-2019		A sensitivity analysis based on zero-inflated negative binomial model is added in Section 6.3.1.2.

SAP version number	Date approved	Rationale	Description of statistical changes
2	06-Aug-2019	To be aligned with protocol amendment 02	The secondary endpoint 'Change in Haem-A-QOL scores in the treatment period' is changed to 'Change in Haem-A-QOL physical health score and total score in the treatment period' in Section 3.2.1 and Section 5.7. The analysis of physical health score is added in Section 6.3.2.4.
2	06-Aug-2019	To clarify how to calculate domain score when item scores are missing for Haem-A-QOL and Haemo-QOL assessments.	The method to calculate domain score when item scores are missing for Haem-A-QOL and Haemo-QOL assessments is added in Section 8.1.
2	06-Aug-2019	[redacted]	For the change in Haem-A-QOL physical health score and total score, the examination of normality assumption based on ANCOVA model and sensitivity analysis based on the non-parametric Wilcoxon-Mann-Whitney test are added in Section 6.3.2.4. In addition, a sensitivity analysis to handle missing assessment is also specified in Section 6.3.2.4.
2	06-Aug-2019	To clarify ANCOVA analysis for Haemo-QOL for small sample size	Clarify that only the descriptive statistics will be provided if ANCOVA model does not converge due to small sample size in Section 6.3.3.4.
2	06-Aug-2019	[redacted]	An exploratory analysis to evaluate the association between the change in Haem-A-QOL physical health and total scores and ABR and concomitant pain medication use is added in Section 6.3.2.4.
2	06-Aug-2019		An exploratory analysis of bleeding symptoms is added in Section 6.3.1.3.

SAP version number	Date approved	Rationale	Description of statistical changes
2	06-Aug-2019	To be aligned with protocol amendment 02	"Adverse events of clinical interest (AECI)" is changed to "Adverse events of special interest (AESI)" throughout. Systemic injection associated reactions (IARs) is added to the criteria of AESI in Section 6.6.2.
2	06-Aug-2019	To be aligned with Sanofi's standard analysis for Lab and vital sign.	Lab analysis by NCI CTCAE grade and shift tables are removed in Section 6.6.3 since PCSA analysis will be performed. Vital sign by PCSA is added in Section 6.6.4.
2	06-Aug-2019	To align the analysis reference date with Day 1 visit date when baseline assessments are done, fitusiran first dose is given, and eDiary is distributed to the patients.	The reference date is changed from randomization to Day 1 visit date in Section 5.2. The baseline definition is changed from randomization to Day 1 visit in Section 5.5.
2	06-Aug-2019	To define geographic regions	Geographic regions are defined in Section 5.11.
2	06-Aug-2019	AT lowering capacity of fitusiran is expected to achieve therapeutic target range at the end of the onset period for the 80 mg fixed dose. ABR by AT lowering analysis does not add much value to the ABR comparison between onset period and efficacy period.	The analysis of ABR by AT lowering in Section 6.4.3 is removed.
2	06-Aug-2019[1]	In addition to the primary analysis of ABR for the recurrence of events, it is also of interest to compare the time to first bleeding event between on-demand treatment and fitusiran prophylaxis treatment.	The exploratory analysis of time to first bleeding event is added in Section 6.3.1.3

SAP version number	Date approved	Rationale	Description of statistical changes
2	06-Aug-2019	To include untreated bleed in the bleeding episode definition	The untreated bleed is included in the bleeding episode definition in Section 6.3.
3	This version	To update Per-protocol Analysis Set definition	The detail deviations are included in the Per-protocol analysis set definition in Section 4.
3	This version	To define Covid-19 Unaffected Set	Covid-19 Unaffected Set is defined in Section 4.
3	This version	To clarify baseline definition for fitusiran group	For fitusiran group only, baseline definition is changed from Day 1 to first dose date in Section 5.5
3	This version	To clarify the multiplicity adjustment for Haem-A-QOL endpoints	For the two Haem-A-QOL scores (physical health score and total score), physical score will be tested first followed by total score.
3	This version	To add patient disposition category for Covid-19 impact summary	Patients discontinue the treatment due to Covid-19 and patient discontinue the study due to Covid-19 are added in Section 6.1
3	This version	Due to the exclusion criteria 6, the analysis of fibroscan/fibrotest result at baseline against worst post-baseline ALT elevation is not necessary	The related analysis is removed in Section 6.6.3
3	This version	To add the efficacy analyses for ABR endpoints due to Covid-19 impact	For ABR, the sensitivity analyses on Covid-19 unaffected set is added in Section 6.3. In addition, a sensitivity analysis to exclude the bleeds during the period of missing at least 2 consecutive doses due to Covid-19 event is added in Section 6.3.

SAP version number	Date approved	Rationale	Description of statistical changes
3	This version	To update the analyses for Haem-A-QoL due to Covid-19 impact	For sensitivity analyses, ANCOVA model will be ran on Covid-19 unaffected set, on the set excluding data collected with Covid-19 impact, on the set of patients whose responses level to EQ-5D dimensions “anxiety/depression” is no change or improved from baseline.
3	This version	To add the sensitivity analysis for Haem-A-QoL baseline assessments	For sensitivity analyses, the same analysis as main but excluding values of those who completed Haem-A-QOL at baseline on the same day but after first dose of fitusiran.
3	This version	To add the AE summary related to COVID-19 infection	AE potentially consistent with COVID-19 will be summarized by SOC and PT and list will also be provided. The search term list is added in the Appendix 8.2
3	This version	To add AE summary by hemophilia type	By hemophilia type summary is added to key AE tables.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective

- To evaluate the efficacy of fitusiran compared to on-demand treatment with factor concentrates, as determined by the frequency of bleeding episodes.

3.1.2 Secondary objectives

- To evaluate the efficacy of fitusiran compared to on-demand treatment with factor concentrates, as determined by:
  - The frequency of spontaneous bleeding episodes
  - The frequency of joint bleeding episodes
  - Health-related quality of life (HRQOL) in patients ≥17 years of age
- To determine the frequency of bleeding episodes during the onset period
- To determine the safety and tolerability of fitusiran

3.1.3 Exploratory objectives

- To evaluate the effects of fitusiran as compared to on-demand treatment with factor concentrates on the following patient reported outcomes:
  - Patient satisfaction with treatment
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To determine the pharmacodynamic (PD) effect, pharmacokinetics (PK), and immunogenicity of fitusiran
- To evaluate the effects of fitusiran as compared to on-demand treatment with factor concentrates on the total weight-adjusted consumption of factor concentrates
- To evaluate the effects of fitusiran as compared to on-demand treatment with factor concentrates on joint status
- To evaluate the effects of fitusiran as compared to on-demand treatment with factor concentrates on patient resource use

3.2 Endpoints

3.2.1 Efficacy endpoints

Primary and secondary endpoints for Global and US protocols are in the table below

	Global Protocol	US Protocol
Primary	Annualized Bleeding Rate (ABR) in the efficacy period	ABR in the treatment period
Secondary	ABR in the treatment period	ABR in the efficacy period
	Annualized spontaneous bleeding rate in the efficacy period	
	Annualized joint bleeding rate in the efficacy period	
	Change in Haem-A-QOL physical health score and total score in the treatment period	
	ABR in the onset period	

Exploratory Efficacy Endpoints

- Change in the following in the treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Haemophilia Activities List (HAL) score
  - Paediatric HAL (pedHAL) score
  - EQ-5D-5L index value and visual analogue scale (VAS) score
  - Haemo-QOL score
  - Hemophilia Joint Health Score (HJHS)
- Number of target joint bleeding episodes
- Annualized weight-adjusted use of factor concentrates
- Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

3.2.2 Pharmacokinetic endpoints

- All patients
  - Plasma PK parameters will be estimated using a population PK approach. The population PK analysis will be described in a separate population PK analysis plan.
- Patients from East Asian sites only

- In addition to population PK analysis, plasma PK parameters for the patients from the East Asian sites only will also be estimated using non-compartmental analysis. The plasma PK parameters will include, but may not be limited to:
  - Maximum plasma concentration (Cmax)
  - Time to maximum plasma concentration (tmax)
  - Elimination half-life ($t_{½\beta}$)
  - Area under the concentration-time curve (AUC)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V/F)
- Fitusiran levels in 0-24 h urine will be reported as cumulative amount of drug excreted unchanged in urine (Ae).
- Additional PK parameters for plasma and/or urine may also be calculated, if considered appropriate.

