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STATISTICAL ANALYSIS PLAN

An open-label, multinational, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B previously receiving factor or bypassing agent prophylaxis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABR:	annualized bleeding rate
ADA:	antidrug antibody formulation
AE:	adverse event
AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AT:	antithrombin
ATC:	anatomic therapeutic class
AUC:	area under the concentration-time curve
BMI:	body mass index
BPA:	bypassing agent
BUN:	blood urea nitrogen
CL/F:	apparent clearance
Cmax:	maximum plasma concentration
CR:	copy reference
CRF:	case report form
ECG:	electrocardiogram
EQ-5D:	EuroQoL - 5 Dimensions
GGT:	gamma-glutamyl transpeptidase
Haem-A-QOL:	Haemophilia Quality of Life Questionnarire for Adults
Haemo-QOL:	Haemophilia Quality of Life Questionnaire for Children and Adolescents
HAL:	Haemophilia Activities List
HJHS:	Hemophilia Joint Health Score
HLGT:	high-level group term
HLT:	high-level term
HRQOL:	health related quality of life
IARs:	injection associated reactions
ICF:	informed consent form
ISRs:	injection systematic reactions
LLT:	lower-level term
MAR:	missing at random
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	multiple imputation
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
pedHAL:	Paediatric HAL
PK:	pharmacokinetics
PT:	preferred term
SAE:	serious adverse event
SD:	standard deviation
SOC:	system organ class

t½β:	elimination half-life
TG:	thrombin generation
tmax:	time to maximum plasma concentration
TSQM:	Treatment Satisfaction Questionnaire for Medication
ULN:	upper limit of normal
V/F:	apparent volume of distribution
WBC:	white blood cell
WHO-DD:	World Heath Organization_Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

This is a multicenter, multinational, open label, Phase 3 switching study designed to characterize the efficacy and safety of fitusiran in male patients, aged ≥12 years, with severe hemophilia A or B, previously receiving factor or bypassing agent (BPA) prophylaxis.

The study consists of 2 cohorts: Cohort A consists of patients with inhibitory antibodies to factor VIII or factor IX. Cohort B consists of patients without inhibitory antibodies to factor VIII or factor IX. A subgroup of Cohort A patients includes hemophilia B patients with inhibitory antibodies to factor IX who are not responding adequately to BPA prophylaxis treatment (historical annualized bleeding rate (ABR) ≥20) (see Inclusion Criteria in Section 5.1 of the study protocol).

The study has 3 periods defined by type of prophylaxis regimen:

- 6-month factor/BPA prophylaxis period in which patients continue their prestudy, regularly scheduled prophylaxis regimen with factor/BPAs.

  The subgroup of Cohort A patients who are not responding adequately to BPA prophylaxis treatment do not participate in this 6-month BPA prophylaxis period and start to directly receive fitusiran (in the 1-month onset period described below) after the screening period.
- 1-month onset period in which patients receive first dose of fitusiran while continuing their factor/BPA prophylaxis for up to 7 days.
- 6-month fitusiran efficacy period in which patients receive fitusiran prophylaxis.

Together, the 1-month onset period and the 6-month fitusiran efficacy period constitute the fitusiran treatment period. An additional 6 months follow-up period for monitoring of AT levels is required for patients who do not enroll in the extension study after the fitusiran treatment period.

Given that the study design employed is a single treatment arm, with a switch from factor/BPA prophylaxis to fitusiran prophylaxis for each patient, the study is not blinded and no randomization is performed.

Approximately 80 patients are planned for enrollment in this study, including approximately 30 patients with inhibitors (Cohort A) and approximately 50 patients without inhibitors (Cohort B). Approximately 18 patients with hemophilia B (including approximately 7 hemophilia B patients in Cohort A, among which are a subgroup of no more than 4 patients who are not responding adequately to BPA prophylaxis), and approximately 7 adolescents (≥12 to <18 years of age) are also planned for enrollment. In the US, only patients from Cohort A are included.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving factor concentrate or bypassing agent (BPA) prophylaxis.

1.2.2 Secondary objectives

- To characterize the following while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis:
  - 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 characterize the frequency of bleeding episodes during the onset and treatment periods in patients receiving fitusiran
- To characterize safety and tolerability of fitusiran
- To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis

1.2.3 Exploratory objectives

- To characterize the effects of fitusiran on the following patient-reported outcomes while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis:
  - Patient satisfaction with fitusiran
  - Patient activity
  - HRQOL in adolescents (≥12 to <17 years of age)
- To characterize the pharmacodynamic (PD) effect, PK, and immunogenicity of fitusiran
- To characterize the effects of fitusiran on joint status while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis
- To characterize the effects of fitusiran on patient resource use, relative to receiving factor or BPA prophylaxis

1.3 DETERMINATION OF SAMPLE SIZE

Sample size is based on clinical considerations. The overall sample size of 80 patients including approximately 30 patients with inhibitor (Cohort A) and approximately 50 patients without inhibitor (Cohort B) was selected recognizing the limited number of patients with hemophilia, and to yield a reasonably robust estimate of the fitusiran bleeding episode rate and address the secondary objectives, including characterization of safety and tolerability. The proposed sample

size is also expected to provide reasonable precision around the ratio of bleeding rate in the fitusiran efficacy period to bleeding rate in the factor/BPA period for both Cohort A and Cohort B.

Since patients participate in multiple periods, within-patient correlation of numbers of bleeding episodes is expected between the periods. Having no prior knowledge of this correlation, different correlation scenarios were considered and the ratio of the bleeding rate in fitusiran efficacy period to the bleeding rate in factor/BPA period along with its 95% CIs were simulated. Below tables summarize the results from 10 000 simulated studies along with the ABR assumptions.

Table 1 - Simulated ratio of rates for Cohort A, with 95% confidence intervals

Correlation	Average Ratio (Average 95% CI Bounds), N=30 Based on 10 000 Simulations	
	Fitusiran period ABR: mean = 4, SD = 6	
	Factor/BPA period ABR: Mean = 16; SD = 14	Factor/BPA period ABR: Mean = 12; SD = 11
0.25	0.24 (0.14, 0.42)	0.32 (0.19, 0.57)
0.50	0.24 (0.15, 0.39)	0.32 (0.20, 0.52)
0.75	0.24 (0.17, 0.35)	0.32 (0.22, 0.47)

Abbreviation: ABR=annualized bleeding rate; BPA=bypassing agent; CI=confidence interval; SD=standard deviation
Note: Correlation = within-patient correlation between bleeding episodes of fitusiran efficacy period and factor or BPA period.

Table 2 - Simulated ratio of rates for Cohort B, with 95% confidence intervals

Correlation	Average Ratio (Average 95% CI Bounds), N=40 Based on 10 000 Simulations	
	Fitusiran period ABR: mean = 4, SD = 6	
	Factor/BPA period ABR: Mean = 4; SD = 5	Factor/BPA period ABR: Mean = 6; SD = 7
0.25	1.04 (0.57,1.94)	0.69 (0.39,1.25)
0.50	1.03 (0.63,1.69)	0.68 (0.43,1.09)
0.75	1.01 (0.72,1.41)	0.67 (0.48,0.93)

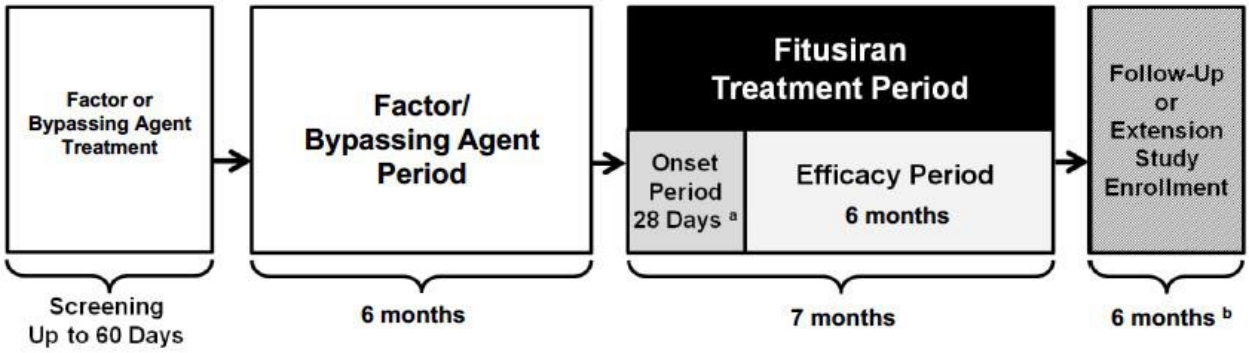
Abbreviation: ABR=annualized bleeding rate; BPA=bypassing agent; CI=confidence interval; SD=standard deviation
Note: Correlation = within-patient correlation between bleeding episodes of fitusiran efficacy period and factor or BPA period.

To maintain the previously planned safety database size of at least 244 patients from ATLAS studies, the planned sample size for this study has increased from approximately 70 patients to approximately 80 patients. The detailed rationale for the sample size increase is documented in the position paper in Appendix F.

1.4 GRAPHIC STUDY PLAN

The study design schema is presented in Figure 1. Patients who complete the study may be eligible for an open-label extension study.

Figure 1 - Study design



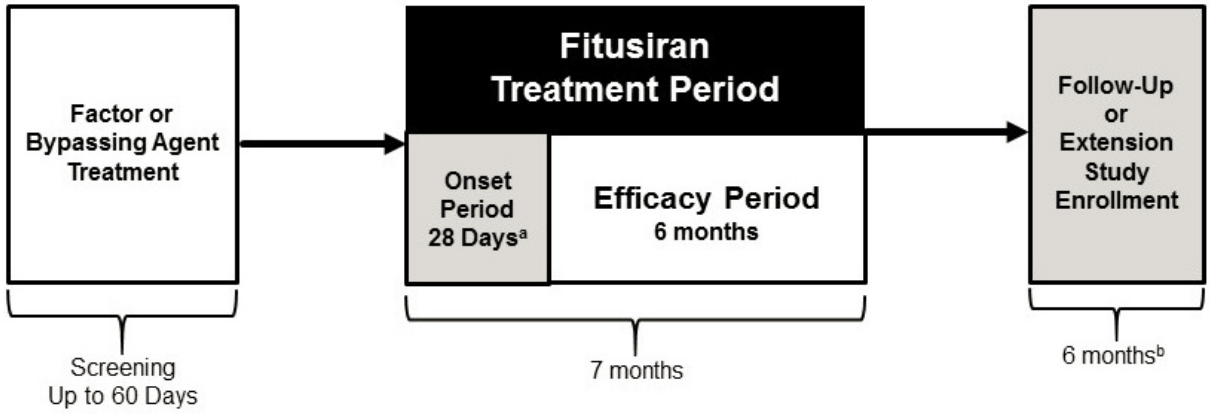
Abbreviations: AT=antithrombin

Note: For subgroup of Cohort A patients enrolling directly into the fitusiran treatment period, see Figure 2.

a Patients will continue to receive prescribed factor concentrate or BPA prophylaxis for the first 7 days of the onset period.

b Following final fitusiran dose, AT activity level will be monitored at monthly intervals following the final fitusiran dose until activity levels return to approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

Figure 2 - Study design (for subgroup of Cohort A patients enrolling directly into the fitusiran treatment period)



Abbreviations: AT= antithrombin

a Patients will continue to receive prescribed factor concentrate or BPA prophylaxis for the first 7 days of the onset period.

b Following final fitusiran dose, AT activity level will be monitored at monthly intervals following the final fitusiran dose until activity levels return to approximately 60% (per the central laboratory) or per Investigator discretion in consultation with the study Medical Monitor.

Please refer to table 1 of the study protocol for the detailed study flow chart.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after the first patient was enrolled. The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

The first patient was enrolled on Sep 21st, 2018. An interim analysis may be conducted as a part of this study.

Table 3 - Protocol amendment statistical changes

Amendment number	Date approved	Rationale	Description of statistical changes
2	31-May-2018	Study expanded to include patients without inhibitory antibodies to factor VIII or factor IX in addition to patients with inhibitory antibodies to factor VIII or factor IX	Text updated for sample size with new Table 9 added for simulated ratio of rates for Cohort A, with 95% confidence intervals Text added "These analyses will be done for Cohort A and Cohort B separately. A pooled analysis will be performed after all patients in the 2 cohorts have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study".
2	31-May-2018	On-treatment strategy is used for the primary analysis of primary endpoint in assessing the primary objective of the study (ICH E9 (R1)).	Text changed from "The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or bypass agent prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190) including bleeding episode data collected after discontinuation of study drug" to "The primary analysis will be performed on the EAS and will include all bleeding episodes occurring in the factor or bypass agent prophylaxis period (Day -162 to Day -1) and the fitusiran efficacy period (Day 29 to Day 190)".
2	31-May-2018	An interim analysis may be conducted as a part of this study to support regulatory filings.	Text changed from "No interim analysis is planned" to "An Interim Analysis may be conducted as a part of this study".
4	18-Dec-2018	Study expanded to enroll a subgroup of hemophilia B patients with inhibitors who are not responding adequately to BPA prophylaxis treatment	Analysis population is updated in Section 8.2.1 of the study protocol.
4	18-Dec-2018	Since the study is not designed as a superiority study and is not powered to detect a statistically significant difference, Bayesian analyses will be added to help interpret the p-value.	The below sentence is added to primary efficacy analysis: The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses will be performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty.

