CLINICAL TRIAL PROTOCOL

Protocol title:	**A Phase 3 open-label, multicenter study of the safety, efficacy and pharmacokinetics of intravenous recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001) in previously treated pediatric patients <12 years of age with severe hemophilia A**
Protocol number:	**EFC16295**
Amendment number:	**Not applicable**
Compound number (INN/Trademark):	**BIVV001**
Study phase:	**Phase 3**
Short title:	**Safety, efficacy and PK of BIVV001 in pediatric patients with hemophilia A (XTEND-Kids)**
Sponsor name: **Legal registered address:**	**Bioverativ Therapeutics Inc. (a Sanofi Company)** **225 Second Avenue** **Waltham, MA 02451** **United States**
Monitoring Team's Representative Name and Contact Information	

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1.1 SYNOPSIS

Protocol title: A Phase 3 open-label, multicenter study of the safety, efficacy, and pharmacokinetics of intravenous recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001) in previously treated pediatric patients <12 years of age with severe hemophilia A

Short title: Safety, efficacy and PK of BIVV001 in pediatric patients with hemophilia A (XTEND-Kids)

Rationale:

BIVV001 is designed to be a new class of blood clotting Factor VIII (FVIII). Preclinical and clinical experience indicate that BIVV001 has an extended half-life ($t_{½}$), which can achieve and maintain higher sustained factor activity levels than currently available treatments, with less frequent administration.

This study is being conducted to determine the safety, efficacy, and pharmacokinetics (PK) of BIVV001 administered as once-weekly (QW) prophylaxis treatment in previously treated pediatric patients <12 years of age with severe hemophilia A.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A	• The occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen modified Bethesda assay)
Secondary	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) (for treated, for untreated, for all bleeding episodes) and by type and location • Percentage of participants who maintain FVIII activity levels over 1%, 3%, 5%, 10%, 15%, and 20% at Day 7
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• Number of injections and dose of BIVV001 to treat a bleeding episode • Percentage of bleeding episodes treated with a single injection of BIVV001 • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale • Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale

Objectives	Endpoints
• To evaluate BIVV001 consumption for prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• Annualized joint bleeding rate (AJBR) • Target joint resolution at Week 52, based on ISTH criteria • Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS)
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score and physical health domain score from baseline to Week 52 (≥4 years old) and via parent proxy version (≥4 years old)
• To evaluate the efficacy of BIVV001 for perioperative management	• Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment on the ISTH 4-point response for surgical procedures scale • Number of injections and dose to maintain hemostasis during perioperative period for major surgery • Total BIVV001 consumption during perioperative period for major surgery • Number and type of blood component transfusions used during perioperative period for major surgery • Estimated blood loss during perioperative period for major surgery
• To evaluate the safety and tolerability of BIVV001 treatment	• The occurrence of adverse events (AEs) and serious adverse events (SAEs) • The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests • The occurrence of embolic and thrombotic events
• To assess the pharmacokinetics (PK) of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	• PK parameters including, but not limited to, maximum activity (C_{max}), elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}), area under the activity time curve (AUC), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels

Abbreviations: ABR = annualized bleeding rate; AE = adverse event; AJBR = annualized joint bleeding rate; aPTT = activated partial thromboplastin time; AUC = area under the activity time curve; CL = total clearance; CL_{ss} = total clearance at steady state; C_{max} = maximum activity; C_{trough} = trough activity; DNAUC = dose-normalized area under the activity-time curve; HJHS = Hemophilia Joint Health Score; IR = incremental recovery; ISTH = International Society on Thrombosis and Haemostasis; MRT = mean residence time; PGA = Physician's global assessment; PK = pharmacokinetics; QoL = Quality of Life; SAE = serious adverse event; $t_{1/2}$ = half-life; V_{ss} = volume of distribution at steady state.

Overall design:

This is a multinational, multicenter, open-label Phase 3 study of the safety, efficacy, and PK of intravenous (IV) BIVV001 in previously treated patients (PTPs) <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). The study is comprised of <6 years and 6 to <12 years age cohorts, where participants will receive BIVV001 at a dose of 50 IU/kg IV QW for 52 weeks. Approximately 65 participants will be enrolled to achieve at least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 exposure days (EDs). Enrollment in a planned open-label extension study will be offered to participants after completion of this study.