3.2.3 Pharmacodynamic endpoints

- AT activity level over time
- Thrombin generation over time

3.2.4 Safety endpoints

- Adverse events
- Concomitant medications
- Clinical laboratory parameters
- Vital signs
- 12-lead ECGs
- Physical examinations

3.2.5 Anti-drug antibody endpoints

- Incidence and titer of antidrug antibodies to fitusiran in the fitusiran treatment arm

4 PATIENT POPULATION

The populations (analysis sets) are defined as follows:

- Intent-to-treat (ITT) Analysis Set: All randomized patients. All by-treatment analyses based on the ITT analysis set will be performed according to the randomized treatment arm. Efficacy Analyses will be conducted using the ITT Analysis Set unless otherwise specified.
- Safety Analysis Set: All patients who received at least 1 dose of study drug or were randomized to on-demand arm. All by-treatment analyses based on the safety analysis set will be according to the actual treatment received. Safety Analyses will be conducted using the Safety Analysis Set unless otherwise specified.
- Per-protocol Analysis Set: All patients in the ITT set who do not have protocol deviations in the following categories:
  - Failure to meet key eligibility criteria, which will be identified prior to database lock.
  - Actual treatment differs from IRS treatment assignment
  - Prophylactic use of factor
  - Other protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the bleeding data.

  The major or critical detail deviations included are as follows.
  - The subject is not male and/or is younger than 12 years, but the subject was randomized.
  - The subject does not have severe hemophilia A or B without inhibitors as evidence by:
    - A laboratory FVIII level <1 % or FIX level ≤2 % at Screening.
    - On-demand use of factor concentrate to manage bleeding episodes for at least the last 6 months prior to Screening, or meeting one of the following criteria:
      - Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening,
      - No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to screening
      - No history of immune tolerance induction therapy within the last 3 years prior to Screening,

    but the subject was randomized.
  - The subject does not have a minimum of 6 bleeding episodes requiring factor concentrate treatment within the last 6 months prior to Screening, but the subject was randomized.
  - The subject has known co-existing bleeding disorders other than hemophilia A or B, but the subject was randomized.
  - The subject currently uses factor concentrates as regularly administered prophylaxis designed to prevent spontaneous bleeding episodes, but subject was randomized.

- The subject's actual treatment differs from randomization group.
- Site provided incorrect stratification data in IRT for patient's randomization.
- The subject initiated use of factor concentrates or bypassing agents as prophylaxis for bleeding episode prevention, including doses related to anticipated hemostatic challenges such as physical activity, during the treatment period but the study drug was not discontinued.

- PK Analysis Set: All patients who receive at least 1 dose of study drug and have evaluable PK data contributing to the estimation of PK parameters.
- Operative Procedure Analysis Set: All patients who received at least 1 dose of study drug or were randomized to on-demand arm and underwent at least 1 operative procedure during the study.
- Covid-19 Unaffected Set: All patients who had no major or critical protocol deviations due to Covid-19 at any visits up to end of study (Month 9).

5 GENERAL STATISTICAL METHODS

5.1 Sample size justification

Assuming a mean ABR of 18 with standard deviation (SD) = 14 in the on-demand arm (patients randomized to receive on-demand factor concentrates) and a mean ABR of no more than 4 with SD = 6 in the fitusiran treatment arm (patients randomized to receive fitusiran) in either the efficacy period or treatment period, with a sample size of 32 evaluable patients in on-demand arm and approximately 64 evaluable patients in the fitusiran treatment arm, it is projected that the study will have greater than 90% power for testing treatment difference in mean ABRs. This power estimation was based on negative binomial regression model with a 2-sided Type I error rate of 0.05.

The planned sample size is 120 randomized patients assuming a 20% drop-out rate.

5.2 General methods

All data listings that contain an evaluation date will contain a study day relative to the day of Day 1 visit when baseline assessments are performed and fitusiran first dose is given, which is designated as Day 1. The Day 1 visit date should coincide with randomization date but could occur within 3 days after the randomization. If the fitusiran first dose is given after Day 1 visit, a study day will be calculated relative to the day of first dose. Study days will be calculated as evaluation date – Day 1 visit date (or first dose date) + 1 and pre-Day 1 visit days will be calculated as evaluation date – Day 1 visit date (or first dose date). For example, the day prior to Day 1 visit will be Day –1 and the day after Day 1 visit will be Day 2, etc. There will be no Study Day 0.

Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using the number of patients (n), mean, SD, median, interquartile range (Q1, Q3), minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The other statistics will be reported to 1 greater decimal place, and the SD will be reported to 2 additional decimal places. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

5.3 Computing environment

All statistical analyses will be performed using SAS statistical software Version 9.4 (or later), unless otherwise noted.

5.4 Timing of analyses

The primary efficacy and safety analyses will be performed after all patients have either completed the 9-month treatment period or withdrawn from the study.

No interim analysis is planned for this study.

5.5 Baseline definitions

Unless noted otherwise, baseline for on demand group will be defined as the last non-missing value on or before Day 1 visit. Baseline for fitusiran group is defined as the last non-missing value before 1st dose of fitusiran or the last non-missing value on or before randomization date for patients who were randomized but never exposed to fitusiran.

ECG measurements are taken in triplicate. For the on demand group, the average of the first triplicate readings on or before Day 1 visit or on screening visit will be used as baseline. For fitusiran group, the average of the last triplicate readings before 1st dose is used as baseline.

For questionnaire assessments, the last non-missing value on or before Day 1 visit will be used as baseline. For fitusiran patients, the last non-missing value on or before date of 1st dose of fitusiran or the last non-missing value on or before randomization date for patients who were randomized but never exposed to fitusiran will be used as baseline.

5.6 Randomization stratification factors

Randomization for this study is stratified by the number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10) and hemophilia type (hemophilia A or B).

5.7 Multiple comparisons/multiplicity

To control for the familywise error rate at 0.05 level in the testing of primary and selected secondary endpoints, a hierarchical testing approach will be used. The endpoints will be tested in the following order:

Global protocol	US protocol	2-Sided alpha
1. ABR in the efficacy period	1. ABR in the treatment period	0.05
2. ABR in the treatment period	2. ABR in the efficacy period	0.05
3. Annualized spontaneous bleeding rate in the efficacy period		0.05
4. Annualized joint bleeding rate in the efficacy period		0.05
5. Change in Haem-A-QOL physical health score and total score in the treatment period		0.05

If testing of any of the endpoints is not statistically significant, formal testing of subsequent endpoints will stop and the null hypothesis for subsequent tests will not be rejected. For endpoint 5, change in Haem-A-QOL physical health score in the treatment period will be tested first followed by change in Haem-A-QOL total score in the treatment period. The testing of the secondary endpoint ABR in the onset period will not be included in this hierarchical testing procedure.

5.8 Missing data

On the eDiary device, it is not possible to leave questions unanswered or to enter partial data.

In the bleeding diary pages of the CRF, it is possible to have missing time of a treatment or a bleed. In that case, it is assumed that the bleeds and treatments with missing time occurred at 12:00 am.

Additional details will be included in the sections describing the analyses corresponding to each endpoint.

5.9 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the clinical protocol. Protocol deviations will be classified by medical review prior to primary analysis and critical and major protocol deviations will be identified. A critical protocol deviation is a deviation that adversely affects data integrity, patient's right and safety. A major protocol deviation is a deviation that potentially can affect data integrity, patient's right and safety. All critical and major deviations related to trial inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be described in the clinical study report.

The Sponsor or designee is responsible for producing the final protocol deviation file. This file will include a description of each protocol deviation and whether or not this deviation is classified as a critical or major protocol deviation. This file will be finalized prior to performing the primary analysis.

5.10 Derived analysis visit windows

A scheduled measurement will be used if it is available. Otherwise, derived analysis visit window will apply to data collected on scheduled visits and early withdrawal visits (such as PD, clinical laboratory parameter, vital signs, etc) to re-allocate a post-baseline unscheduled measurement to a scheduled measurement, except for PK and ECG, using Study Day (defined in Section 5.2), according to the following allocation table:

Analysis visit label	Target study day	Derived Window in study days	
		lower bound	upper bound
Baseline	1	-INF	1
Day 15	15	2	21
Day 29	29	22	35
Day 43	43	36	49
Day 57	57	50	70
Day 85	85	71	98
Day 113	113	99	126
Day 141	141	127	154
Day 169	169	155	182
Day 197	197	183	210
Day 225	225	211	238
Day 253	253	≥239	Actual EOS/ET visit date if EOS/ET visit is ≥239
Day 281	28 days after EOS/ET for patients who complete the AT F/U visits	1 day after EOS/ET visit	999
Endpoint	Last non-missing post-baseline assessment on or before EOS/ET visit		

If more than one data point is within a window the visit closest to the target study day will be selected. If there are multiple visits with the same distance from the scheduled visit day, the last value will be selected.