Amendment number	Date approved	Rationale	Description of statistical changes
4	18-Dec-2018	Correction of a discrepancy with the corresponding secondary study objective	Secondary endpoint 'Change in Haem-AQOL physical health score and total score in the fitusiran treatment period' is changed to 'Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period' The below sentence is added to secondary efficacy analysis: Change in Haem-A-QOL physical health score and total score (in patients ≥17 years of age) in the factor or BPA prophylaxis period and fitusiran treatment period will be summarized descriptively. A mixed model for repeated measures analysis may be performed as deemed appropriate.
4	18-Dec-2018	A secondary objective and endpoint are included to further assess fitusiran efficacy.	"To characterize the annualized weight-adjusted consumption of factor/BPA while receiving fitusiran treatment, relative to receiving factor or BPA prophylaxis" is added as a secondary objective. "Annualized weight-adjusted consumption of factor/BPA" is added as a secondary endpoint

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarizes major changes in statistical analysis plan to the protocol statistical section, with emphasis on changes after the first patient is enrolled. 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 Sep 21st, 2018. An interim analysis may be conducted as a part of this study.

Table 4 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	02-Jan-2020	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 190) defined in the protocol is changed to (Day 29, earliest of (Day 190, or the last day of bleeding follow up), excluding the period for each intercurrent event.

SAP version number	Date approved	Rationale	Description of statistical changes
		Added exclusion periods due to fitusiran treatment discontinuation, major or minor surgery, prophylaxis 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 2.1.3.1
		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 Appendix B.
		To maintain the regulatory agency agreed upon safety database size of at least 244 patients from ATLAS studies	The planned sample size for this study has increased from approximately 70 patients to approximately 80 patients.
2	04-Sep-2020	To clarify the definition of number of bleeding episodes prior to screening	"Number of bleeds reported in the last 6 months prior to screening" was modified to "number of bleeding episodes prior to screening (ie, number of bleeds reported in the last 6 months prior to screening for Cohort A and number of bleeds reported in the last 12 months prior to screening for Cohort B) in Section 2.1.1.
		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 2.2.
		To update Per-protocol Analysis Set definition	The detail deviations are included in the Per-protocol analysis set definition in Section 2.3.
		To define Covid-19 Unaffected Set	Covid-19 Unaffected Set is defined in Section 2.3.
		To add statistical analysis by hemophilia type	By hemophilia type and overall summary is added in Section 2.4.1, 2.4.2 and 2.4.3. By hemophilia type summary is added for key AE tables in Section 2.4.5.1.
		To clarify the baseline definition for efficacy analysis	The baseline definition for efficacy analysis is modified from "the last non-missing value before first dose of fitusiran/enrollment date" to "the last non-missing value on or before the first dose date of fitusiran/enrollment date" in Section 2.4.4.
		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 2.4.4.1. In addition, a sensitivity analysis to exclude the bleeds during the period of missing at least 2 consecutive fitusiran doses due to Covid-19 event and the period from 6 months after enrollment to the date of delayed first fitusiran dose due to Covid-19 is added in Section 2.4.4.1.

SAP version number	Date approved	Rationale	Description of statistical changes
		To add the analyses for Haem-A-QoL due to Covid-19 impact	For sensitivity analyses, MMRM model will be run 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 prophylaxis baseline in Section 2.4.4.2.4.
		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 in Section 2.4.4.2.4.
		To be consistent with the statistical model of primary analysis	The covariate "Number of bleeding episodes prior to screening" was removed from the statistical model of exploratory analysis and secondary efficacy analysis in Section 2.4.4.1.3 and Section 2.4.4.2.4.
		To clarify the analysis of the annualized weight-adjusted consumption of factor/BPA	The parameters to be summarized for the consumption of factor/BPA is modified to: annualized weight-adjusted factor/BPA consumption for both treating bleeds and prophylaxis purpose, number of factor/BPA injections per bleed/per subject, weight adjusted total dose per bleed/per subject. The summary of compliance to the bleed management guideline is added.
		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 G.
		To add AE summary by hemophilia type	By hemophilia type summary is added to key AE tables.
		Due to the exclusion criteria 5, the analysis of fibroscan/fibrotest result at baseline against worst post-baseline ALT elevation is not necessary	The related analysis is removed in Section 2.4.5.2.
		Appendix A Potentially clinically significant abnormalities criteria is not applicable to this study	Appendix A Potentially clinically significant abnormalities criteria is removed
3	This version	Removed 80mg for fitusiran dosing and fitusiran prophylaxis period	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Added safety analysis set 1, safety analysis set 2, efficacy analysis set 1, and efficacy analysis set 2	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Removed pharmacokinetics analysis set	No PK analysis planned in this SAP

SAP version number	Date approved	Rationale	Description of statistical changes
		Added one more major pd which will lead to PPS exclusion: The participant did not administer prophylaxis therapy with minimum frequency as per protocol (table 5) during the prophylaxis period	To exclude patient with poor compliance during prophylaxis period.
		Clarified Covid-19 Unaffected Set is a subset of EAS 1	To add clarification.
		Updated the intercurrent event of fitusiran treatment discontinuation	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Updated the intercurrent event of prophylaxis treatment	Prophylaxis BPA and Factor are prohibited.
		Added AESI of Cholecystitis and Cholelithiasis	Added AESI per protocol V6.0.
		Clarified the patients with 80mg QM and participants with 50mg Q2M will be analyzed separately and relevant scope	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Clarified the treatment duration will be calculated for patients with 80mg QM	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Removed “covariates as in the primary analysis” in bayesian negative binomial model	To correct the wording due to no covariates will be considered.
		Added one more sensitivity analysis with Bayesian model with prior mean of 1 for ABR ratio and clarified the MCMC procedure in SAS	To add sensitivity analysis and clarify the SAS procedure.
		Clarified period of missing at least two fitusiran doses for participants with 50mg Q2M	To accommodate the new dose regimen of 50mg Q2M per protocol V6.0.
		Clarified the impact of intercurrent event on time to first bleeding event analysis for on-treatment strategy	To add clarifications.
		Added study drug related AE/SAE of special interest in the AE overview tables	To add more information in AE overview table.
		Removed three redundant AESI tables	To Remove redundant tables.
		Added plots for liver function parameters: The mean of ALT, AST, and total bilirubin will be plotted over time. The Kaplan-Meier curve for the time to first onset of ALT>3ULN, AST>3ULN and AST/AST >3ULN	To add plots and better visualize the liver function changes.

SAP version number	Date approved	Rationale	Description of statistical changes
		Updated COVID-19 infection be based on appendix G to a search on MedDRA SMQ COVID-19 (narrow)	MedDRA SMQ COVID-19 (narrow) is released.
		Defined the ADA endpoint and analysis in the section of exploratory endpoint, rather than the section of safety	Removed redundant wordings in the section of safety.
		Replaced subject with participant	To standardize the wording.
		Administrative and editorial changes	

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

Demographic characteristics

Demographic variables are:

- Age in years (quantitative and qualitative variable: ≥12 to <18, ≥18 to <65 and ≥65 years)
- Sex (Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not available/not reported)
- Weight in kg
- Height in cm
- Body Mass Index (BMI) in kg/m^2
- Geographic Region (Defined in Section 2.5.6)

Medical or surgical history

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the patient.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics

The following disease characteristics are summarized

- Hemophilia type
- Inhibitor status
- Number of bleeding episodes prior to screening (ie, number of bleeds reported in the last 6 months prior to screening for Cohort A and number of bleeds reported in the last 12 months prior to screening for Cohort B)
- Age at diagnosis
- Time from diagnosis to screening

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

Concomitant medications are defined as all medications other than study drug administered to a patient from the study enrollment until the end of the study.

Local standard treatment of hemophilia, which is considered to be, but not limited to, IV infusion of FVIII or FIX concentrates, aPCC or rFVIIa are used for Factor/BPA Prophylaxis and bleeding episode management. Use of these agents will be captured in the patient's eDiary.

Other concomitant medications including all prescription medications, herbal preparations, over the counter medications, vitamins, and minerals are to be reported in the case report form (CRF) pages.

Prior medications for HCV treatment before study enrollment are also collected at screening visit.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint

Global protocol: The primary efficacy endpoint of the study is annualized bleeding rate (ABR) in the fitusiran efficacy period and the factor/BPA prophylaxis period.

US protocol: The primary efficacy endpoint of the study is annualized bleeding rate (ABR) in the fitusiran treatment period and the BPA prophylaxis period.

Bleeding Episode Definitions

The primary source of bleeding data is 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 factor or BPA infusion, eg, hemarthrosis, muscle, or mucosal bleeding episodes.

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

A spontaneous bleeding episode is a bleeding event that occurs for no apparent or known reason, particularly into the joints, muscles, and soft tissues.

Bleeding episodes sustained during sports and recreation will be counted as traumatic bleeding episodes.

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.

A joint bleeding episode is characterized by an unusual sensation in the joint ("aura") in combination with 1) increasing swelling or warmth over the skin over the joint, 2) increasing pain or 3) progressive loss of range of motion or difficulty in using the limb as compared with baseline.

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

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 with BPA/factor will be included in the primary analysis of endpoints evaluating bleeding.

Annualized bleeding rate will be calculated as described in Section 2.4.4.1.1.

Efficacy Period and factor/BPA prophylaxis Period

In the protocol, for the purpose of ABR calculation, the factor/BPA prophylaxis period and fitusiran "Onset Period", "Efficacy Period" and "Treatment Period" are defined. The factor/BPA prophylaxis period is defined as the 6 months period before the first dose of fitusiran, during which patients continue their pre-study, regularly scheduled prophylaxis regimen with factor concentrates or BPAs. 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.

Period	Definition
Factor/BPA prophylaxis period	Day -168 to the earlier of Day -1 or the last day of bleeding follow up
Fitusiran onset period	Day 1 to the earlier of Day 28 or the last day of bleeding follow up
Fitusiran efficacy period	Day 29 to the earlier of Day 190 or the last day of bleeding follow up
Fitusiran 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 in the fitusiran treatment period, 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 factor/BPA prophylaxis period, fitusiran 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.

- Permanent fitusiran treatment discontinuation during treatment period: Exclude events occurring on any dates starting from the date of the last dose within treatment period +29 days. For patients whose last dose is on 50 mg/20 mg Q2M regimen, the "29 days" adjustment will be replaced with 57 days.
- 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.

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

2.1.3.2 Secondary efficacy endpoints

	Global protocol	US protocol
Key secondary endpoint		ABR in the fitusiran efficacy period
Secondary endpoints	ABR in the treatment period	
	Annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period	Annualized spontaneous bleeding rate in the fitusiran efficacy period and the BPA prophylaxis period
	Annualized joint bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period	Annualized joint bleeding rate in the fitusiran efficacy period and the BPA prophylaxis period
	Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period	Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period
	ABR in the onset period	ABR in the onset period
	Annualized weight-adjusted consumption of factor/BPA	Annualized weight-adjusted consumption of BPA

2.1.3.2.1 HRQOL Instruments: Haem-A-QOL and Haemo-QOL

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QOL) and Haemophilia Quality of Life Questionnaire for Children and Adolescents (Haemo-QOL) are psychometrically tested QOL assessment instruments for patients with hemophilia. The Haem-A-QOL are 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 Haemo-QOL (Children's short version for age groups II/III [8-16 years of age]) are provided to patients <17 years of age.

Both Haem-A-QOL and Haemo-QOL test are assessed at Month -6, Day 1 and Month 7 visit.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) including SAEs and other safety information, such as clinical laboratory data, vital signs, weight and height, physical examination, ECG findings, and ADA detection/assessment.

Observation period:

- Factor/BPA prophylaxis period is defined as the time from enrollment (Month-6 visit) up to the 1st dose of fitusiran.
- Fitusiran prophylaxis period is defined as the time after the 1st dose of fitusiran up to the end of the study (defined as last protocol planned visit). It includes the following 2 periods:
  - Fitusiran treatment period is defined as the time after the 1st dose of fitusiran to the EOS/ET visit,
  - Follow up period is defined as the time after Fitusiran treatment period up to the end of the study.

The treatment-emergent adverse event period equals fitusiran prophylaxis period.

On-study observation period includes both factor/BPA prophylaxis period and fitusiran prophylaxis period.

2.1.4.1 Adverse events variables

AE observation period:

- Pretreatment AEs are defined as those AEs that developed or worsened during factor/BPA prophylaxis period.
- Treatment emergent AEs are defined as those AEs that developed or worsened during treatment-emergent adverse event period.

All adverse events (including serious adverse events [SAEs] and adverse events of special interests [AESI]) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at the time of database lock.

Record the occurrence of adverse events (including serious adverse events and adverse events of special interest) from the time of signed informed consent until the end of the study.