Following a washout period (at least 3 to 4 days, depending on age), the first 24 participants from the 2 age cohorts (at least 12 participants <6 years of age and at least 12 participants 6 to <12 years of age) will undergo PK sampling after their first dose of BIVV001 (Baseline). For all participants included in the PK subgroup, existing PK information with the participant's pre-study FVIII product ($t_{1/2}$ and incremental recovery [IR]) should be available.

Participants who undergo major surgery during the study will be included in the surgery subset. The definition of major surgery is included in Appendix 7, Section 10.7.1.

Disclosure Statement: This is a single arm treatment study that is open label for PTPs <12 years of age with severe hemophilia A.

Number of participants:

Approximately 65 PTPs will be enrolled to obtain at least 50 participants with at least 50 EDs at the end of the study. The first 24 participants (the first 12 [<6 years] and first 12 [6 to <12 years]) will be included in the PK subgroup.

Intervention groups and duration:

Participants will receive QW dose of BIVV001 for 52 weeks.

Study intervention(s)

Investigational medicinal product(s)

- Study drug: Recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein.
- Route(s) of administration: IV
- Dose regimen: 50 IU/kg IV QW for 52 weeks.

Statistical considerations:

Primary endpoint:

The primary endpoint is the occurrence of inhibitor development, defined as an inhibitor result of ≥0.6 Bethesda units [BU]/mL that is confirmed by a second test result from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay. The incidence of inhibitor formation for all (≥0.6 BU/mL), "high (≥5.0 BU/mL)" and "low (≥0.6 BU/mL and <5.0 BU/mL)" titer inhibitors from the central laboratory will be summarized for each age cohort and overall; a 95% confidence interval (CI) using Clopper-Pearson method will be calculated for each incidence.

For the incidence calculations, any participant who develops an inhibitor following the initial BIVV001 administration will be included in the numerator, regardless of the number of EDs to BIVV001; the denominator will include participants who have an inhibitor as well as participants with a valid inhibitor test following at least 50 EDs to BIVV001. The calculation will also be performed with a denominator that includes all participants with a valid inhibitor test following at least 25 EDs to BIVV001 and a denominator that includes all participants with a valid inhibitor test, regardless of how many days they were exposed to BIVV001.

Main secondary endpoints:

Participants who receive at least 1 dose of BIVV001 will be included in the Full Analysis Set (FAS). Efficacy analyses will be based on the FAS. The efficacy and surgical/rehabilitation periods will be defined in the statistical analysis plan (SAP) for the purpose of determining the study periods during which data will be used for selected efficacy analyses. Data on bleeding and BIVV001 consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

Analysis of efficacy endpoints that are visit-based will include data from all study visits, whether or not in the efficacy period, unless a visit is coincidental with a surgical/rehabilitation period for a major surgery, in which case it would be excluded.

Annualized Bleeding Rate (ABR)

The mean and 95% CI of annualized bleeding rate (ABR) will be estimated using a Negative-Binomial model. The model will include number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration. Individual ABR will also be calculated for each patient. All analyses of bleeding endpoints will be based on treated bleeding episodes, except for the summary of ABR for all bleeding episodes which will include both treated and untreated bleeding episodes. Bleeding episodes that occur during surgical/rehabilitation period will be excluded and summarized separately.

In addition, ABR will be summarized descriptively by type of bleed (spontaneous or traumatic) and location of bleed (joint, muscle, internal, or skin/mucosa).

Hemophilia Joint Health Score

Changes in total Hemophilia Joint Health Score (HJHS) score and specific domains such as swelling and strength will be summarized descriptively.

Secondary Safety Endpoints

All safety analyses will be performed on the Safety Analysis Set. Safety will be assessed through descriptive summaries of adverse events (AEs), serious adverse events (SAEs), laboratory results, physical examination, and vital signs.

The incidence of AEs will be summarized by system organ class and preferred term for each age cohort and overall. Clinical laboratory values will be summarized for change from baseline, shifts, and potentially clinically significant abnormalities.

The occurrence of embolic and thrombotic events will be described. The analysis will consist of a search of TEAE data using the Embolic and Thrombotic Events Standard MedDRA Query (SMQ). Medical adjudication of the search results will also be performed.

Pharmacokinetics

Any participant with adequate BIVV001 PK data will be included in the PK Analysis Set. A noncompartmental analysis will be performed for each participant's BIVV001 baseline PK profile. Any participant who does not have adequate PK data will be excluded from the PK analysis. An additional participant will be enrolled in the PK subgroup to ensure that at least 24 participants have adequate PK data for analysis. Instructions for wash-out and PK sampling are provided in Appendix 7, Section 10.7.4.