5.11 Geographic region

Geographic region will consist of the following categories: North America, Europe, Asia, Other. The countries in each region are the following:

- North America (United States)
- Europe (Bulgaria, Denmark, France, Germany, Hungary, Italy, Portugal, Spain, Turkey, Ukraine, United Kingdom)
- Asia (China, India, Japan, Korea, Malaysia, Taiwan)
- Other (Australia, Israel, South Africa)

6 STATISTICAL ANALYSES

6.1 Patient disposition

Patient disposition will be tabulated for the following categories:

- patients screened
- patients screen failed
- patients randomized
- patients in each analysis population
- patients treated (fitusiran arm only)
- patients who completed the study treatment (9-month treatment period, fitusiran arm only)
- patients who discontinued study drug and primary reasons for study drug discontinuation (fitusiran arm only)
- patients who discontinued study drug and primary reasons for study drug discontinuation due to Covid-19 (fitusiran arm only)
- patients who completed the study
- patients who withdrew prior to completing the study but completed Month 9 visit
- patients who withdrew prior to completing the study and primary reasons for withdrawal.
- Patients who withdrew prior to completing the study and primary reasons for withdrawal due to Covid-19

Patient disposition will be presented by randomized treatment arm and overall, as applicable.

Patients randomized by country, site and randomization stratification factor stratum will be summarized by randomized treatment arm and overall.

6.2 Demographics and baseline characteristics

Demographic and baseline characteristics, baseline disease characteristics, and medical history information will be summarized by treatment arm and overall for the ITT analysis set, safety analysis set (if different from the ITT analysis set), and the per-protocol analysis set. No formal statistical comparisons will be performed.

Age, height, weight, and body mass index (BMI) will be summarized using descriptive statistics. Age group, sex, race, ethnicity, and region will be summarized by presenting the numbers and percentages of patients in each category.

The following baseline disease characteristics will be summarized: age at diagnosis, time from diagnosis to randomization, hemophilia type, and number of bleeding episodes in the last 6 months prior to the study.

6.3 Efficacy analysis

Bleeding Episode Definitions

The primary source of bleeding data will be the eDiary. Additional bleeding data may be captured from the bleeding diary pages of the CRF, if not reported in the eDiary. Any other sources of bleeding data will be discussed in the CSR.

A bleeding episode is defined as any occurrence of hemorrhage that may require administration of BPA or factor. A traumatic bleeding episode is one that is caused by a known injury or trauma. Bleeding episodes sustained during sports and recreation will be counted as traumatic bleeding episodes.

Bleeding or any symptoms of bleeding at the same location that occur within 72 hours of the last injection used to treat a bleed or 72 hours after an untreated bleed at that location will be considered a part of the original bleeding event, and will count as one bleeding episode. Any bleeding symptoms that begin more than 72 hours from the last injection used to treat a bleed or 72 hours after an untreated bleed at that location will constitute a new bleeding event.

Traumatic bleeds that occur in different locations simultaneously (same date/time) in the same patient will be considered as one bleeding episode. Spontaneous bleeds that occur simultaneously (same date/time) in different locations in the same patient will be considered as separate bleeds.

Efficacy analysis will focus on observed data as collected, unless otherwise specified. Patients who discontinue study drug during the study will be strongly encouraged to continue study participation including the recording of bleeding episode data. Only bleeding episodes that are treated will be include in the primary analysis of endpoints evaluating bleeding.

Efficacy Period and Treatment Period

In the protocol, for the purpose of ABR calculation, fitusiran "Onset Period", "Efficacy Period" and "Treatment Period" are defined. The Onset Period is defined as the first 28 days after the first dose of fitusiran, during which the AT lowering capacity of fitusiran is increasing but has not yet reached therapeutic levels. The Efficacy Period is defined as starting on Day 29 when the AT lowering capacity of fitusiran has achieved therapeutic target range. The Treatment Period is defined as the onset period plus the efficacy period. The window for each period is summarized in the table below. The corresponding window is applied to on-demand arm for analysis purpose.

	Fitusiran arm/On-demand arm
Onset Period	Day 1 to the earlier of Day 28 and the last day of bleeding follow up
Efficacy Period	Day 29 to the earliest of (Day 246, or the last day of bleeding follow up)

Treatment Period	Onset period plus the efficacy period

The last day of bleeding follow up is defined as the deactivation date captured in eDiary.

If a patient does not have bleeding episode data collected after Day 28 due to early study discontinuation, the efficacy period will be from Day 1 to the earlier of date of study discontinuation and the last day of bleeding follow up.

The onset period, efficacy period and treatment period also exclude the period of following intercurrent events to avoid confounding of treatment effect for the primary efficacy analysis based on On-Treatment Strategy.

- After one month (28 days) from fitusiran treatment discontinuation in the fitusiran efficacy period. Excluding bleeding data after one month from fitusiran treatment discontinuation is considered reasonable and adequate considering that fitusiran is dosed monthly and EOS is one month after last dose of fitusiran.
- Perioperative period of major surgery. The perioperative period is defined as the day of the surgery through the final day on which supplemental hemostatic or antithrombotic treatments are administered as part of the perioperative treatment plan.
- Period of minor surgery is defined as the Perioperative period of surgery above or to 72 hours from the end of surgery, whichever is later.
- Period of Antithrombin treatment is defined as the first day of antithrombin treatment through the final day on which antithrombin or other anticoagulant therapies are administered plus 5 half-lives of that specific product.
- After prophylactic treatment with emicizumab, BPA or factor.

The summary statistics for number of patients who are lost-to-follow-up and who had each intercurrent event will be provided.

6.3.1 Primary endpoint

6.3.1.1 Primary efficacy analysis based on on-treatment strategy

The primary objective of this study is to assess the efficacy of fitusiran on prevention or reduction of bleeding. Including bleeding events in the period of intercurrent events such as use of prophylactic medication or surgery or after fitusiran treatment discontinuation could significantly bias fitusiran effect and make the comparisons difficult to interpret. The on-treatment strategy is considered of greatest relevance in assessing this primary objective (ICH E9 (R1), 2018). The primary efficacy analysis population will be the ITT Analysis Set as defined in Section 4.

Global Protocol

The number of bleeding episodes will be annualized for each patient using the following formula:

$$\text{Annualized bleeding rate (ABR)} = \frac{\text{total number of bleeding episodes}}{\text{total number of days in the respective period}} \times 365.25.$$

The primary efficacy analysis will include all bleeding episodes occurring in the efficacy period.

Let λ_F represent the ABR for fitusiran arm and λ_O represent the ABR for on-demand arm. The null and alternative hypotheses of the primary analysis, respectively, can be written as follows:

$$H_o: \frac{\lambda_F}{\lambda_O} = 1 \qquad H_A: \frac{\lambda_F}{\lambda_O} \neq 1$$

An estimated ABR ratio $\frac{\lambda_F}{\lambda_O} < 1$ and two-sided p-value < 0.05 from the significance test will lead to the rejection of H_0 in favor of H_A; it will be concluded that prophylactic use of fitusiran reduces the frequency of bleeding episodes compared to the on-demand therapy.

The ABR ratio λ_F/λ_O will be estimated using a negative binomial model:

$$\log(\text{number of bleeding episodes}) = \beta_0 + \beta_1 \cdot Treatment + \beta_2 \cdot ABR_0 + \beta_3 \cdot Hemophilia\ type + \log(duration).$$

The number of bleeding episodes is the response variable. The treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry (ABR_0) and randomization strata of hemophilia type are treated as fixed effects. The logarithm of the duration (in years) that each patient spends in the efficacy period matching the bleeding episode data being analyzed is included as an offset variable to account for unequal follow-up time due to early withdrawal, surgery, etc.

The ratio of ABR in the fitusiran treatment arm to the on-demand arm, its 95% CI, and the p-value for the hypothesis above will be presented. The estimated mean ABRs in the 2 treatment arms along with their 95% CIs from the model will be presented. In addition, median and interquartile range (Q1, Q3) for the observed ABR will be summarized descriptively by treatment arm.

For patients who don't have bleeding episode data collected after Day 28 (eg, due to early study discontinuation), the available bleeding episode data starting from Day 1 will be used in the primary analysis. A summary of missing data pattern by treatment arm will be provided. To evaluate the impact from this single imputation, a sensitivity analysis will be performed based on imputed bleeding data in the efficacy period using multiple imputation (MI) method as described in Section 6.3.1.2 below.