Adverse events of special interest include the following terms:

- ALT or AST elevations >3 × ULN,
- Suspected or confirmed thrombosis,
- Severe or serious 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 fitusiran,
- Systemic IARs (injection associated reactions), defined as hypersensitivity reactions which are related or possibly related to IMP.
- Cholecystitis
- Cholelithiasis

The cholecystitis and cholelithiasis will be identified by medical adjudication on a listing of adverse event searched with SMQ Biliary disorders (broad) and SMQ Acute pancreatitis (narrow), since these two AESIs were added in protocol V6.0 near the end of study.

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study period,
- Death on factor/BPA prophylaxis: deaths occurring during the factor/BPA prophylaxis period,
- Death on fitusiran treatment: deaths occurring during the fitusiran treatment period,
- Death on follow up: death occurring during the follow up period.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion are analyzed in standard international units and international units are used in listings and tables.

Blood samples for clinical laboratories are taken at screening visit, every month in factor/BPA prophylaxis period, every half month in the first two months of fitusiran treatment period and then every month in the remaining study period.

The laboratory parameters are classified as follows:

- Hematology
  - Red blood cells and platelets: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, red blood cell count, platelet count
  - White blood cells: white blood cell (WBC) count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, CD4 in HIV-positive patients (at screening only)
  - Coagulation: Prothrombin time, Activated partial thromboplastin time, INR, Fibrinogen, D-dimer, Prothrombin fragment 1, 2
- Clinical chemistry
  - Metabolism: glucose, albumin
  - Electrolytes: sodium, potassium, chloride, calcium, phosphate, Carbon dioxide
  - Renal function: creatinine and eGFR (using the MDRD formula), blood urea nitrogen (BUN)
  - Liver function: aspartate aminotransferase (AST), ALT, ALP, GGT, bilirubin (total and direct)
- Factor Activity (are assessed at screening only): FVIII activity for patients with hemophilia A, FIX activity for patients with hemophilia B
- Hepatic tests (are assessed at screening and Day 1 visit):
  - Hepatitis A, including: HAV antibody IgM and IgG
  - Hepatitis B, including: HBc antibody IgM and IgG
  - Hepatitis C, including: HCV antibody and HCV RNA PCR - qualitative and quantitative assays
  - Hepatitis E, including: HEV antibody IgM and IgG
- Thrombophilia Screening (are assessed at screening only): Protein C deficiency, Protein S deficiency, Factor V Leiden (genetic testing), Prothrombin mutation (genetic testing)

Urine samples are collected as follows:

- Urinalysis (assessed at screening, Month -6 and Month 7 visit): Visual inspection for appearance and color, pH (dipstick), ketones, protein, glucose, RBCs, urobilinogen, bilirubin, Nitrite, microscopic (if clinically indicated), Leukocytes, specific gravity.

2.1.4.4 Physical examination and vital signs variables

Physical examination and vital signs are done at screening visit, every month in factor/BPA prophylaxis period, every half month in the first two months of fitusiran treatment period and then every month in the remaining study period.

Physical examination may be full or directed.

Full physical examinations include general appearance, head, eyes, ears, nose and throat; respiratory, cardiovascular, gastrointestinal, musculoskeletal, and dermatological systems; thyroid, lymph nodes, and neurological status.

Directed physical examinations include systems associated or common for signs and symptoms of thrombosis, bleeding, and arthropathy: neurologic, chest/respiratory, heart/cardiovascular, dermatological/skin, gastrointestinal/liver, and musculoskeletal/extremities. Other organ systems may be evaluated as indicated by patient symptoms. In patients undergoing a surgical procedure, a directed physical examination will also be performed as specified in the Perioperative Schedule of Assessments in the protocol.

A full physical examination is done at screening only; a directed physical exam is done at all other visits.

Physical examination notes regarding any observed abnormalities are recorded on the eCRF.

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs are measured predose in the seated or supine position, after the patient has rested comfortably for 10 minutes.

Body temperature is recorded in degrees Celsius. Heart rate is counted for a full minute and recorded in beats per minute, and respiration rate is counted for a full minute and recorded in breaths per minute.

For the safety of the patient, additional vital sign assessments may be added at the discretion of the Investigator.

Vital signs results are recorded in the eCRF.

Measurements of weight and height are also collected at above scheduled visits for physical examination and vital signs.

2.1.4.5 Electrocardiogram variables

Triplicate standard 12-lead ECGs, with readings approximately 1 minute apart, are recorded at screening, Month -6, Day 1, Month 5 and Month 7 visits.

The electrophysiological parameters assessed are rhythm, ventricular rate, RR interval, PR interval, QRS duration, QT interval, Bazett-corrected QT interval (QTcB), and Fridericia corrected QT interval (QTcF).

The Investigator or qualified designees review all ECGs to assess whether the results have changed since the Day 1 visit and to determine the clinical significance of the results. These assessments are recorded on the eCRF. Additional ECGs may be collected at the discretion of the Investigator. Recordings are archived according to the Study Manual.

2.1.5 Pharmacokinetic variables

For all patients

- Plasma PK parameters are estimated using a population PK approach. The population PK analysis is described in a separate population PK analysis plan

For patients from East Asian sites only

- In addition to population PK analysis, plasma PK parameters for the patients from the East Asian sites only are also estimated using non-compartmental analysis. The plasma PK parameters include, but may not be limited to:
  - Maximum plasma concentration (C_{max})
  - Time to maximum plasma concentration (t_{max})
  - Elimination half-life ($t½\beta$)
  - Area under the concentration-time curve (AUC)
  - Apparent clearance (CL/F)
  - Apparent volume of distribution (V/F)
- Fitusiran levels in 0-24 h urine are 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

2.1.6 Pharmacodynamic endpoints

In this study AT activity level and thrombin generation (TG) over time are collected as measurements of PD effect and coagulation assessments are collected for exploratory analyses of PD effect.

AT activity level and TG are assessed at screening, Day 1 and then every half month in the first two months of fitusiran treatment period and then every month in the remaining study period.

During the factor/BPA prophylaxis period (before fitusiran treatment), patients undergo a coagulation and peak thrombin/thrombin generation response assessment with timed blood collections both before and following a dose of their routine factor/BPA prophylaxis doses.

2.1.7 Exploratory endpoints

Exploratory endpoints include:

- Change in the following in the fitusiran treatment period:
  - Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores
  - Haemophilia Activities List (HAL) score

  - Paediatric HAL (pedHAL) score
  - EuroQol -5 Dimensions (EQ-5D) score
  - Haemo-QOL score
  - Hemophilia Joint Health Score (HJHS)
- Number of target joint bleeding episodes
- Incidence and titer of antidrug antibodies to fitusiran in the fitusiran treatment period
- AT activity level over time
- TG over time
- Fitusiran plasma levels
- Change in patient resource use (eg, work/school attendance, visits to doctor/hospital)

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patient who signed the informed consent.

Enrolled patients are defined as any patient with a signed informed consent form (ICF) who met all the inclusion criteria and none of the exclusion criteria.

This is an open-label, single-arm, before and after switch study without randomization.

For patient study status, the total number of patients in each of the following categories is presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screened failure patients and reasons for screen failure (if data are available)
- Enrolled patients
- Patients treated without entering factor/BPA prophylaxis period
- Patients who entered factor/BPA prophylaxis period (run-in)
- Patients who completed the factor/BPA prophylaxis period
- Patients who did not complete factor/BPA prophylaxis period, with corresponding reasons
- Patients who did not complete factor/BPA prophylaxis period, with corresponding reasons due to Covid-19
- Patients treated after factor/BPA prophylaxis period
- Patients who completed the study treatment (7-month treatment period)

- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation due to Covid-19
- Patients who completed the study
- Patients who did not complete the study but complete the 7-month treatment period
- Patients who did not complete the study, with corresponding reasons.
- Patients who did not complete the study, with corresponding reasons due to Covid-19.

For all categories of patients (except for the screened categories), percentages are calculated using the number of enrolled patients as the denominator. Reasons for treatment discontinuation are supplied in tables giving numbers and percentages.

All critical or major deviations potentially impacting efficacy analyses, and other major or critical deviations are summarized in tables giving numbers and percentages.

Additionally, the analysis populations (analysis sets) for safety and efficacy are summarized in a table.

- Efficacy Analysis Set 1
- Efficacy Analysis Set 2
- Per-protocol Analysis Set
- Safety Analysis Set 1
- Safety Analysis Set 2
- Operative Procedure Analysis Set
- Covid-19 Unaffected Set

2.3 ANALYSIS POPULATIONS

The populations (analysis sets) are defined as follows:

- **Safety Analysis Set 1 (SAS 1) :** All patients who enrolled and then received any dose of fitusiran before dose resumption. Safety Analyses for patients who were treated with fitusiran in 80mg QM dose regimen before dose resumption will be conducted using the Safety Analysis Set 1 unless otherwise specified.
- **Safety Analysis Set 2 (SAS 2) :** All patients who enrolled and then received any dose of Fitusiran after dose resumption. Safety Analyses for patients who were treated with fitusiran in 50mg Q2M after dose resumption will be conducted using the Safety Analysis Set 2 unless otherwise specified.

- **Efficacy Analysis Set 1 (EAS1) 1:** All patients in the safety analysis set 1 who received factor or BPA prophylaxis and any dose of fitusiran before dose resumption. Efficacy Analyses before dose resumption will be conducted using EAS 1 unless otherwise specified.
- **Efficacy Analysis Set 2 (EAS 2) :** All patients in the safety analysis set 2 who received factor or BPA prophylaxis and any dose of fitusiran. Efficacy Analyses after dose resumption will be conducted using EAS 2 unless otherwise specified.
- **Per-protocol Analysis Set (PPS):** All patients in the EAS 1 who do not have protocol deviations in the following categories:
  - Failure to meet key Eligibility criteria, which will be identified prior to database lock,
  - Other protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the bleeding data.

  The major or critical deviations to be considered are as follows.

  - The participant is not male and/or is younger than 12 years, but the participant was enrolled.
  - The participant does not have severe hemophilia A or B as evidenced by a laboratory FVIII level <1% or FIX level ≤2% at Screening or by documented medical record, but the participant was enrolled.
  - The participant does not have a minimum of:
    - 2 bleeding episodes requiring bypassing agent treatment within the last 6 months prior to Screening for participants with inhibitory antibodies to FVIII or FIX (Cohort A),
    - 1 bleeding episode requiring factor treatment within the last 12 months prior to Screening for patients without inhibitory antibodies to FVIII or FIX (Cohort B), but the participant was enrolled.
  - The participant was enrolled, but does not meet either the definition of inhibitor or non-inhibitor as below:

    Inhibitor, as evidenced by:
    - Use of bypassing agents for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening,
    - Meeting one of the following Nijmegen-modified Bethesda assay results criteria:
      - Inhibitor titer of ≥0.6 BU/mL at Screening, or
      - Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of 2 consecutive titers ≥0.6 BU/mL, or
      - Inhibitor titer of <0.6 BU/mL at Screening with medical record evidence of anamnestic response,

- The subgroup of patients in Cohort A patients must additionally meet the following criteria to be eligible to start treatment with fitusiran directly after the screening period:
  - Hemophilia B with inhibitory antibody to FIX as defined above and
  - Not responding adequately to BPA treatment (historical ABR ≥20) prior to enrollment and
  - In the opinion of the Investigator, with approval of sponsor medical monitor, 6-month BPA prophylaxis period should be omitted.

  Non-inhibitor, as evidenced by:
- Use of factor concentrates for prophylaxis and for any bleeding episodes for at least the last 6 months prior to Screening,
- Meeting each of the following criteria:
  - Nijmegen-modified Bethesda assay inhibitor titer of <0.6 BU/mL at Screening and
  - No use of bypassing agents to treat bleeding episodes for at least the last 6 months prior to Screening and
  - No history of immune tolerance induction therapy (ITI) within the past 3 years prior to Screening,

- The participant did not receive prescribed prophylactic treatment of hemophilia with factor concentrates or bypassing agents for at least 6 months prior to Screening, or did not receive a prophylactic regimen consistent with the approved prescribing information for the product or local recommendations, allowing for adjustment to individual patient response, and designed to decrease spontaneous bleeding, but the participant was enrolled.
- The participant has known co-existing bleeding disorders other than hemophilia A or B, but the participant was enrolled
- The participant discontinued prophylactic treatment or withdrew consent during the factor/bypassing agent prophylaxis period, but participant was not withdrawn from the study.
- The participant continued or reinitiated use of factor concentrates or bypassing agents as prophylaxis for bleeding episode prevention, during the fitusiran prophylaxis treatment period but the study drug was not discontinued.
- The participant did not administer prophylaxis therapy with minimum frequency as per protocol (table 5) during the prophylaxis period:
  - Standard half-life FVIII (Twice weekly)
  - Extended half-life FVIII (Once weekly)
  - Standard half-life FIX (Once weekly)
  - Extended half-life FIX (Once biweekly)

- aPPC (Twice weekly)
- rFVIIa (Every other day)

- **Operative Procedure Analysis Set:** All SAS 1 patients underwent at least 1 operative procedure during the study.
- **Covid-19 Unaffected Set:** All EAS 1 patients who had no major or critical protocol deviations due to Covid-19 at any visits up to end of study (Month 7).