Pharmacokinetic parameters of BIVV001 activity including but not limited to the maximum activity (C_{max}), $t_{½}$, total clearance (CL), total clearance at steady state (CLss), volume of distribution at steady state (V_{ss}), area under the activity-time curve (AUC), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), IR, trough activity (C_{trough}) and time above 1% FVIII activity measured by activated partial thromboplastin time (aPTT) clotting assay and chromogenic assay will be determined for BIVV001. Pharmacokinetic parameters will be summarized for each age cohort for BIVV001 with geometric means and their corresponding 95% CIs.

Other Secondary endpoints

All other secondary endpoints will be summarized descriptively.

The number and percentage of participants achieving trough FVIII activity levels above 1%, 3%, 5%, 10%, 15%, and 20% will be summarized. In these summaries, FVIII activity level will be based on the average trough samples (ie, nominal 168 hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52) using the one-stage aPTT assay and chromogenic assay. Participants with trough samples that are outside 168 ±5 hours from the previous dose will be excluded from this analysis.

The percentage of participants with resolution of at least 1 target joint and the percentage of total target joints that are resolved at 52 weeks will be summarized. A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) into which ≥3 spontaneous bleeding episodes occurred in a consecutive 6-month period and resolution is achieved when ≤2 bleeding episodes occur into that joint during 12 months of continuous exposure.

The consumption of BIVV001 will be annualized and summarized.

The number of injections and total dose of BIVV001 to treat a bleeding episode will be summarized on both a per-bleeding-episode and a per participant basis, where the per-participant basis will be determined as the average over all bleeding episodes for a given participant.

The participant's response to treatment of individual bleeding episodes will be summarized as the number and percentage of bleeding episodes with each response (excellent, good, moderate, or none).

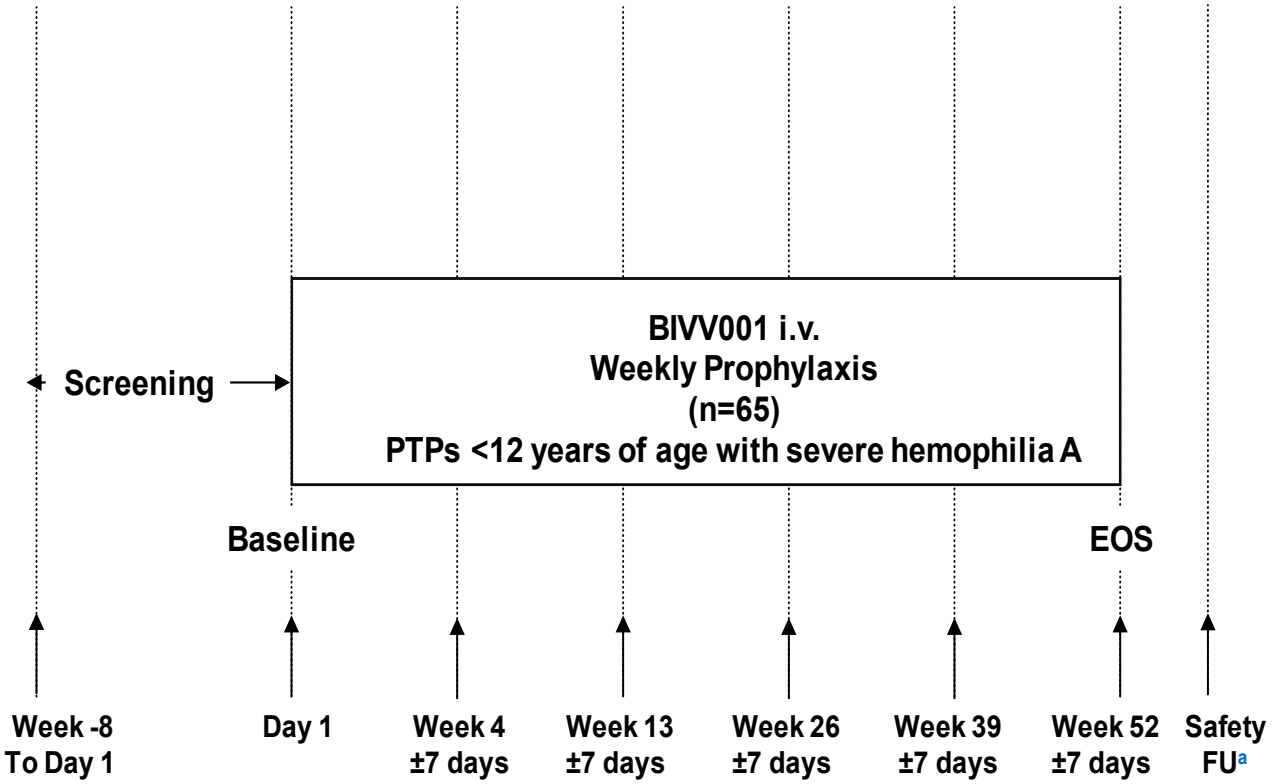
The physician's global assessment of the participant's overall response to BIVV001 treatment will be summarized for each study visit and across all visits as the number and percentage classified as excellent, effective, partially effective, and ineffective.