US Protocol

The number of bleeding episodes will be annualized for each patient using the following formula:

$$\text{Annualized bleeding rate (ABR)} = \frac{\text{total number of bleeding episodes}}{\text{total number of days in the respective period}} \times 365.25.$$

The primary efficacy analysis will include all bleeding episodes occurring in the treatment period.

Let λ_F represent the ABR for fitusiran arm and λ_O represent the ABR for on-demand arm. The null and alternative hypotheses of the primary analysis, respectively, can be written as follows:

$$H_o: \frac{\lambda_F}{\lambda_O} = 1 \qquad H_A: \frac{\lambda_F}{\lambda_O} \neq 1$$

An estimated ABR ratio $\frac{\lambda_F}{\lambda_O} < 1$ and two-sided p-value < 0.05 from the significance test will lead to the rejection of H_0 in favor of H_A; it will be concluded that prophylactic use of fitusiran reduces the frequency of bleeding episodes compared to the on-demand therapy.

The ABR ratio λ_F/λ_O will be estimated using a negative binomial model:

$$\log(\text{number of bleeding episodes}) = \beta_0 + \beta_1 \cdot Treatment + \beta_2 \cdot ABR_0 + \beta_3 \cdot Hemophilia\ type + \log(duration).$$

The number of bleeding episodes is the response variable. The treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry (ABR_0) and randomization strata of hemophilia type are treated as fixed effects. The logarithm of the duration (in years) that each patient spends in the treatment period matching the bleeding episode data being analyzed will be included as an offset variable to account for unequal follow-up time due to early withdrawal, surgery, or etc.

The ratio of ABR in the fitusiran treatment arm to the on-demand arm, its 95% CI, and the p-value for the hypothesis above will be presented. The estimated mean ABRs in the 2 treatment arms along with their 95% CIs from the model will be presented. In addition, median and interquartile range (Q1, Q3) for the observed ABR will be summarized descriptively by treatment arm.

Given that the primary analysis is based on on-treatment strategy, primary and secondary bleeding-related data during the efficacy and treatment periods are expected to be complete. No sensitivity analysis about the missing data mechanism will be performed.

6.3.1.2 Efficacy analysis based on treatment policy strategy

A supportive efficacy analysis will be performed by including all bleeding episodes collected through the end of the study, regardless of any premature treatment discontinuation, excluding only events due to major or minor surgeries based on ITT Analysis Set as in the primary analysis. The same negative binomial model as in the primary analysis will be used. It assesses the benefits of the fitusiran treatment policy strategy relative to on-demand treatment.

A sensitivity analysis to the above treatment policy analysis will be performed by including all bleeding events (ie, not excluding bleeding events due to surgeries).

Missing data sensitivity analyses using controlled imputation

The above efficacy analysis assumes the uncollected bleeding events after study discontinuation are missing at random (MAR). Sensitivity analyses will be performed to assess the robustness of this treatment policy analysis by imputing the missing data based on different missing data mechanism. The missing data will be imputed using multiple imputation (MI) methods for recurrent event data based on pattern mixture models (Keene et al, 2014) to assess the impact of different assumptions about the statistical behavior of post-withdrawal outcomes. The post-withdrawal part of each pattern-specific distribution will be modelled using MAR and Copy Reference (CR) approaches. The MI will be carried out in the following steps:

1. Fit a Bayesian negative binomial model with a non-informative prior to the observed data with same set of covariates as in the primary analysis and obtain the posterior distributions of the event rate for both treatment arms.

2. Draw 100 independent samples from the conditional distribution of missing counts given the observed count and period of each patient with missing data based on different post-withdrawal imputation models, described below, for the treatment arms. The conditional distribution is also negative binomial.

3. The observed counts and imputed counts for each patient with missing data are summed.

4. Each 100 imputed datasets will then be analyzed using the same negative binomial regression model. Estimates from the model such as least squares means and standard errors are then combined across imputation datasets using Rubin's formula, as implemented in the MIANALYZE procedure. These and their 95% confidence interval limits are then exponentiated to obtain the estimate of ABR for each arm and the estimate of the ABR ratio and associated p-value.

MAR and CR approaches are described below:

1. Missing at Random (MAR) Approach: Post-withdrawal missing bleeding events in both fitusiran arm and on-demand arm will be imputed under the randomized arm.

2. Copy Reference (CR) Approach: The expected ABR for a patient in the fitusiran arm both pre- and post-withdrawal is assumed to be the same as that in the on-demand arm. This accounts for a gradual loss of fitusiran effectiveness post-withdrawal. If a patient in fitusiran arm has more events pre-withdrawal than expected if this patient had been in the on-demand arm, then this 'positive residual' will feed through into a higher than expected ABR in the post-withdrawal period. This is because this patient's earlier observed ABR higher than mean event rate suggests the patient has a higher propensity to have events. Post-withdrawal data in the on-demand arm are imputed under randomized arm (assumes MAR approach).

The efficacy analysis based on treatment policy strategy may serve as sensitivity analyses for the primary efficacy analysis based on on-treatment strategy. It is important to note that the estimand based on on-treatment strategy (the primary efficacy analysis) is considered most relevant and applicable in assessing and reporting clinical efficacy of fitusiran vs. on demand treatment.

Per-protocol analysis

Efficacy analysis will be repeated on the per-protocol analysis set as defined in Section 4.

Zero-inflated negative binomial model

To address the concern of potential excessive zero bleeding events, the above on-treatment and treatment policy efficacy analyses will be repeated using the zero-inflated negative binomial model and the results will be presented if model converges.

Covid-19 related sensitivity analysis

To address the impact of Covid-19, the above on-treatment and treatment policy efficacy analyses in the treatment and efficacy periods will be repeated on the Covid-19 unaffected set as defined in Section 4. In addition, a sensitivity analysis based on on-treatment strategy will be performed excluding the bleeding events in the period of missing at least two fitusiran doses in consecutive scheduled visits due to Covid-19 which is defined as one month after last dose (ie, last dose date + 28 days) before missing doses due to Covid-19 to one month after starting of re-dosing (ie, first re-dose date + 28 days). The same negative binomial model as in the primary analysis will be used.

6.3.1.3 Exploratory analysis

All bleeding episodes (treated or untreated)

The on-treatment and treatment policy efficacy analyses will be performed by including all bleeding episodes, regardless of administration of factor concentrates or bypassing agent infusion using the same negative binomial model as used for the primary analysis, which only includes treated bleeding episodes.

Time to first bleeding event

The time to first treated bleeding event in the treatment period will be calculated as the number of days between Day 1 and the onset date of the first treated bleeding event during the treatment period. The patient will be censored at the earlier of (Day 246, date of first intercurrent event) if no treated bleeding event has occurred. The time to first treated bleeding event in the efficacy period will be calculated similarly from Day 29 as the start of efficacy period. If a patient does not have bleeding episode data collected after Day 28 due to early study discontinuation, the time to first treated bleeding event in the efficacy period will be imputed from Day 1 as in the treatment period.

The time to first treated spontaneous bleeding event will be calculated similarly.

The proportion of patients who are bleeding free at the end of study (Month 9) will be estimated using the Kaplan-Meier method and compared using a Cox proportional hazards (PH) regression model with robust variance estimation and the treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry and randomization strata of hemophilia

type are treated as fixed effects . Plots of cumulative mean functions for the number of treated bleeds in the efficacy period and treatment period will be provided.

Symptoms related to bleeding

Descriptive statistics will be provided for symptoms related to bleeding events by each treatment arm.

6.3.1.4 Subgroup analysis

The on-treatment and treatment policy efficacy analyses for the primary endpoint and the secondary endpoints based on bleeding episodes will be repeated for the following subgroups:

- Hemophilia type (Type A vs B)
- Number of bleeding episodes during the 6 months prior to study (<=10 vs >10)
- Age group, years (<18, 18-64, ≥ 65)

In addition, region- and/or country-specific analyses will be performed to support regulatory submission as needed.

Negative binomial regression model will be applied only for subgroups that have at least 3 patients in each treatment arm and the model converges. Otherwise, only summary statistics will be presented.

6.3.2 Secondary endpoints

6.3.2.1 ABR in the treatment period (Global Protocol), ABR in the efficacy period (US Protocol)

Analysis will include all bleeding episode data in the specified period. The on-treatment and treatment policy efficacy analyses will be repeated with this endpoint.

6.3.2.2 Annualized spontaneous bleeding rate in the efficacy period

Analysis will include spontaneous bleeding episodes occurring in the efficacy period. The on-treatment and treatment policy efficacy analyses will be repeated with this endpoint.

6.3.2.3 Annualized joint bleeding rate in the efficacy period

Analysis will include joint bleeding episodes occurring in the efficacy period. The on-treatment and treatment policy efficacy analyses will be repeated with this endpoint.