In addition:

Patients treated without entering factor/BPA prophylaxis period are included in the safety analysis set, but are not part of the efficacy analysis set; however, their efficacy data are presented separately.

Patients who entered factor/BPA prophylaxis period but not treated with fitusiran are not included in either safety analysis set or efficacy analysis set, however, their safety data are reported separately.

2.4 STATISTICAL METHODS

All the below statistical analyses are done for Cohort A and Cohort B separately. A pooled analysis is performed after all patients in the 2 cohorts have either finished the Month 7 visit during the fitusiran treatment period or discontinued from the study. Participants treated with fitusiran of 80mg QM and participants treated with fitusiran of 50mg Q2M will be analyzed separately. All the analysis will mainly focus on the participants treated with fitusiran of 80mg QM. The key efficacy, pharmacodynamic and safety data from participants treated with fitusiran of 50mg Q2M will mainly be listed due to the small sample size (only 2 participants). When safety analysis are mentioned in this doc, it refers to SAS1 and/or SAS 2 in this SAP.

2.4.1 Demographics and baseline characteristics

Continuous data are summarized using the number of patients (n), mean, standard deviation (SD), median, minimum, Q1, Q3, and maximum. Categorical and ordinal data are summarized using the number and percentage of patients.

Parameters are summarized by hemophilia type and overall on the EAS and Per-protocol analysis set. Analyses for the safety analysis set are included in the appendices if the size of the safety analysis set is different (>10%) from the size of EAS.

Medical and surgical history are summarized by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC.

No statistical testing on demographic and baseline characteristic data are performed.

No specific description of the safety parameters are provided at baseline. If relevant, the baseline values are described along with each safety analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications are summarized by hemophilia type and overall for the safety analysis set.

Prior and concomitant medications are coded using the World Health Organization-Drug Dictionary (WHO-DD) currently in effect at Sanofi at the time of database lock. Results will be tabulated by anatomic therapeutic class (ATC) and preferred term.

Concomitant medications are tabulated by observation period (factor/BPA prophylaxis period and fitusiran prophylaxis period) and summarized separately for Factor/BPA prophylaxis medications, bleeding treatment medications and other concomitant medications. Any medications that did not end prior to first visit of the study are included. If an end date is missing or the medication is ongoing, the medication is included.

2.4.3 Study duration, extent of study treatment exposure and compliance

Fitusiran is the study treatment which is administrated by SC injection during the fitusiran treatment period for a total of 7 months.

Study duration, extent of study treatment exposure and compliance are assessed and summarized by hemophilia type and overall in the safety population.

Study duration in factor/BPA prophylaxis period in days is calculated as first dose date of fitusiran - enrollment date. Study duration in fitusiran treatment period in days is calculated as EOS/ET visit date -first dose date of fitusiran +1. Total study duration including AT follow-up in days is calculated as date of last follow up - enrollment date +1. The number of patients in each 2 months interval and summary statistics for the study duration are presented.

The extent of study treatment exposure is assessed by duration of treatment exposure in days and total number of fitusiran administrations received. Both of them will be summarized for fitusiran treatment period only.

For participants treated with fitusiran 80mg QM dose regimen, duration of treatment exposure in days is calculated as date of the last dose of fitusiran − the date of the first dose of fitusiran + 28. The number 28 is the number of days between two scheduled doses of fitusiran. For example, if the last dose of fitusiran 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 is calculated as the total mg dose received as the percentage of total mg dose expected to receive. Fitusiran treatment compliance is summarized.

2.4.4 Analyses of efficacy endpoints

Analyses for all the primary and secondary efficacy endpoints are conducted using EAS 1 as defined in Section 2.3. Listings of ABR will be provided for participants in EAS 2.

Baseline for fitusiran treatment period is defined as the last non-missing value on or before the date of first dose of fitusiran. Baseline for factor/BPA prophylaxis period is defined as the last non-missing value on or before the enrollment date (Month -6 visit date).

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis based on on-treatment strategy

The primary objective of this study is to characterize the frequency of bleeding episodes while receiving fitusiran treatment, relative to the frequency of bleeding episodes while receiving factor/BPA prophylaxis. Including bleeding events in the period of intercurrent events such as use of prophylactic medication during fitusiran treatment period 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 (1)).

Global protocol

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

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

The primary analysis includes all bleeding episodes occurring in the factor/BPA prophylaxis period and the fitusiran efficacy period.

Let λ_F represent the ABR during fitusiran efficacy period and λ_O represent the ABR during factor/BPA prophylaxis period. The null and alternative hypotheses of the primary analysis, respectively, can be written as follows:

$$H_0: \frac{\lambda_F}{\lambda_O} = 1 \quad H_A: \frac{\lambda_F}{\lambda_O} \neq 1$$

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

The ABR ratio λ_F/λ_O is estimated using a repeated measures negative binomial model:

$$\log(\text{number of bleeding episode}) = \beta_0 + \beta_1 \cdot \text{study period} + \log(\text{duration})$$

The number of bleeding episodes is the response variable. The study period (fitusiran efficacy period or factor/BPA prophylaxis period) is treated as a fixed effect and a robust sandwich covariance matrix is constructed to account for the within participant dependence. The logarithm of the duration (in years) that each patient spends in each study 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 efficacy period to the factor/BPA prophylaxis period, its 95% CI and p-value will be presented. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analysis is performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. The estimated mean ABRs in these 2 periods along with their 95% CIs are presented from this model. In addition, median and interquartile range (Q1, Q3) for the observed ABR are summarized descriptively for each study periods.

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 visit is used in the primary analysis.

US protocol

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

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

The primary analysis includes all bleeding episodes occurring in the BPA prophylaxis period and the fitusiran treatment period.

Let λ_F represent the ABR during fitusiran treatment period and λ_O represent the ABR during BPA prophylaxis period. The null and alternative hypotheses of the primary analysis, respectively, can be written as follows:

$$H_0: \frac{\lambda_F}{\lambda_O} = 1 \quad H_A: \frac{\lambda_F}{\lambda_O} \neq 1$$

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

The ABR ratio λ_F/λ_O is estimated using a repeated measures negative binomial model:

$$\log(\text{number of bleeding episode}) = \beta_0 + \beta_1 \cdot \text{study period} + \log(\text{duration})$$

The number of bleeding episodes is the response variable. The study period (fitusiran treatment period or BPA prophylaxis period) is treated as a fixed effect and a robust sandwich covariance matrix is constructed to account for the within participant dependence. The logarithm of the duration (in years) that each patient spends in each study 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 period to the BPA prophylaxis period, its 95% CI and p-value are presented. The p-value should be interpreted with caution. In addition, as a contrast Bayesian analyses are performed to summarize the point estimates of the posterior probability of a clinically significant treatment effect, along with associated measures of uncertainty. The estimated mean ABRs in these 2 periods along with their 95% CIs are presented from this model. In addition, median and interquartile range (Q1, Q3) for the observed ABR are summarized descriptively for each study periods.

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 is performed.

2.4.4.1.2 Efficacy analysis based on treatment policy strategy

A supportive efficacy analysis is 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 EAS as in the primary analysis. The same repeated measures negative binomial model as in the primary analysis is used. It assesses the benefits of the fitusiran treatment policy strategy relative to factor/BPA prophylaxis treatment.

A sensitivity analysis to the above treatment policy analysis is 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 are performed to assess the robustness of this treatment policy analysis by imputing the missing data based on different missing data mechanism. The missing data is imputed using multiple imputation (MI) methods for recurrent event data based on pattern mixture models (Keene et al, 2014(2)) to assess the impact of different assumptions about the statistical behavior of post-withdrawal outcomes. The post-withdrawal part of each pattern-specific distribution is modelled using MAR and Copy Reference (CR) approaches. No missing data imputation is done for factor/BPA prophylaxis period since all the patients in EAS 1 complete factor/BPA prophylaxis period.

The MI is carried out in the following steps:

1. Fit a Bayesian negative binomial model with a noninformative prior to the observed data and obtain the posterior distributions of the event rate for both study periods.
2. Draw 100 independent samples from the conditional distribution of missing counts given the observed count and duration of each patient with missing data based on different post-withdrawal imputation models, described below, for fitusiran efficacy period (fitusiran treatment period for US protocol). 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 are then analyzed using the same repeated measure negative binomial regression model as in the primary analysis. Estimates from the model such as least square 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 study period and the estimate of the ABR ratio.

MAR and CR approaches are described below:

1. Missing at Random (MAR) Approach: Post-withdrawal missing bleeding events in fitusiran efficacy period (fitusiran treatment period for US protocol) are imputed using only the observed data during that period.
2. Copy Reference (CR) Approach: The expected ABR for a patient in the fitusiran efficacy period (fitusiran treatment period for US protocol) both pre- and post-withdrawal is assumed to be the same as that in the factor/BPA prophylaxis period. This accounts for a gradual loss of fitusiran effectiveness post-withdrawal. If a patient in fitusiran efficacy period (fitusiran treatment period for US protocol) has more events pre-withdrawal than expected if this patient had been in the factor/BPA prophylaxis period, then this "positive residual" feeds 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.

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 characterizing the frequency of bleeding episodes while receiving fitusiran treatment, relative to bypassing agent (BPA) prophylaxis.

Per-protocol analysis

Efficacy analysis will be repeated on the per-protocol analysis set as defined in Section 2.3.

Zero-inflated negative binomial model

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

Bayesian analysis

A supportive efficacy analysis will be performed for the primary endpoint by using the Bayesian repeated measure Negative Binomial regression model. The informative prior distributions of the model parameters (eg, treatment effect, random effect, dispersion) may be used in the model. The ratio of ABR in the fitusiran efficacy period (fitusiran treatment period for US protocol) to the factor/BPA prophylaxis period, its 95% CI and the posterior probability of clinically significant treatment effect will be estimated. To assess sensitivity of the posterior distribution to this informative prior, an additional analysis will be performed using a neutral prior assuming mean ABR ratio of 1.

This Bayesian analysis will be implemented via PROC MCMC in SAS.

Covid-19 related sensitivity analysis

To address the impact of Covid-19, the above on-treatment and treatment policy efficacy analyses will be repeated on the Covid-19 unaffected set as defined in Section 2.3. In addition, a sensitivity analysis based on on-treatment strategy will be performed by excluding the additional following intercurrent events:

- 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 + 29 days) before missing doses due to Covid-19 to one month after starting of re-dosing (ie, first re-dose date + 28 days). For participants treated with fitusiran 50mg Q2M dose regimen, replace the number of 28 with 56.
- Period from 6 months after enrollment of factor/BPA prophylaxis period to the date of first fitusiran dose if the date of first fitusiran dose was delayed due to Covid-19

The same negative binomial model as in the primary analysis will be used.

2.4.4.1.3 Exploratory analysis

All bleeding episodes (treated or untreated)

The on-treatment and treatment policy efficacy analyses are 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 factor or BPA prophylaxis period is calculated as the number of days between Day -168 and the onset date of the first treated bleeding event during the factor or BPA prophylaxis period. The patient is censored at the earlier of Day -1 if no treated bleeding event has occurred. The time to first treated bleeding event in the fitusiran treatment period is 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 is censored at the earlier of Day 190 if no

treated bleeding event has occurred. The time to first treated bleeding event in the efficacy period is 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 is imputed from Day 1 as in the treatment period.

The time to first treated spontaneous bleeding event is calculated similarly.

For on-treatment analysis, time to first treated bleeding episode will be adjusted by intercurrent events.

The proportion of patients who are bleeding free in fitusiran treatment period and factor or BPA prophylaxis period will be estimated using the Kaplan-Meier method and compared using a Cox proportional hazards (PH) regression model with a robust sandwich covariance matrix to account for the within participant dependence, and the study period as a fixed effect. Plots of cumulative mean functions for the number of treated bleeds in the fitusiran treatment period and factor or BPA prophylaxis period will be provided.

Symptoms related to bleeding

Descriptive statistics are provided for symptoms related to bleeding events by each study period.

2.4.4.1.4 Subgroup analysis

Based on the mechanism of action of fitusiran, there should not be difference in the safety or efficacy of fitusiran between hemophilia A or B, either with or without inhibitors. Nevertheless, the subgroup efficacy analysis based on hemophilia type and inhibitor status will be part of subgroup analyses specified below without formal statistical testing due to exploratory nature of these analyses.

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

- Hemophilia type (Type A vs B)
- Number of bleeding episodes prior to screening (<=10 vs >10)
- Age group, years (<18, 18-64, ≥65)
- Cohort A vs Cohort B

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

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

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 ABR in the fitusiran efficacy period (Key secondary endpoint for US protocol)

Analysis includes all bleeding episodes occurring in the fitusiran efficacy period. The on-treatment and treatment policy efficacy analysis are repeated with this endpoint. Estimated mean ABR and its 95% CI will be presented. No formal hypothesis testing will be performed.

2.4.4.2.2 Annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period

Analysis includes spontaneous bleeding episodes occurring in the factor/BPA prophylaxis period and the fitusiran efficacy period. The on-treatment and treatment policy efficacy analyses are repeated with this endpoint.