For Haemo-QoL, total score and physical health domain score will be summarized descriptively over time.

Surgical endpoints will be summarized descriptively for the surgical subgroup. Continuous endpoints will be summarized using the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical endpoints will be summarized by counts and percentages.

Data Monitoring Committee: Yes

1.



Abbreviations: EOS = end of study; FU = follow-up; IV = intravenous; PTP = previously treated patient.

a The safety follow-up call or visit will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1 - Overall schedule of activities from screening to safety follow-up call or visit

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
Informed consent[f]	X								
Assessment of eligibility	X	X							
Demographics[g]	X								
Weight	X	X	X	X	X	X	X		
Height	X				X		X		
Medical, surgical, and hemophilia history[h]	X								
FVIII activity (1-stage aPTT assay)[j]	X								
Genotype[i]				X					
In-clinic BIVV001 dosing[k]		X	X	X	X	X	X		
Safety									
Physical exam	X	X	X		X		X	X	
Vital signs[l]	X	X	X		X		X	X	
HIV, HBV, and HCV status[m]	X								
CD4 count, viral load[n]	X								
Hematology[o]	X	X	X	X	X	X	X		
Coagulation parameters[p]		X			X		X		
Clinical chemistry[q]	X	X	X	X	X	X	X		

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
von Willebrand Comprehensive Panel[r]		X	X	X	X	X	X		
Nijmegen-modified Bethesda assay (inhibitor assay)[j]	X	X	X	X	X	X	X		
Anti-rFVIIIFc-VWF-XTEN Antibody (ADA)[j]	X	X	X	X	X	X	X		
Adverse event/serious adverse event recording[s]	<<ongoing; monitor and record at all visits>>								
Prior and concomitant medications and concomitant therapies and procedures[t]	<<ongoing; monitor and record at all visits>>								
Monthly telephone call[u]	<<ongoing; once per month, after Week 4>>								
Efficacy									
HJHS joint assessments (≥4 years old)[v]		X			X		X		
Investigator's target joint assessment		X							
Physician's global assessment of response to treatment (PGA)				X			X		
Investigator's assessment of participant's response to treatment of bleeding episodes at the study site[w]		<<ongoing>>							
Left-over serum and plasma samples material preserved for future research[x] (optional)	X	X	X	X	X	X	X		
Electronic patient diary (ePD) training/administration/review[y]	X	X	<<ongoing>>						

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
Caregiver completion of ePD including at-home dosing, bleeding episodes, and assessment of response to bleeding episodes[z]		<<ongoing>>							
Pharmacokinetics									
Pharmacokinetic sampling[aa]		X (for participants in the PK subgroup)							
FVIII peak and trough sampling[bb]		X (for participants not in the PK subgroup)	X	X	X	X	X		
Caregiver- and/or Patient-Reported Clinical Outcome Assessments (COA)									
PROMIS-SF Assessments[cc]		X			X		X		
Haemo-QoL[dd]		X			X		X		
EQ-5D-Y[ee]		X			X		X		
Caregiver interviews (only in selected countries)							X (or subsequent post-study follow-up visit)		
Healthcare Resource Utilization		X			X		X		