6.3.2.4 Haem-A-QoL

The Haem-A-QoL will be provided to patients ≥17 years of age and includes 46 items contributing to 10 QoL domains (physical health, feelings, view of yourself, sports and leisure,

work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item is based on a 5-point Likert scale (never, rarely, sometimes, often, and all the time), and higher scores represent greater impairment. The change from baseline in physical health score and total score of Haem-A-QoL at the end of the study will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects of treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10) and randomization strata of hemophilia type (A vs B), baseline Haem-A-QoL physical health score and total score as covariates. Least square means of the physical health score and total score in each treatment arm and the difference of the least square means of the physical health score and total score in the two arms (along with the 95% CI and p-value) will be presented. The normality assumption based on ANCOVA model will be examined and a sensitivity analysis based on the non-parametric Wilcoxon-Mann-Whitney test will be performed. Domain scores, standardized scale scores, and transformed scale scores for Haem-A-QoL and their changes from baseline will be summarized. The above ANCOVA analysis is based on observed data. For patient with missing assessment due to early withdrawal, a sensitivity analysis will also be performed by imputing the domain score and total score as the worst score if the reason of withdrawal is treatment-related in the corresponding treatment arm, and as the average score for other reasons of withdrawal that are not treatment related in the corresponding treatment arm. The same analysis as main will be performed as a sensitivity analysis by excluding values of those who completed Haem-A-QoL at baseline after first dose of fitusiran.

To evaluate the impact of Covid-19, the same ANCOVA model will also be repeated on Covid-19 unaffected set. In addition, a sensitivity analysis using same ANCOVA model will be performed excluding the data impacted by Covid-19 major/critical protocol deviation. A supportive analysis will be repeated on the patients whose responses level to EQ-5D dimensions “anxiety/depression” is no change or improved from baseline.

To evaluate the association between the change in Haem-A-QoL and other clinical measures, the analysis of change from baseline in the Haem-A-QOL physical health score and total score will be stratified by ABR level (0, >0 to <=5, >5) and concomitant pain medication use (Y, N). The ABR level is based on on-treatment strategy during the efficacy period.

The summary of adherence with Haem-A-QOL measurement will also be provided.

6.3.2.5 ABR in the onset period

Analysis will include all bleeding episodes between Day 1 visit and Day 28 (inclusive). The primary efficacy analysis will be repeated with this endpoint. No formal hypothesis testing will be performed; p-value will be deemed exploratory.

6.3.3 Exploratory endpoints

6.3.3.1 TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM) version 9 will assess patient satisfaction with treatment. The TSQM Scale scores and their changes from baseline will be summarized.

6.3.3.2 HAL and pedHAL

The Haemophilia Activities List (HAL, in patients ≥18 years of age) and pediatric HAL (pedHAL, in patients <18 years of age) questionnaires assess subjective functional ability to perform activities of daily living. Overall score, component scores, domain scores, and their changes will be summarized by scheduled visits.

6.3.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of QOL outcome. Index value index value and visual analogue scale (VAS) score and their changes from baseline will be summarized. Numbers and percentages of patient by level and dichotomized level (1 = no problems, 2 to 5 = "problems") of each dimension will be reported.

6.3.3.4 Haemo-QOL

The Haemo-QOL will be provided to patients<17 years of age. The change from baseline in total score of Haemo-QOL will be analyzed using an analysis of covariance (ANCOVA) model with fixed effects of treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10) and randomization strata of hemophilia type (A vs B), baseline Haemo-QOL total score as a covariate. Domain scores for Haemo-QOL and their changes from baseline will be summarized descriptively. Only the descriptive statistics will be provided if ANCOVA model does not converge due to the small sample size.

6.3.3.5 Number of target joint bleeding episodes

A target joint is defined as a joint where 3 more spontaneous bleeding episodes in a single joint within a consecutive 6-month period have occurred. The target joints are identified at baseline and their bleeding episodes are captured and monitored during the study. An exploratory analysis of the number of target joint bleeding episodes may be performed using the same negative binominal model as the primary analysis.

6.3.3.6 HJHS

Joint health status will be assessed via the HJHS, as administered by a healthcare professional trained in the use of anthropometric measures. Response will be summarized. If the joint score is evaluated with 2 weeks after a joint or adjacent muscle bleeding episode or a surgery is performed on a joint and the joint score is evaluated from start date of surgery to the end of perioperative

procedure period + 7 days, then the data for that joint will be excluded. A sensitivity analysis excluding the non-evaluable results will be performed.

6.3.3.7 Annualized weight-adjusted consumption of factor concentrates

Factor concentrate dose will be recorded by the patient in the eDiary and reviewed by the Investigator (and Sponsor or delegate) for the study duration to assess on-demand factor concentrate use as treatment of breakthrough bleeding episodes. Weight-adjusted factor usage will be calculated programmatically.

The annualized weight-adjusted factor consumption, number of factor injections per bleed/per subject, weight adjusted total dose per bleed/per subject, and results of patient-reported evaluation of effectiveness of treatment for each bleed (excellent, good, moderate or none) as assessed by both patient and caregiver (Blanchette, 2014) will be summarized by study period. Factor concentrates consumption during Day 1 to Day 8 period under standard factor concentrates regimen will be summarized as appropriate. Day 1 to Day 8 period is from Day 1 to the earlier of Day 8 and the last day of bleeding follow up. Additional summary will be provided by bleed location, causality and severity. The compliance to the bleed management guideline will be summarized after Day 8 to the end of study,

6.3.3.8 Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

Change in patient resource use (eg, work/school attendance, visits to doctor/hospital) from baseline will be summarized descriptively.

6.4 Pharmacodynamic analysis

Pharmacodynamic analyses will be conducted using the Safety Analysis Set.

6.4.1 Antithrombin

AT levels and AT lowering (% lowering from baseline) will be summarized descriptively. In addition, mixed model repeated measures (MMRM) analyses will be performed on AT lowering with fixed effects of treatment arm, randomization strata of number of bleeding episodes in the 6 months prior to study entry (≤10 vs >10), randomization strata of hemophilia type (A vs B), visit and baseline AT level. A suitable covariance structure will be chosen to minimize Bayesian information criteria (BIC).

6.4.2 Peak thrombin

Peak thrombin values collected within 48 hours of factor, BPA or antifibrinolytic administration will be excluded from all analysis. Peak thrombin values will be summarized descriptively. In addition, MMRM analyses will be performed on change from baseline in peak thrombin with fixed effects of treatment arm, randomization strata of number of bleeding episodes in the

6 months prior to study entry (≤10 vs >10), randomization strata of hemophilia type (A vs B), visit and baseline peak thrombin level. The covariance structure will be chosen to minimize BIC.

Both analyses in AT and peak thrombin may also be performed on a logarithmic scale. The estimates along with 90% confidence intervals will be back transformed to the original scale.

6.4.3 AT Lowering and peak thrombin

Correlation between AT (actual AT levels and AT lowering) and thrombin will be computed on paired assessments, where both parameters are measured on the same day. Log transformation may be used.

6.5 Pharmacokinetic analysis

Non-compartmental analysis for PK parameter estimation in East Asian patients from East Asian sites is described in this analysis plan. Population PK analysis is planned for all patients in the study and will be described in a separate population PK analysis plan.

Pharmacokinetic parameters to be estimated using noncompartmental analysis will include, but will not be limited to: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), elimination half-life ($t_{½\beta}$), area under the concentration-time curve (AUC), apparent clearance (CL/F), and apparent volume of distribution (V/F). Other parameters may be calculated, if deemed necessary. PK analysis is not in the scope of this SAP and will be reported separately.

6.6 Safety analyses

Safety analyses will be conducted using the Safety Analysis Set. All safety summaries will be presented by treatment arm and may include the overall column as specified.

6.6.1 Study duration, study drug exposure and compliance

Study duration in treatment period in days is calculated as EOS/ET visit date – Day 1 visit date (or date of first dose of study drug for fitusiran arm) +1. Total study duration including AT follow-up in days is calculated as date of last follow-up – Day 1 visit date (or date of first dose of study drug for fitusiran arm) +1. The number of patients in each 2 month interval and summary statistics for the study duration by treatment group will be presented.

Exposure to study medication in days and the total number of study drug SC administrations received will be summarized for Fitusiran arm.

Duration of treatment exposure in days is calculated as date of the last dose of study drug − the date of the first dose of study drug + 28. The number 28 is the number of days between two scheduled doses of study drug. For example, if the last dose of study drug is taken on Day 31, the treatment exposure would be calculated as (31−1) + 28 = 58 days.

Dose interruptions and compliance are not taken into account for duration of exposure.