2.4.4.2.3 Annualized joint bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period

Analysis includes joint bleeding episodes occurring in the factor/BPA prophylaxis period and the fitusiran efficacy period. The on-treatment and treatment policy efficacy analyses are repeated with this endpoint.

2.4.4.2.4 Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period and the factor or BPA prophylaxis period

Change from baseline in Haem-A-QOL physical health score and total score (in patients ≥17 years of age) in the factor or BPA prophylaxis period and fitusiran treatment period are analyzed using a mixed model for repeated measure analysis (MMRM) with robust sandwich covariance matrix, with fixed effects of study period (factor or BPA prophylaxis period and fitusiran treatment period), baseline Haem-A-QoL physical health score and total score for each study period as covariates. Least square means of the physical health score and total score in each treatment period and the difference of the least square means of the physical health score and total score in the two periods (along with the 95% CI and p-value) are presented. The normality assumption based on MMRM model is examined and a sensitivity analysis based on the non-parametric Wilcoxon signed-rank test is performed. For patient with missing assessment due to early withdrawal, a sensitivity analysis is performed by imputing the domain score and total score as the worst score if the reason of withdrawal is treatment-related in the fitusiran treatment period, and as the average score for other reasons of withdrawal that are not treatment related in the fitusiran treatment period. 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 MMRM model will also be repeated on Covid-19 unaffected set. In addition, a sensitivity analysis using same MMRM 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 of factor or BPA prophylaxis period.

Change from baseline in Haem-A-QOL physical health score and total score in the factor or BPA prophylaxis period and fitusiran treatment period are also summarized descriptively by study period.

Domain scores, standardized scale scores, and transformed scale scores for Haem-A-QoL and their changes from baseline in the factor or BPA prophylaxis period and fitusiran treatment period are summarized by study period.

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 are stratified by ABR level (0, 1-5, >5) and concomitant pain medication use (Y, N). The ABR level is based on on-treatment strategy during the fitusiran treatment period and factor or BPA prophylaxis period.

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

2.4.4.2.5 ABR in the onset period

Analysis includes all bleeding episodes occurring in the onset period. The on-treatment and treatment policy efficacy analysis are repeated with this endpoint. Estimated mean ABR and its 95% CI are presented. No formal hypothesis testing is performed.

2.4.4.2.6 ABR in treatment period (Global protocol)

Analysis includes all bleeding episodes occurring in the fitusiran treatment period. The on-treatment and treatment policy efficacy analysis are repeated with this endpoint. Estimated mean ABR and its 95% CI are presented. No formal hypothesis testing is performed.

2.4.4.2.7 Annualized weight-adjusted consumption of factor/BPA

Factor/BPA 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/BPA usage, as treatment of breakthrough bleeding episodes as well as prophylaxis factor/BPA usage. Weight-adjusted factor/BPA usage will be calculated programmatically.

The annualized weight-adjusted factor/BPA consumption for both treating bleeds and prophylaxis purpose, number of factor/BPA injections per bleed/per participant, weight adjusted total dose per bleed/per participant, 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 for both factor/BPA prophylaxis period and fitusiran treatment period. 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.

2.4.4.3 Multiplicity issues

No multiplicity control is provided for this study

2.4.5 Analyses of safety data

General common rules

All safety analyses will be performed on the safety analysis set (SAS1 or SAS 2) as defined in Section 2.3, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety analysis set (eg, entered factor or BPA prophylaxis period and not treated with fitusiran) are listed separately
- The baseline value for fitusiran prophylaxis period is defined as the last non-missing value before the first dose of fitusiran. The baseline value for factor or BPA prophylaxis period is defined as the last non-missing value before the enrollment date.
- For ECG measurements, which are taken in triplicate, the average of the last triplicate readings before first dose of fitusiran/enrollment date is used as baseline for fitusiran prophylaxis period/factor or BPA prophylaxis period.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs
- PCSA criteria determines which patients had at least 1 PCSA during each observation period (factor or BPA prophylaxis period and fitusiran prophylaxis period), taking into account all evaluations performed during each observation period, including nonscheduled or repeated evaluations. The number of all such patients is the numerator for the PCSA percentage in each observation period.
- The PCSA denominator for a given parameter is based on the number of patients assessed for that given parameter in each observation period on the safety analysis set. Number (%) of patients with at least 1 PCSA is summarized regardless of baseline PCSA status and also by baseline PCSA status by observation period.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics are used to summarize results and change from baseline values by visit and observation period. Summaries include the endpoint value which is defined as the last non-missing post-baseline assessment on or before EOS/ET visit for fitusiran prophylaxis period and on or before the day before first dose date of fitusiran for factor/BPA prophylaxis period.
- The analysis of the safety variables is essentially descriptive and no systematic testing is planned.
- All safety values including unscheduled measurements are assigned to the appropriate safety analysis visit window defined in Section 2.5.4.

2.4.5.1 Analyses of adverse events

Generalities

The focus of adverse event reporting is on treatment-emergent adverse events and pre-treatment adverse events. Adverse events occurring in the screening period are analyzed separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete (missing time, day, month or year), an imputation algorithm is used to classify the adverse event as pretreatment and treatment-emergent. The algorithm for imputing date/time of onset is conservative and classifies an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

AEs are summarized by observation period (factor/BPA prophylaxis period and fitusiran prophylaxis period) and 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 is counted only once in the respective AE category. Patients who report multiple occurrences of the same AE (preferred term) are classified according to the most related or most severe occurrence, respectively.

All AE summaries are presented (frequency counts and percentages) by system organ class and/or preferred term, unless specified otherwise. The SOC is presented by internationally agreed order and the preferred term is sorted within each SOC in decreasing order of frequency in fitusiran prophylaxis period.

Analysis of all adverse events

An overall summary of AEs includes the number and percentage of patients with any:

- AE
- AE assessed by the Investigator as related to study drug (fitusiran only, possibly related or definitely related)
- severe AE
- severe AE related to study drug
- serious AE (SAE)
- SAE related to study drug
- AE/SAE of special interest
- Study drug related AE/SAE of special interest
- AE/SAE leading to study drug discontinuation
- Study drug related AE/SAE leading to study drug discontinuation
- AE/SAE leading to study withdrawal

- Study drug related AE/SAE leading to study withdrawal
- SAE with a fatal outcome.
- AEs potentially consistent with COVID-19

The overall summary of AEs will also be provided by hemophilia type.

Tabulations by SOC and PT are produced for the following:

- AEs
- AEs by severity
- AEs by hemophilia type
- SAEs
- AEs related to study drug (fitusiran prophylaxis period only)
- AEs related to study drug by hemophilia type (fitusiran prophylaxis period only)
- SAEs related to study drug (fitusiran prophylaxis period only)
- SAEs related to study drug by hemophilia type (fitusiran prophylaxis period only)
- AESI
- AESI by hemophilia type
- AEs leading to study drug discontinuation (fitusiran prophylaxis period only)
- SAEs leading to study drug discontinuation (fitusiran prophylaxis period only)
- AESIs leading to study drug discontinuation (fitusiran prophylaxis period 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 on MedDRA SMQ COVID-19 (narrow).

Tabulations by PT in decreasing order of frequency in the fitusiran prophylaxis period are produced for the following:

- AEs
- AEs by hemophilia type
- SAEs
- AEs related to study drug (fitusiran prophylaxis period only)
- SAEs related to study drug (fitusiran prophylaxis period only)

All AEs collected are listed along with the information collected on those AEs, eg, AE relationship to study drug, AE outcome etc. AEs that are not treatment-emergent are 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.

2.4.5.2 Analyses of laboratory variables

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

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

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

A listing is 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 is produced to summarize the number and percentage of patients in each of below categories at any post-baseline time point by observation period.

- 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) is plotted against the peak AST, the peak ALT, and the peak AST or ALT levels at any time post-baseline by observation period. The mean of ALT, AST, and total bilirubin will be plotted over time. The Kaplan-Meier curve for the time to first onset of ALT>3ULN, AST>3ULN and AST/AST >3ULN will be provided.

For hematology and blood chemistry, summary tables of potentially clinically significant abnormalities (PCSA) are provided by observation period.

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

2.4.5.3 Analyses of physical examination and vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital sign variables are calculated for each visit or study assessment in factor or BPA prophylaxis period and fitusiran prophylaxis period. Summary table of potentially clinically significant abnormalities (PCSA) are provided by observation period.

Vital sign measurements are presented for each patient in a data listing as appropriate, with abnormal vital signs flagged.

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

2.4.5.4 Analyses of electrocardiogram variables

PR, QRS, QT, QTc and RR intervals and their change from baseline values are summarized by scheduled visit for each observation period. Besides, their change from time-matched and pre-dose baseline are also summarized in fitusiran prophylaxis period by scheduled visit. Participants are 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 participants in each category are summarized.

For post-baseline assessments where ECG is performed in triplicate, the average of the 3 (or all available) readings is used for analysis.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Analyses of pharmacodynamic variables

2.4.6.1.1 Antithrombin

AT levels and AT lowering (% lowering from baseline) in the fitusiran prophylaxis period are summarized descriptively.

2.4.6.1.2 Peak thrombin

Peak thrombin values collected within 48 hours of factor, BPA or antifibrinolytic administration are excluded from all analysis. Peak thrombin values in the fitusiran prophylaxis period are summarized descriptively.

2.4.6.1.3 AT lowering and peak thrombin

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

2.4.6.2 Analyses of pharmacokinetic variables

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 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 would be reported separately.

2.4.7 Analyses of exploratory endpoints

2.4.7.1 TSQM-9

The Treatment Satisfaction Questionnaire for Medication (TSQM) version 9 assesses patient satisfaction with treatment. The TSQM Scale scores, and their changes from baseline in the factor or BPA prophylaxis period and fitusiran treatment period are summarized descriptively.

2.4.7.2 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 from baseline in the factor or BPA prophylaxis period and fitusiran treatment period are summarized descriptively.

2.4.7.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of QOL outcome. Index value and visual analogue scale (VAS) score and their changes from baseline in the factor or BPA prophylaxis period and fitusiran treatment period are summarized descriptively. Numbers and percentages of patient by level and dichotomized level (1 = no problems, 2 to 5 = “problems”) of each dimension are reported.

2.4.7.4 Haemo-QOL

The Haemo-QOL will be provided to patients<17 years of age. The change from baseline in total score of Haemo-QOL in the factor or BPA prophylaxis period and fitusiran treatment period are analyzed using a mixed model for repeated measure analysis (MMRM) with a robust sandwich covariance matrix, with fixed effects of study period (factor or BPA prophylaxis period and fitusiran treatment period), baseline Haemo-QOL total score for each treatment period as covariates. Domain scores for Haemo-QOL and their changes from baseline are summarized descriptively. Only the descriptive statistics are provided if MMRM model does not converge due to the small sample size.

2.4.7.5 HJHS

Joint health status is assessed via the HJHS, as administered by a healthcare professional trained in the use of anthropometric measures. Response is summarized. If the joint score is evaluated within 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.

2.4.7.6 Number of target joint bleeding episodes

An exploratory analysis of the number of target joint bleeding episodes may be performed using the same negative binominal model as the primary analysis.

2.4.7.7 Incidence and titer of antidrug antibodies to fitusiran in the fitusiran treatment period

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

2.4.7.8 AT activity level over time

Please refer to Section 2.4.6.1.1.

2.4.7.9 Thrombin generation over time

Please refer to Section 2.4.6.1.2.

2.4.7.10 Fitusiran plasma levels

Fitusiran plasma concentrations and PK parameters including but not limited to C_{max}, t_{max}, $t_{½\beta}$, AUC, CL/F, and V/F will be summarized descriptively.

2.4.7.11 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 in the factor or BPA prophylaxis period and fitusiran treatment period are summarized descriptively.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

All data listings that contain an evaluation date will contain a study day relative to the first dose date of fitusiran, which is designated as Day 1. Study days after first dose date of fitusiran will be calculated as evaluation date - first dose date +1 and study days before first dose date of fitusiran will be calculated as evaluation date -first dose date. For example, the day prior to first dose date of fitusiran will be Day -1 and the day after first dose date of fitusiran 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 mean, median and SD will be reported to 1 greater decimal place. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

2.5.2 Data handling conventions for secondary efficacy variables

Not Applicable.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered as a concomitant medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first dose of fitusiran is missing, all adverse events that occurred on or after the first day of fitusiran treatment period (M0/D1) should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to fitusiran is missing, then the relationship to fitusiran has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or > upper limit of normal (ULN) if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling of bleeding events with missing bleed/treatment time

On the eDiary device, it is not possible to leave questions unanswered or to enter partial date for bleeds or bleeding treatments.

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.