Fitusiran treatment compliance will be calculated as the total mg dose received as the percentage of total mg dose expected to receive. Fitusiran treatment compliance will be summarized.

6.6.2 Adverse events

All AEs will be coded using the MedDRA coding system (version used at the time of the database lock) and displayed in tables and data listings using system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent, and will be referred to as TEAEs. Treatment emergent AE is defined as any AE with onset date after first fitusiran dose for fitusiran arm or after Day 1 visit for the on-demand arm. Events with a fully or partially missing onset date will be assumed to be treatment emergent unless it can be unequivocally determined (from the partial onset date and/or a partial or complete stop date) that the event occurred prior to the first dose for fitusiran arm or prior to Day 1 visit for the on demand arm.

AEs will be summarized by the numbers and percentages of patients reporting at least one AE, having at least one AE by primary System Organ Class (SOC) and Preferred Term (PT). A patient with multiple occurrences of an AE will be counted only once in the respective AE category. Patients who report multiple occurrences of the same AE (preferred term) will be classified according to the most related or most severe occurrence, respectively.

All AE summaries will be presented (frequency counts and percentages) by system organ class and/or preferred term, unless specified otherwise. The SOC will be presented alphabetically and the preferred term will be sorted within each SOC in decreasing order of frequency in the fitusiran arm.

The following events are considered to be AEs of special interest (AESI):

- ALT or AST elevations >3× ULN
- Suspected or confirmed thromboembolic events
- Severe or serious injection site reactions (ISRs), ISRs that are associated with a recall phenomenon (reaction at the site of a prior injection with subsequent injections) or, those that lead to temporary dose interruption or permanent discontinuation of study drug.
- Systemic injection associated reactions (IARs), defined as hypersensitivity reactions which are related or possibly related to study drug.

An overall summary of AEs will include the number and percentage of patients with any AE, any AE assessed by the Investigator as related to study drug (fitusiran only, possibly related or definitely related), any severe AE, any severe AE related to study drug, any serious AE (SAE), any SAE related to study drug, any AE/SAE of special interest; any AE/SAE leading to study drug discontinuation, any study drug related AE/SAE leading to study drug discontinuation, any AE/SAE leading to study withdrawal, any study drug related AE/SAE leading to study

withdrawal, AE potentially consistent with COVID-19 and any deaths. The overall summary of AEs will also be provided by hemophilia type.

Tabulations by SOC and PT will be produced for the following:

- all AEs;
- AEs by severity;
- AEs by hemophilia type
- all SAEs;
- AEs related to study drug (fitusiran arm only);
- AE s related to study drug by hemophilia type (fitusiran arm only);
- SAEs related to study drug (fitusiran arm only);
- SAEs related to study drug by hemophilia type (fitusiran arm only);
- AESI;
- AESI by hemophilia type;
- SAEs of special interest;
- SAEs of special interest by hemophilia type;
- AEs leading to study drug discontinuation (fitusiran arm only);
- SAEs leading to study drug discontinuation (fitusiran arm only);
- AESIs leading to study drug discontinuation (fitusiran arm only);
- Serious AESIs leading to study drug discontinuation (fitusiran arm only);
- AEs leading to study withdrawal;
- SAEs leading to study withdrawal.
- AEs potentially consistent with COVID-19;

COVID-19 infection will be identified based on the search term list in Appendix 8.2.

Tabulations by PT in decreasing order in frequency in the fitusiran arm will be produced for the following:

- all AEs;
- all AEs by hemophilia type;
- all SAEs;
- AEs related to study drug (fitusiran arm only);
- SAEs related to study drug (fitusiran arm only);

All AEs collected will be listed along with the information collected on those AEs, eg, AE relationship to study drug, AE outcome etc. AEs that are not treatment-emergent will be flagged in the listings. By-patient listings will also be provided for the following: all patient deaths, all

SAEs, and all AEs leading to study drug discontinuation or study withdrawal, all AEs leading to death, AEs potentially consistent with COVID-19.

6.6.3 Laboratory data

Clinical laboratory values will be expressed in Standard International (SI) units. Laboratory data collected and recorded as below the limit of detection will be set equal to the lower limit of detection for the calculation of summary statistics.

Summary data for each laboratory parameter will be presented for each continuous clinical laboratory parameter (including hematology, serum chemistry, coagulation studies and thyroid and liver function tests). Descriptive statistics will be presented for the actual values, change from baseline, and percent change from baseline by visit.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges.

A listing will be produced for all patients with abnormal liver function tests defined as an ALT >3×ULN, AST >3×ULN, and/or total bilirubin >2×ULN at any time point.

A table will be produced to summarize the number and percentage of patients in each of below category at any post-baseline time point.

- ALT >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALT or AST >1 & ≤3, >3 & ≤5, >5 & ≤10, >10 & ≤20, >20×ULN,
- ALP >1.5×ULN,
- Total Bilirubin >1.5 & ≤2, >2 & ≤3, >3 & ≤5 and >5×ULN,
- Total Bilirubin >2×ULN concurrent with ALT or AST >3×ULN,
- INR >1.2.

In separate figures, the peak total bilirubin (at any time post-baseline) will be plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time post-baseline.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities (PCSA) will be provided.

Laboratory data will be provided in data listings as appropriate. Values met PCSA criterion or out-of-range laboratory results when no PCSA criterion is defined will be identified in the listings.

6.6.4 Vital signs and physical examination

Descriptive statistics will be provided for vital signs, including blood pressure, pulse rate, oral body temperature and respiration rate. Summary table of potentially clinically significant abnormalities (PCSA) will be provided.

Vital sign measurements will be presented for each patient in a data listing as appropriate, with PCSA vital signs flagged.

All physical examination findings will be presented in a by-patient data listing.

6.6.5 Electrocardiogram

Electrocardiogram (ECG) findings will include rhythm, ventricular rate, PR interval, QRS duration, QT interval, and QTc interval. For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings will be used for analysis.

Corrected QT interval (QTc), if not collected, will be calculated using both Bazett's and Fridericia's correction formulas.

PR, QRS, QT, QTc and RR intervals and their change from time-matched and pre-dose baseline will be summarized for each treatment group by scheduled visit. Patients will be categorized into ≤450, >450 - 480, >480 - 500, or >500 ms per their maximum post-baseline absolute QTc interval and ≤30, >30 - 60, or >60 ms per their maximum change from baseline QTc interval. The number and percentage of patients in each category will be summarized by treatment group.

6.6.6 Medical history

Medical history will be summarized by MedDRA coding system (version 18.0 or later) SOC, high level term (HLT), and PT. A patient contributes only once to the count for a given condition (overall, by SOC, by HLT, by preferred term). Listing will be provided including medical condition or event, start date and end date.

6.6.7 Concomitant medications

Concomitant medication is defined as all medications other than study drug administered to a patient with the medication taken after first fitusiran dose for fitusiran arm or after Day 1 visit for the on-demand arm.

Concomitant medications will be coded using the WHO Drug Dictionary (version in use at the time of database lock). Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Concomitant medications collected will be tabulated by treatment arm and summarized separately for the bleeding treatment medications (as captured in the eDiary) and other medications (as captured in the CRF). Any medications that did not end prior to first fitusiran dose for fitusiran arm or prior to Day 1 visit for on-demand arm will be included. If an end date is missing or the medication is ongoing, the medication will be included.

6.7 Anti-drug antibody analysis

The ADA population includes all patients in the safety analysis set with at least one post baseline ADA result. Number of patients testing positive for ADA pre-study-drug (baseline positive) and post-study-drug administration will be summarized by Hemophilia type (A/B) and incidence of ADA positivity will be presented by frequency and as a percent by Hemophilia type and across all patients. In addition, maximum ADA titer and range of titer values will be presented by Hemophilia type and across all patients.

7 REFERENCES

1. Barnard J, Rubin D (1999). Small sample degrees of freedom with multiple imputations. Biometrika, 1999;86(4):984-55.
2. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A (2014). Definitions in hemophilia: communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2014;12(11):1935-9.
3. Keene, O. N., Roger, J. H., Hartley, B. F., & Kenward, M. G. (2014). Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical statistics. 2014;13(4):258-64.
4. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. 2018.