2.5.4 Windows for time points

A scheduled measurement will be used if it is available. Otherwise, derived analysis visit window will apply to data collected on unscheduled 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 2.5.1), according to the following allocation table:

Analysis visit label	**Target study day**	**Derived Window in study days**	
		Lower bound	**Upper bound**
Baseline for factor/BPA prophylaxis period	The last non-missing assessment before enrollment date	-INF	Enrollment date
Day -168	-168	1 day after enrollment date	-155
Day -140	-140	-154	-127
Day -112	-112	-126	-99
Day -84	-84	-98	-71
Day -56	-56	-70	-43
Day -28	-28	-42	-1
Baseline for fitusiran prophylaxis period	1	1	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

Analysis visit label	Target study day	Derived Window in study days	
		Lower bound	Upper bound
Day 197	197	≥183	EOS/ET visit date if EOS/ET visit is ≥183
Day 225	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.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be included in the by-visit summaries, computation of baseline, and PCSAs.

Unscheduled visit measurements of efficacy endpoints will be included in the efficacy analysis and computation of baseline.

2.5.6 Pooling of centers for statistical analyses

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

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

An interim analysis may be conducted as a part of this study.

4 DATABASE LOCK

The database is planned to be locked at 28 days after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

1. European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. 2020.

2. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharm Stat. 2014;13(4):258-64.

7 LIST OF APPENDICES

Appendix A: Summary of statistical analysis

Appendix B: Questionnaire/scoring: Haem-A-QOL and Haemo-QOL

Appendix C: Questionnaire/scoring: Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores

Appendix D: Questionnaire/scoring: Haemophilia Activities List (HAL)/Paediatric HAL (pedHAL) score

Appendix E: Questionnaire/scoring: EuroQol-5 dimension 5 level (EQ-5D-5L) score

Appendix F: Position paper

Appendix A Summary of statistical analyses

Efficacy Analyses

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
Annualized bleeding rate (ABR) in the fitusiran efficacy period (fitusiran treatment period for US protocol) and the factor/BPA prophylaxis period.	EAS 1	Repeated measures negative binomial regression model with On-Treatment Strategy	Yes. Repeated measures negative binomial regression model with Treatment Policy Strategy	Yes. Subgroups are hemophilia type, number of bleeding episodes during the 6 months prior to study, age group, Cohort A vs B, region- and/or country-	Per-protocol analysis Exploratory analysis Zero-inflated negative binomial model Bayesian analysis MI for treatment policy strategy
Secondary endpoints					
Annualized spontaneous bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period	EAS 1	Repeated measures negative binomial regression model with On-Treatment Strategy	Yes. Repeated measures negative binomial regression model with Treatment Policy Strategy	Subgroup analysis will be performed if deemed necessary	No
Annualized joint bleeding rate in the fitusiran efficacy period and the factor/BPA prophylaxis period	EAS 1	Repeated measures negative binomial regression model with On-Treatment Strategy	Yes. Repeated measures negative binomial regression model with Treatment Policy Strategy	Subgroup analysis will be performed if deemed necessary	No
Change in Haem-A-QOL physical health score and total score in the fitusiran treatment period	EAS 1	Descriptive statistics and Mixed Model with repeated measures (MMRM)	Non-parametric Wilcoxon signed-rank test	Subgroup analysis will be performed if deemed necessary	No
ABR in the onset period	EAS 1	negative binomial regression model with On-Treatment Strategy	Yes. negative binomial regression model with Treatment Policy Strategy	Subgroup analysis will be performed if deemed necessary	No

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
ABR in the treatment period (ABR in the efficacy period for US protocol)	EAS 1	negative binomial regression model with On-Treatment Strategy	Yes. negative binomial regression model with Treatment Policy Strategy	Subgroup analysis will be performed if deemed necessary	No
Annualized weight-adjusted consumption of factor/BPA	EAS 1	Descriptive statistics		Subgroup analysis will be performed if deemed necessary	
Other endpoints					
Exploratory variables	EAS 1	Descriptive statistics, MMRM, Repeated measures negative binomial regression model with On-Treatment Strategy	No	No	No

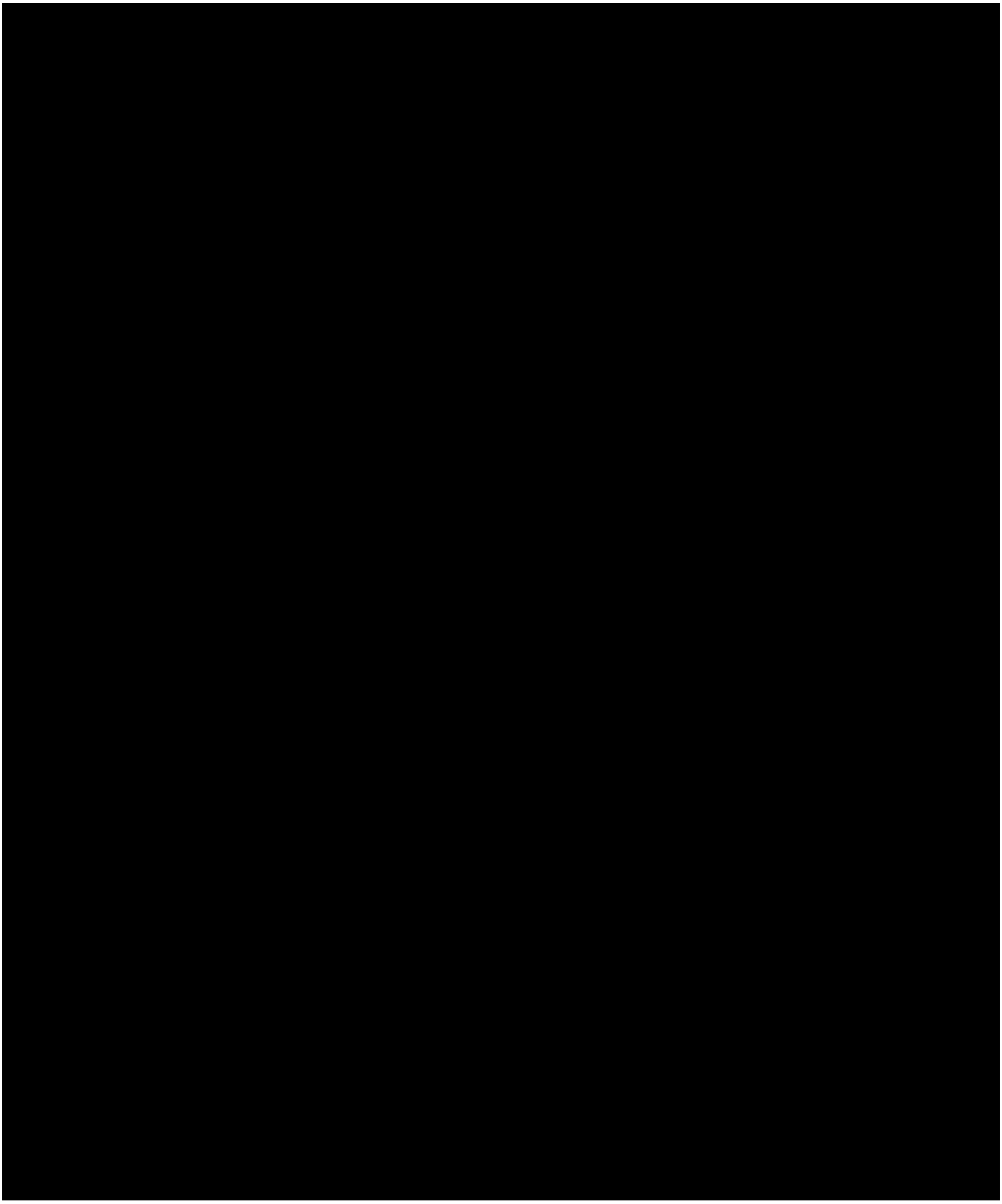
Note: Listings of ABR will be provided for participants in EAS 2.

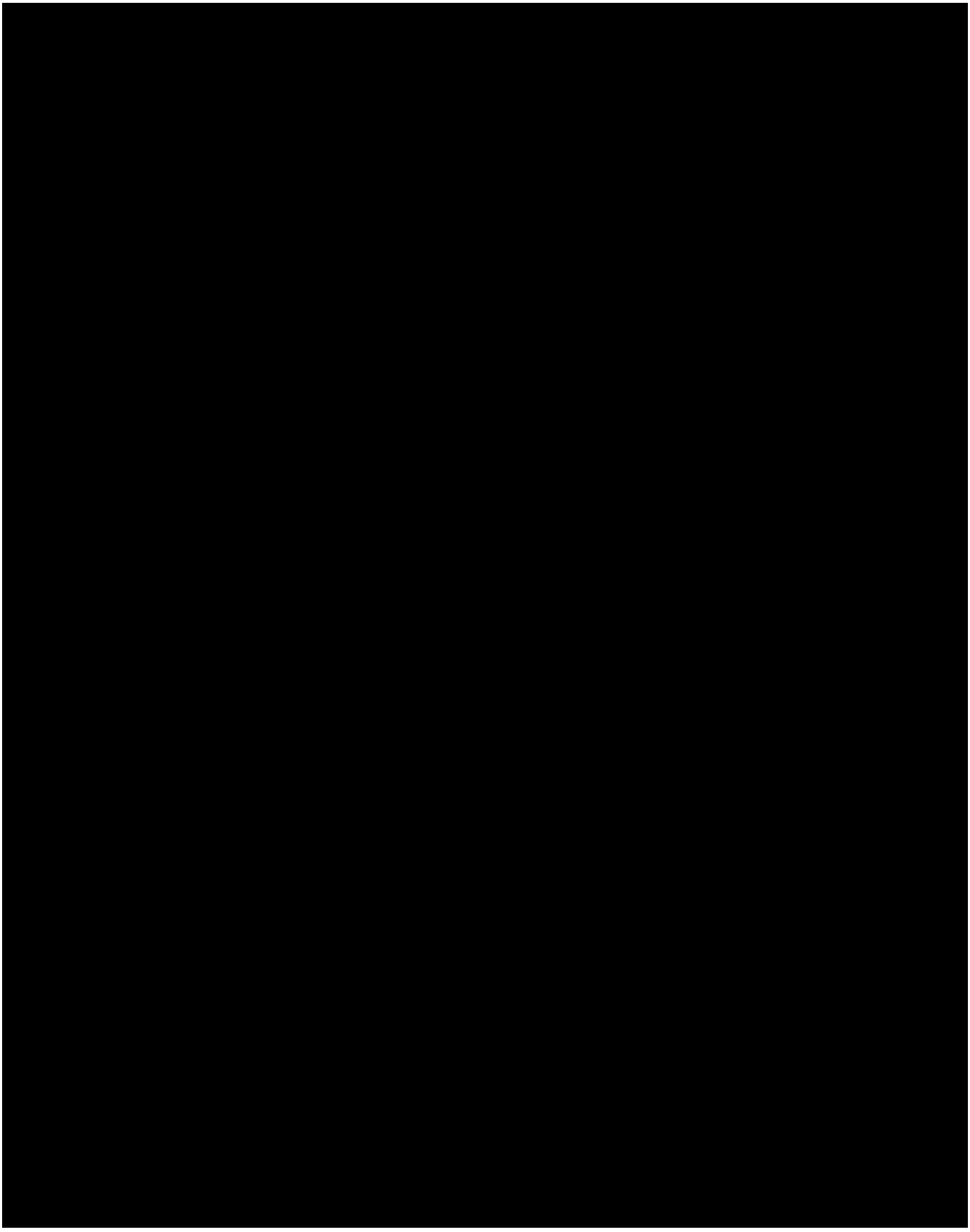
Safety analyses

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Adverse events	Safety analysis set 1	Follow safety guidelines	No	No	No
Laboratory variables	Safety analysis set 1	Descriptive statistics and Incidence of PCSAs	No	No	Listings of out-of-range laboratory results or values met PCSA criterion
Vital sign and physical examination variables	Safety analysis set 1	Descriptive statistics and Incidence of PCSAs	No	No	Listings of abnormal findings/values
ECG variables	Safety analysis set 1	Descriptive statistics and incidence of PCSAs	No	No	Listings of abnormal findings/values
Antidrug antibody formation (ADA)	Safety analysis set 1	Descriptive statistics	No	No	No
pharmacodynamic variables	Safety analysis set 1	Descriptive statistics, MMRM	No	No	No