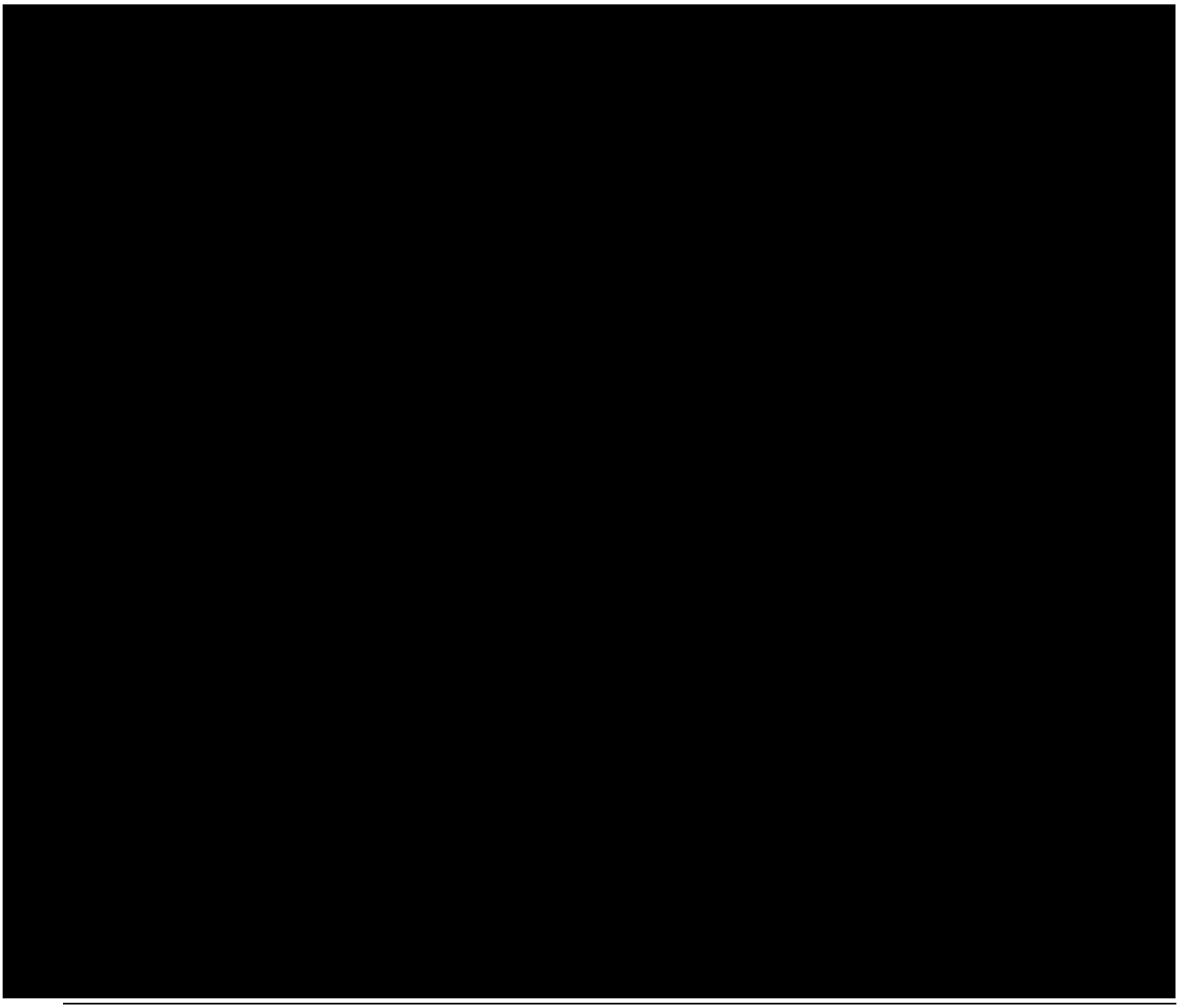
8 APPENDICES

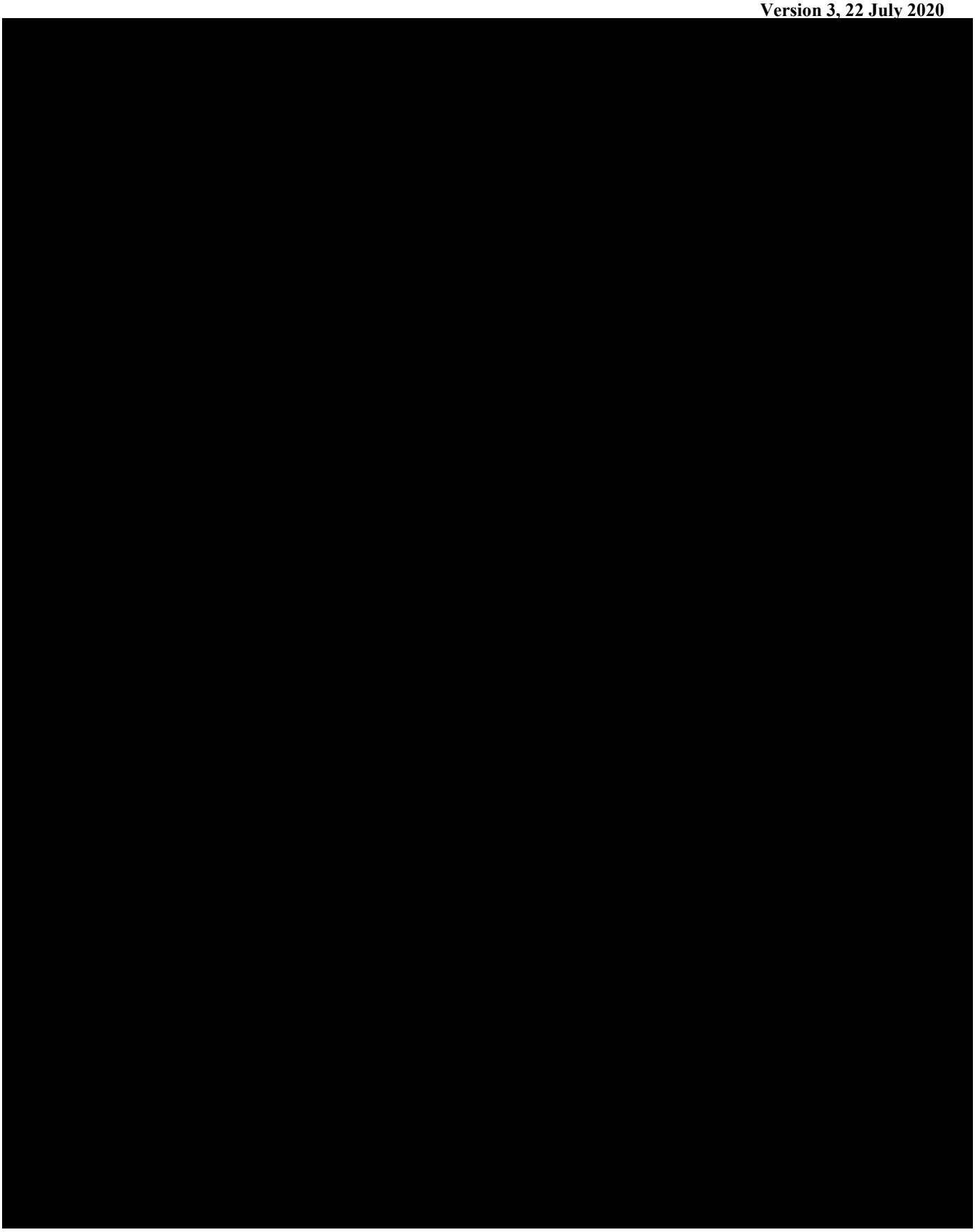
8.1 Questionnaire/Scoring

8.1.1 Haem-A-QOL and Haemo-QOL

The Haem-A-QOL and Haemo-QOL questionnaires are psychometrically tested QOL assessment instruments for patients with hemophilia.

The Haem-A-QOL will be provided to patients ≥17 years of age, and includes 46 items contributing to 10 QOL domains (physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality). Scoring for each item is based on a 5-point Likert scale (never, rarely, sometimes, often, and all the time), and higher scores represent greater impairment.





8.1.2 Treatment satisfaction questionnaire for medication (TSQM) domain scores

The Treatment Satisfaction Questionnaire for Medication (TSQM) will assess patient satisfaction with treatment. The TSQM is a validated psychometric tool that provides a general measure of patient satisfaction with medication.

The TSQM Scale scores will be computed by adding the items loading on each factor. The lowest possible score is subtracted from this composite score and divided by the greatest possible score minus the lowest possible score. This provides a transformed score between 0 and 1 that should be multiplied by 100; see Table 2. Note that only one item may be missing from each scale before the subscale should be considered invalid for that respondent.

Table 2 - TSQM scale scores

Factor	Calculation	In case of missings
Effectiveness	([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100	*If one item is missing:* ([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100
Convenience	([Sum(Item 4 to Item 6) – 3] divided by 18) * 100	*If one item is missing:* ([(Sum(Item4? to Item6?)) – 2] divided by 12) * 100
Globel Satisfaction	([Sum(Item 7 to Item 9) – 3] divided by 14) * 100	*If either Item 7 or 8 is missing:* ([(Sum(Item7? to Item9?)) – 2] divided by 10) * 100 *If Item 9 is missing:* ([(Sum(Item7 and Item8)) – 2] divided by 8) * 100

8.1.3 Haemophilia activities list (HAL)/paediatric HAL (pedHAL) score

The HAL and pedHAL questionnaires will assess subjective functional ability to perform activities of daily living. The HAL will be assessed in patients ≥18 years of age, and the pedHAL will be assessed in patients <18 years of age.

HAL scores can be calculated for each of the seven domains of the HAL. Additionally, three component scores can be calculated (Activities involving the Upper Extremities, Basic activities involving the Lower Extremities and Complex activities involving the Lower Extremities) as well as an overall score. If there is missing item score within a domain or a component, the normalized score for that domain or component will be calculated based on the number of items answered if at least 50% of those scores are non-missing and otherwise it is set to missing. Before summarizing the individual item scores, recoding is required (see Table 3); a higher raw score represents more functional limitations; possible scoring ranges are given (Table 4). Normalized scores for the domains, components, and the full questionnaire can also be obtained. Missing values are controlled for and the possible scores range from 0 to 100, where 0 represents the worst possible functional status and 100 the best possible functional status (Table 5).

Table 3 - Recoding

Score	Recode	Meaning
8	0	N/A
1	6	Impossible
2	5	Always problems
3	4	Mostly problems
4	3	Sometimes problems
5	2	Rarely problems
6	1	Never problems

Table 4 - Scores

Score		Items	Score range
Lying/sitting/kneeling/standing	LSKS	1-8 (8)	8 - 48
Functions of the legs	LEGS	9-17 (9)	9 - 54
Functions of the arms	ARMS	18-21 (4)	4 - 24
Use of transportation	TRANS	22-24 (3)	3 - 18
Self care	SELFC	25-29 (5)	5 - 30
Household tasks	HOUSEH	30-35 (6)	6 - 36
Leisure activities and sports	LEISPO	36-42 (7)	7 - 42
Upper Extremity Activities	UPPER *	(9)	9 - 54
Basic Lower Extremity Activities	LOWBAS **	(6)	6 -36
Complex Lower Extremity Activities	LOWCOM ***	(9)	9 - 54
Sum score	SUM 1-42	(42)	42 - 252

* Items for UPPER-component: 18, 19, 20, 21, 25, 26, 27, 28, 29. (9 items)
** Items for LOWBAS-component: 8, 9, 10, 11, 12, 13. (6 items)
*** Items for LOWCOM-component: 3, 4, 6, 7, 14, 15, 16, 17, 22. (9 items)

Table 5 - Normalization

Score	Normalisation
LSKS	100 - ((Σ1−8 - valid) * (100/(5 * valid)))
LEGS	100 - ((Σ9−17 - valid) * (100/(5 * valid)))
ARMS	100 - ((Σ18−21 - valid) * (100/(5 * valid)))
TRANS	100 - ((Σ22−24 - valid) * (100/(5 * valid)))
SELFC	100 - ((Σ25−29 - valid) * (100/(5 * valid)))
HOUSEH	100 - ((Σ30−35 - valid) * (100/(5 * valid)))
LEISPO	100 - ((Σ36−42 - valid) * (100/(5 * valid)))
UPPER	100 - ((Σ18−21;25−29 - valid) * (100/(5 * valid)))
LOWBAS	100 - ((Σ8−13 - valid) * (100/(5 * valid)))
LOWCOM	100 - ((Σ3−7;14−17;22 - valid) * (100/(5 * valid)))
SUM	100 - ((Σ1−42 - valid) * (100/(5 * valid)))

"valid" = number of items scored within the specific domain/component.
Items with "n/a"-response are to be considered NOT valid

8.1.4 EuroQol-5 dimension 5 level (EQ-5D-5L) score

The EQ-5D-5L is a standardized instrument for use as a measure of QoL outcome. It consists of a descriptive system and a visual analog scale (VAS).

1) EQ-5D descriptive system: has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems).
2) EQ-5D VAS: is a continuous score ranging from 0 to 100.
3) EQ-5D Valuation index: The information of the 5 dimensions of the descriptive system summarized into one index. The EQ-5D-5L index value is calculated using the crosswalk link function and the individual responses to the EQ-5D5L descriptive system. If any of the 5 dimensions have missing values at a given time point, the index value will not be computed.

8.2 List of search terms for COVID-19 (MedDRA v23.0)

Code	PT	Primary SOC
10084510	N/A	Infections and infestations
10084459	Asymptomatic COVID-19	Infections and infestations
10084467	Asymptomatic COVID-19	Infections and infestations
10053983	Coronavirus infection	Infections and infestations
10051905	Coronavirus infection	Infections and infestations
10084382	COVID-19	Infections and infestations
10084268	COVID-19	Infections and infestations
10084401	COVID-19	Infections and infestations
10084270	COVID-19	Infections and infestations
10084272	COVID-19	Infections and infestations
10084381	COVID-19 pneumonia	Infections and infestations
10084380	COVID-19 pneumonia	Infections and infestations
10084383	COVID-19 pneumonia	Infections and infestations
10084451	Suspected COVID-19	Infections and infestations
10084452	Suspected COVID-19	Infections and infestations
10084461	SARS-CoV-2 carrier	Infections and infestations
10084456	Exposure to SARS-CoV-2	Injury, poisoning and procedural complications
10084394	Occupational exposure to SARS-CoV-2	Injury, poisoning and procedural complications
10084353	Coronavirus test	Investigations
10084269	Coronavirus test negative	Investigations
10070255	Coronavirus test positive	Investigations
10084508	SARS-CoV-2 test	Investigations
10084507	SARS-CoV-2 test	Investigations

10084500	SARS-CoV-2 test	Investigations
10084441	SARS-CoV-2 test	Investigations
10084499	SARS-CoV-2 test	Investigations
10084431	SARS-CoV-2 test	Investigations
10084356	SARS-CoV-2 test	Investigations
10084501	SARS-CoV-2 test	Investigations
10084493	SARS-CoV-2 test	Investigations
10084434	SARS-CoV-2 test	Investigations
10084440	SARS-CoV-2 test	Investigations
10084354	SARS-CoV-2 test	Investigations
10084481	SARS-CoV-2 test false negative	Investigations
10084480	SARS-CoV-2 test false negative	Investigations
10084495	SARS-CoV-2 test negative	Investigations
10084492	SARS-CoV-2 test negative	Investigations
10084504	SARS-CoV-2 test negative	Investigations
10084436	SARS-CoV-2 test negative	Investigations
10084502	SARS-CoV-2 test negative	Investigations
10084432	SARS-CoV-2 test negative	Investigations
10084357	SARS-CoV-2 test negative	Investigations
10084509	SARS-CoV-2 test negative	Investigations
10084494	SARS-CoV-2 test negative	Investigations
10084435	SARS-CoV-2 test negative	Investigations
10084438	SARS-CoV-2 test negative	Investigations
10084273	SARS-CoV-2 test negative	Investigations
10084505	SARS-CoV-2 test positive	Investigations
10084496	SARS-CoV-2 test positive	Investigations
10084498	SARS-CoV-2 test positive	Investigations
10084437	SARS-CoV-2 test positive	Investigations
10084503	SARS-CoV-2 test positive	Investigations
10084433	SARS-CoV-2 test positive	Investigations
10084355	SARS-CoV-2 test positive	Investigations
10084491	SARS-CoV-2 test positive	Investigations
10084497	SARS-CoV-2 test positive	Investigations
10084442	SARS-CoV-2 test positive	Investigations
10084439	SARS-CoV-2 test positive	Investigations
10084271	SARS-CoV-2 test positive	Investigations
10084458	COVID-19 prophylaxis	Surgical and medical procedures

10084460	COVID-19 treatment	Surgical and medical procedures
10084457	COVID-19 immunisation	Surgical and medical procedures
10084464	COVID-19 immunisation	Surgical and medical procedures
10084465	COVID-19 immunisation	Surgical and medical procedures
10084463	COVID-19 immunisation	Surgical and medical procedures
10084466	COVID-19 immunisation	Surgical and medical procedures
10084462	COVID-19 immunisation	Surgical and medical procedures
10084469	Patient isolation	Surgical and medical procedures
10084470	Quarantine	Surgical and medical procedures
10084468	Quarantine	Surgical and medical procedures

Signature Page

efc14769-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	[redacted]
Approve & eSign	[redacted]