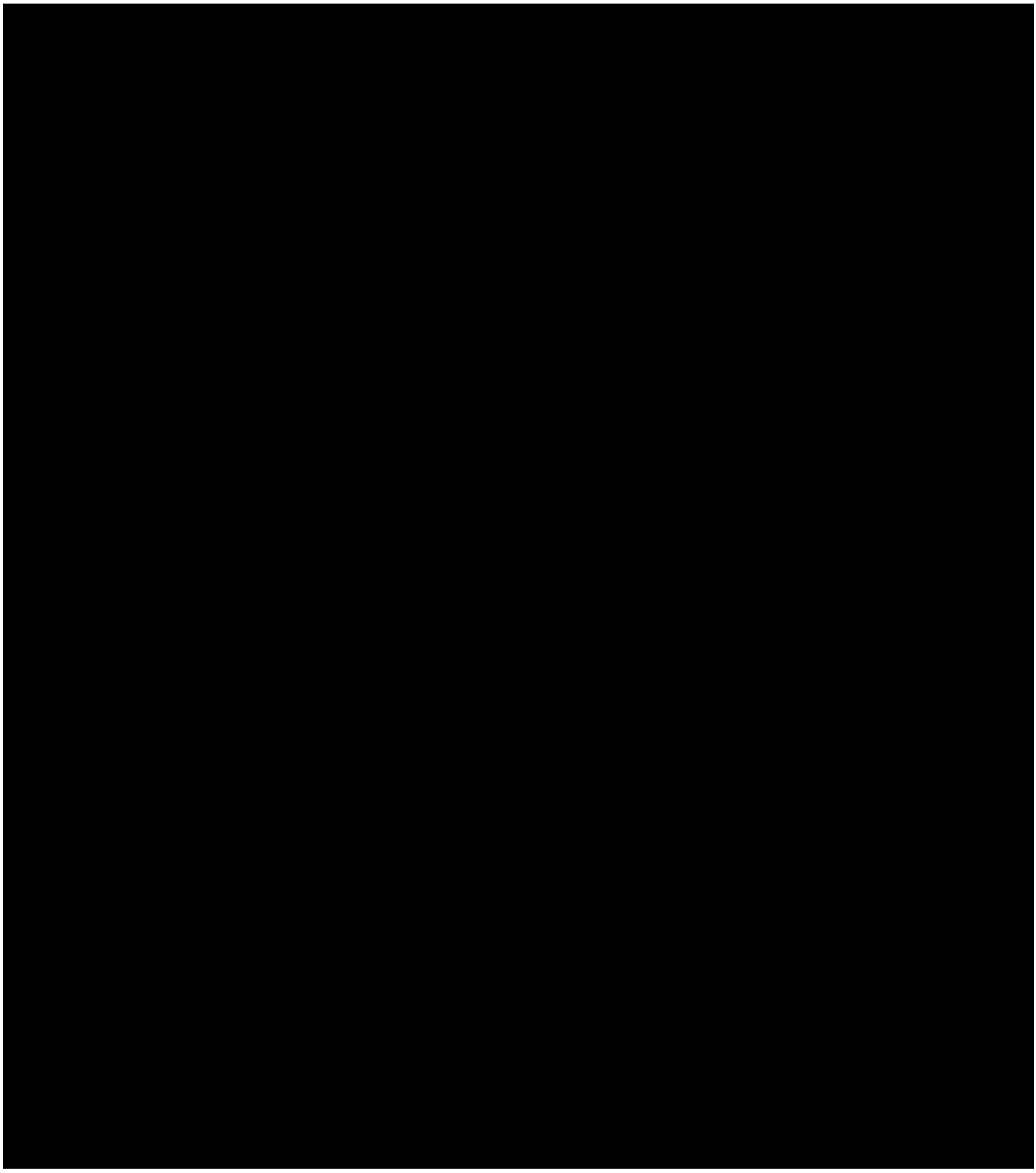
Note: Listings of safety data will be provided for participants in safety analysis set 2.

Appendix B Questionnaire/scoring: Haem-A-QOL and Haemo-QOL

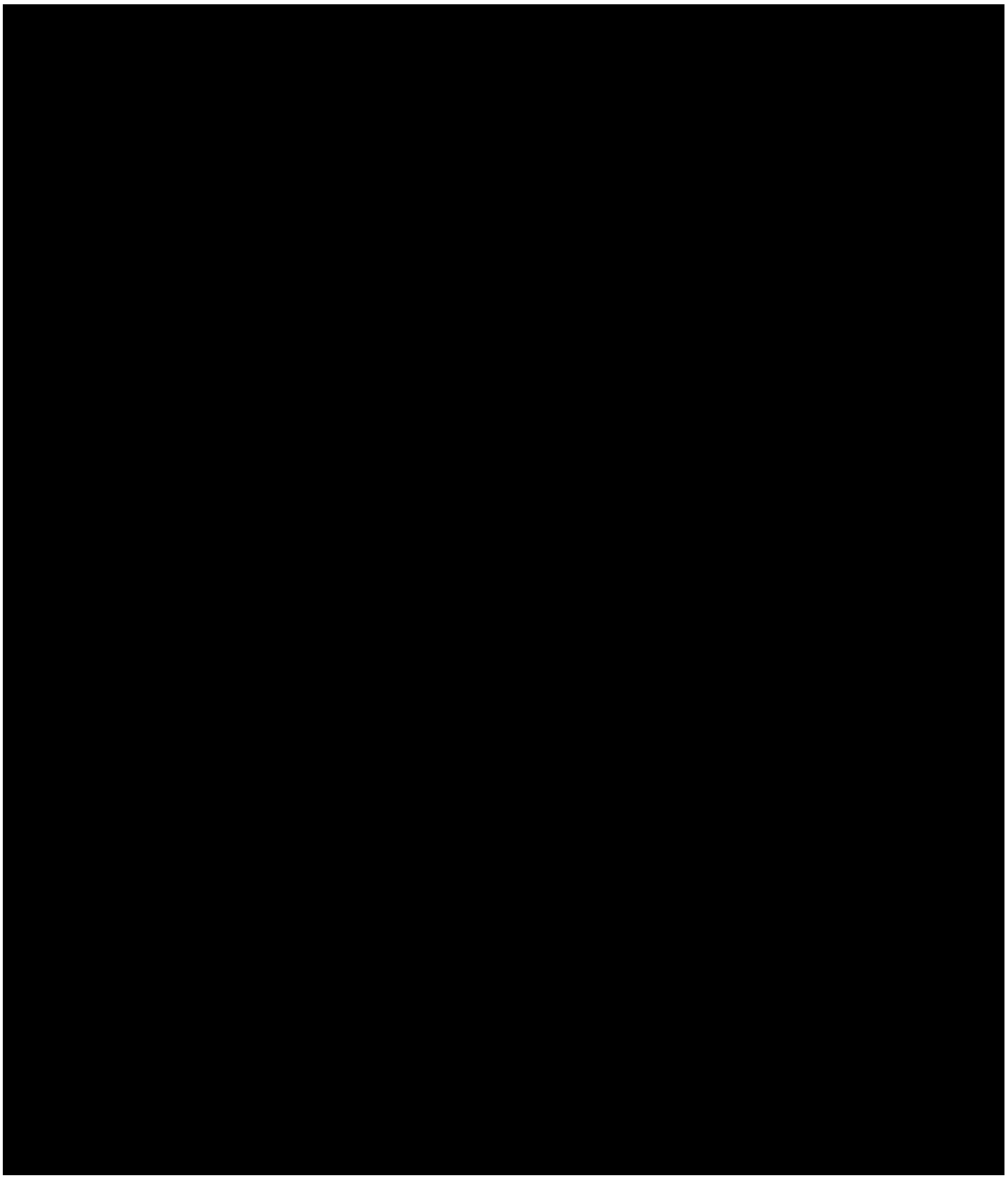


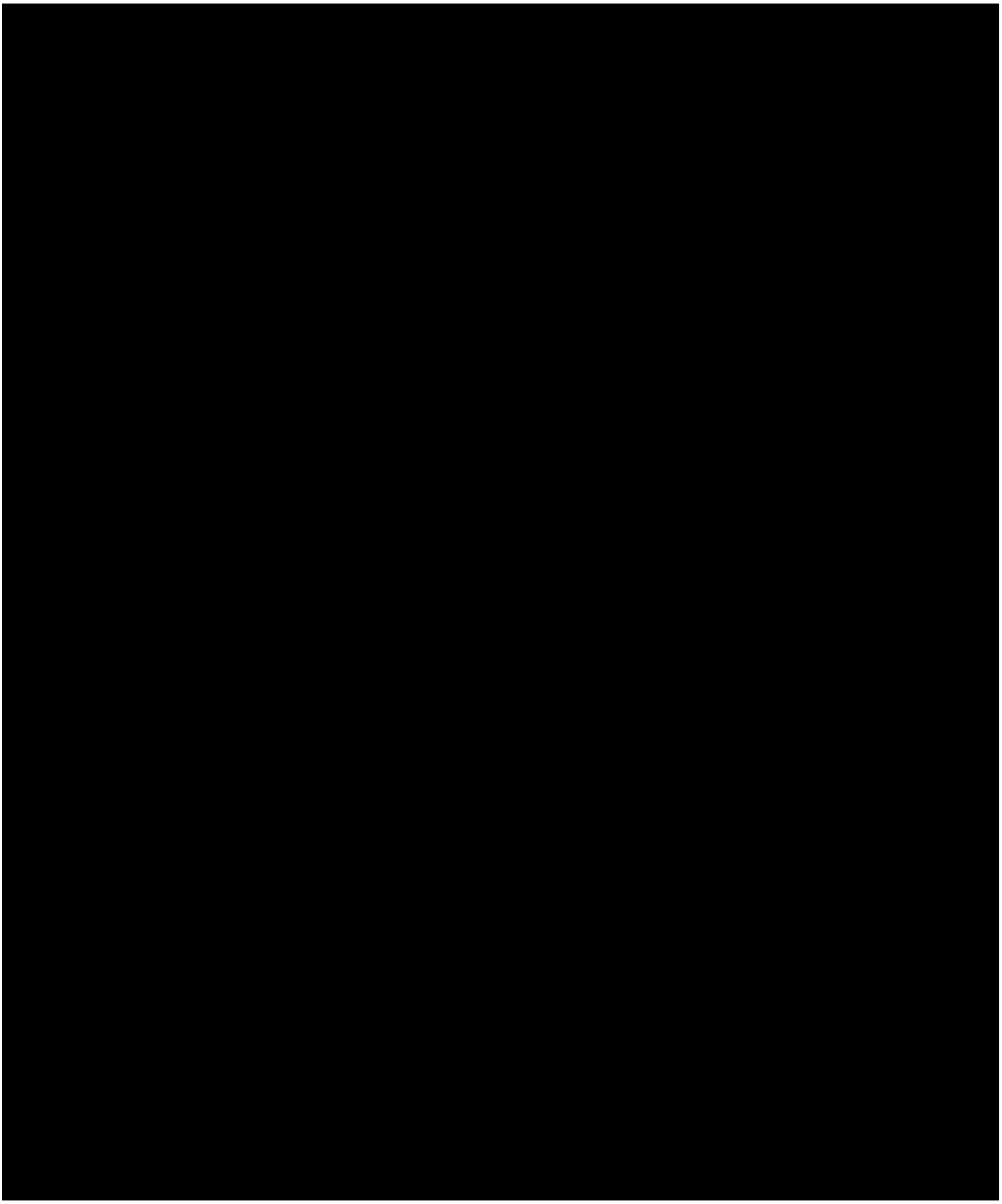


Appendix C Questionnaire/scoring: Treatment Satisfaction Questionnaire for Medication (TSQM) domain scores

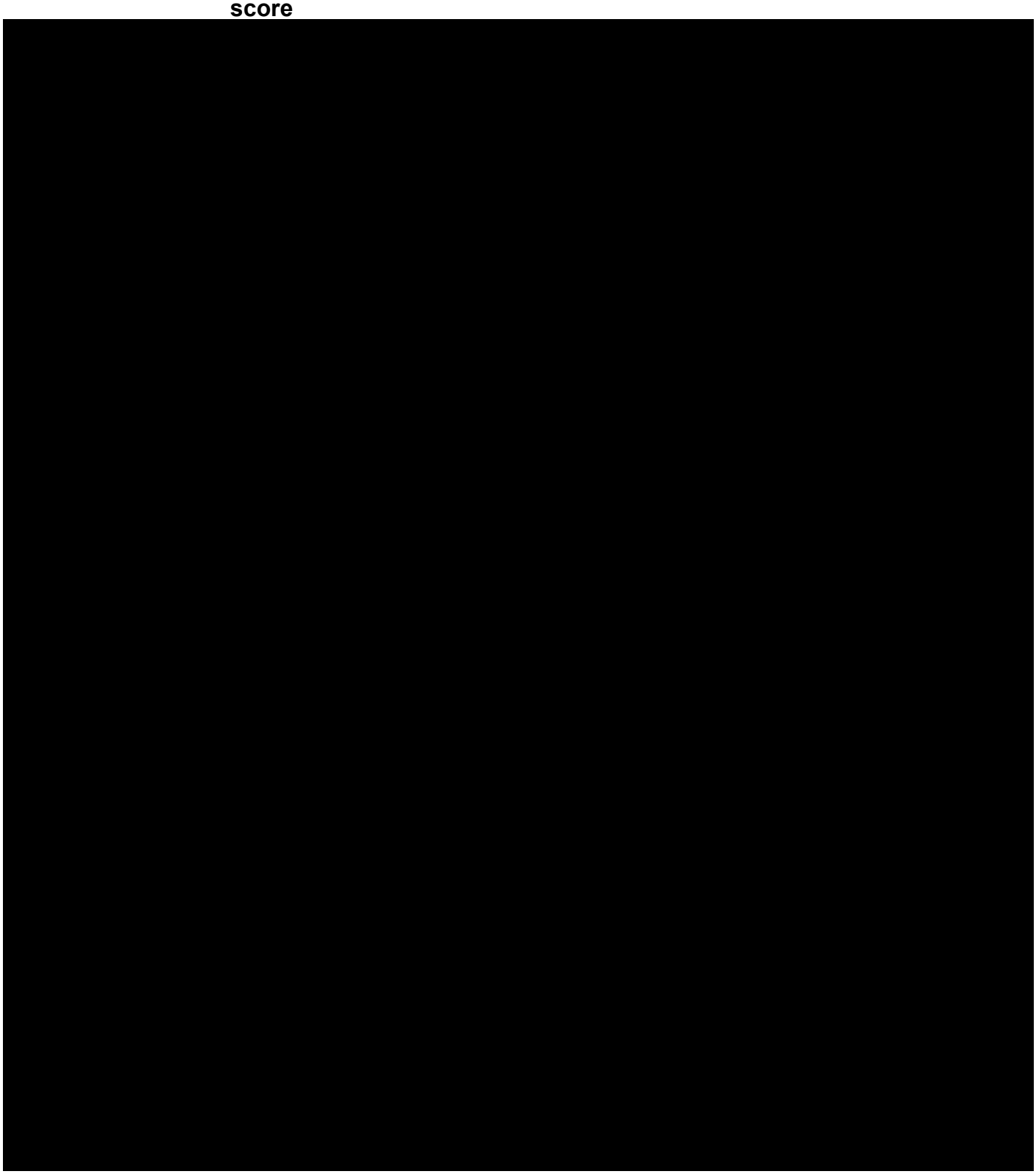


Appendix D Questionnaire/scoring: Haemophilia Activities List (HAL)/Paediatric HAL (pedHAL) score

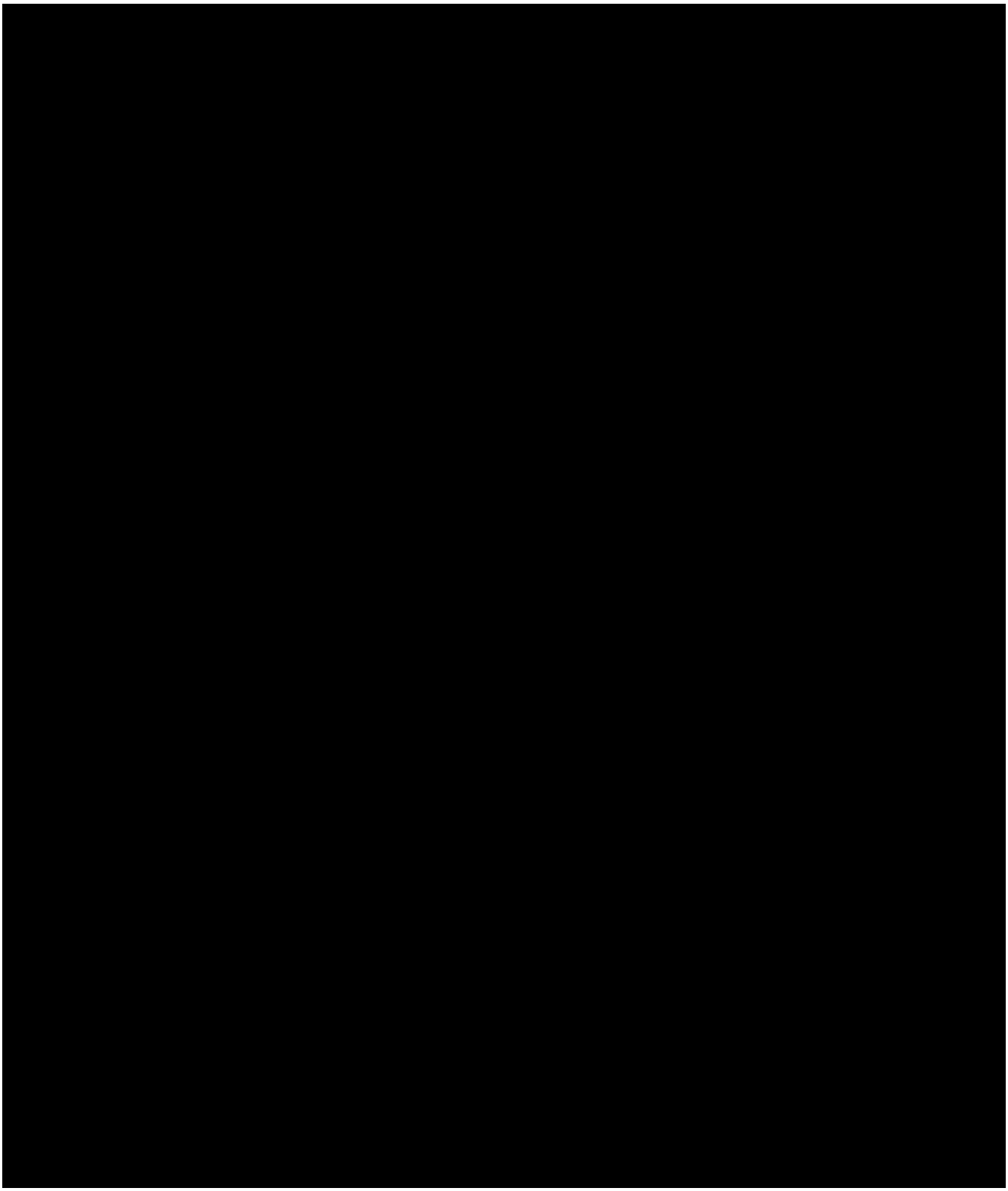


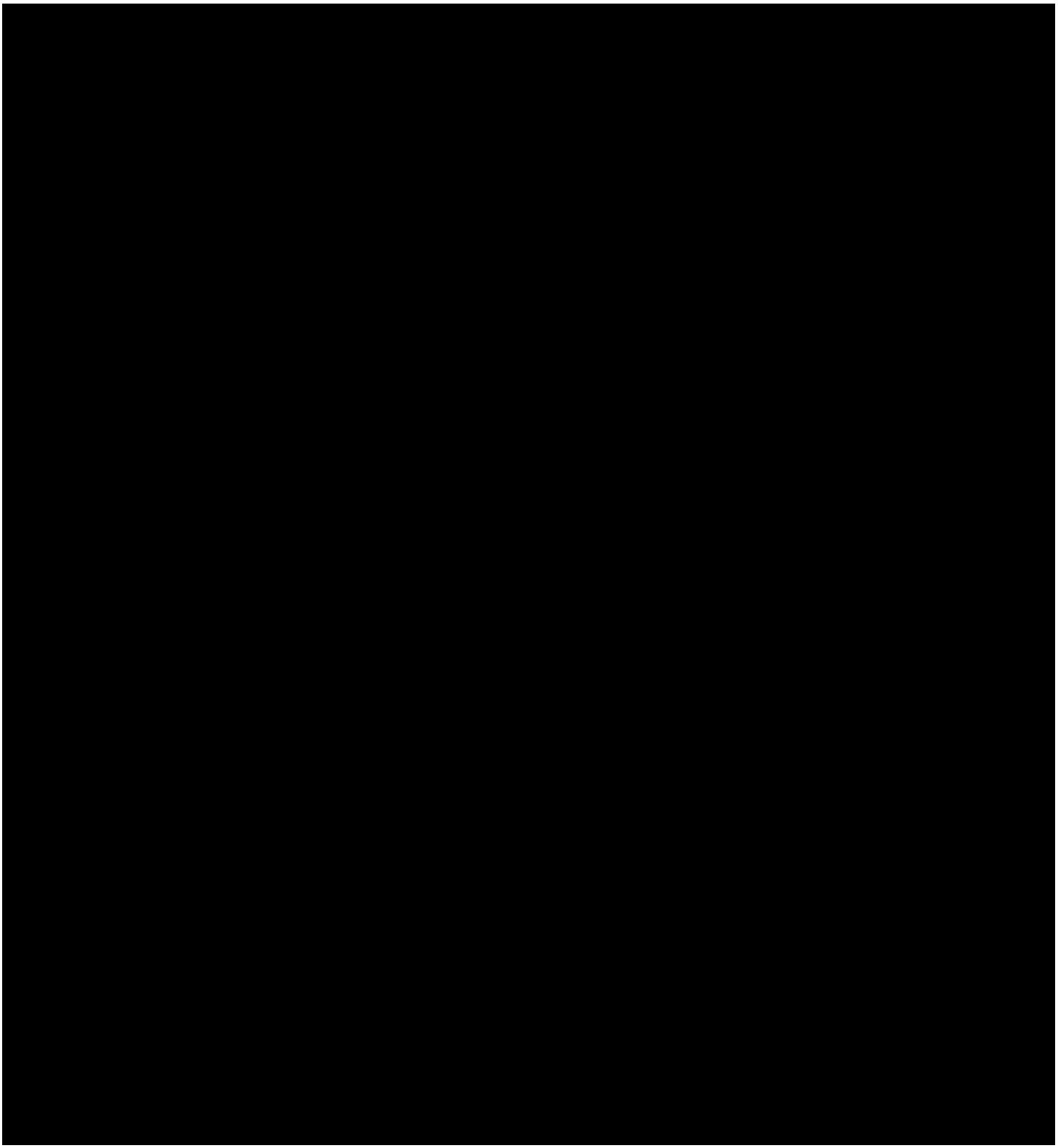


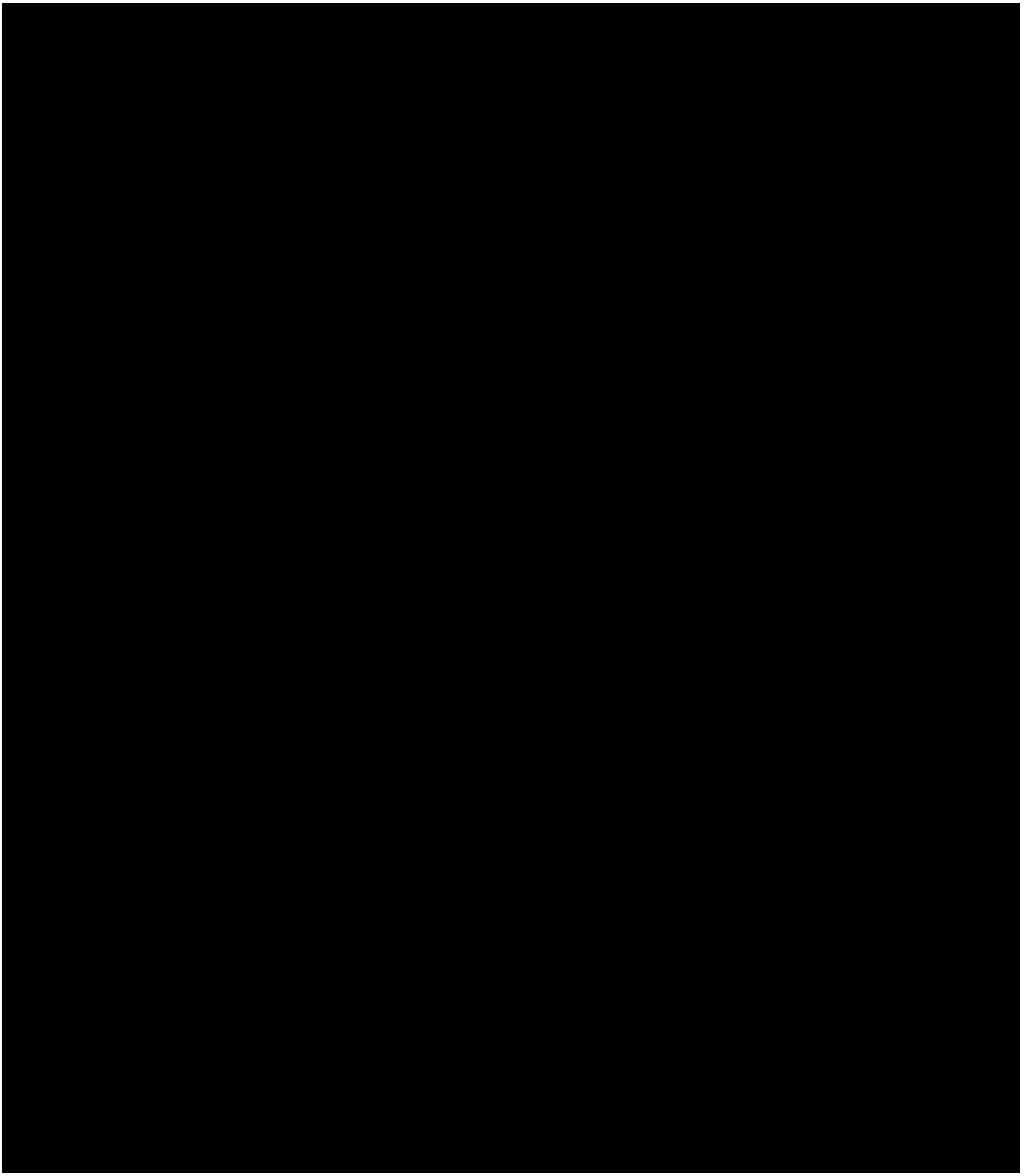
Appendix E Questionnaire/scoring: EuroQol-5 dimension 5 level (EQ-5D-5L) score



Appendix F Position paper







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