Abbreviations: AE = Adverse event; ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin assay; AST = aspartate aminotransferase; BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation Factor VIII Fc - von Willebrand factor - XTEN fusion protein); BU = Bethesda units; BUN = blood urea nitrogen; COA = clinical outcome assessment; eCRF = electronic Case Report Form; EOS = End of study; ePD = electronic patient diary; EQ-5D-Y = EuroQoL-Youth; ET = early termination; FVIII = Factor VIII; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; Hct=hematocrit; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; HJHS = Hemophilia Joint Health Score; HLA = Human leukocyte antigen; ICF = informed consent form; ISTH=International Society on Thrombosis and Haemostasis; PGA = Physician's Global Assessment; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; RBC = red blood cell; SAE = serious adverse events; VWF = von Willebrand; WBC = white blood cell.

a Washout prior to the Screening inhibitor test is at least 48 hours to obtain interpretable test results. Screening may be accomplished over the course of more than 1 study visit if needed. The Screening Period is up to 8 weeks before Baseline. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice maximum. Individuals who rescreen will sign the informed consent form (ICF) again and repeat all screening assessments.

b Washout prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) for 6 to <12 years participants and at least 72 hours (3 days) for <6 years participants. The washout period prior to Day 1 BIV001 dose administration may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with the medical monitor. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests).

c Participants should schedule their study visits to be 7 ±1 day after the previous prophylactic dose of BIVV001.

d Unscheduled visits may be necessary during the study to repeat any blood sampling if required, or at the discretion of the Investigator. If a participant has an unscheduled visit, the Investigator will record data as appropriate based on the purpose of the visit. Vital signs should be taken after the participant has been resting supine for 5 minutes. If BIVV001 is being administered at an unscheduled visit, vital signs will be measured pre-injection and 30 (+/-15) minutes from the start of injection. If an unscheduled visit occurs only for purposes of prophylactic administration of BIVV001, collection of physical exam and vital sign data is not required.

e This call or visit will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study.

f Informed consent from the participant's legal guardian MUST be obtained prior to any study-related procedures, including washout of current FVIII therapy specifically for entry into the study. Participant assent must also be obtained where applicable (according to the study site's local regulations).

g Demographics include sex, race, ethnicity, and date of birth (year of birth only), as permitted by local regulations. Race and ethnicity will be collected for reasons described in Section 10.1.4

h Includes hemophilia history assessment of disease severity, blood type, and Rh factor if not previously documented. For Repeat Screening Visit, update with any changes since original Screening Visit.

i Collection of samples for genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate ICF. Human leukocyte antigen (HLA) genotype will not be needed if previously documented. If blood volume is limiting, this assessment may be performed at a subsequent visit. The participant's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period.

j Washout prior to scheduled visits other than screening and baseline should be at least 7 ±1 days. Inhibitor and anti-drug antibody (ADA) samples will be collected prior to BIVV001 dosing. Separate samples for ADA testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 Bethesda units (BU)/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks. Testing for potential ADA formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN- specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to FVIII, Fc, D'D3, or XTEN.

k Participants will have BIVV001 doses given at each applicable scheduled visit delivered via a slow push intravenous injection at a rate of administration recommended in the protocol (Section 6.1.2) and determined by the participant's comfort level. Injection start and stop time will be recorded in the electronic Case Report Form (eCRF). Other doses may be self/caregiver administered at home (or in clinic).

l Vital signs include blood pressure, pulse rate, respiratory rate, and oral, tympanic, axillary or temporal temperature (°C). Vital signs should be taken after the participant has been resting supine for 5 minutes. Vital signs will be measured pre-injection and 30 (±15) minutes from the start of injection at clinic visits.

m For participants who have been historically negative, viral testing will be performed at a central laboratory. Human immunodeficiency virus (HIV) tests will include HIV-1 antibodies, HIV-2 antibodies and HIV-1 p24 antigen. Hepatitis B virus (HBV) tests will include HBV surface antigen, anti-HBV surface antibody and anti-HBV core antibody. Hepatitis C virus (HCV) tests will include anti-HCV antibodies.

n For participants known to be HIV antibody positive, CD4 count and viral load tests must be performed at the central laboratory if results are not available from within 26 weeks prior to screening.

o Hematology parameters include red blood cell (RBC) count, white blood cell (WBC) count and differential, platelet count, hemoglobin (Hgb), and hematocrit (Hct). Blood samples for hematology analysis will be collected prior to BIVV001 dosing.

p Coagulation parameters include activated partial thromboplastin time (aPTT).

q Clinical chemistry parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, blood urea nitrogen (BUN), creatinine, nonfasting glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to BIVV001 dosing.

r The von Willebrand (VWF) comprehensive panel includes assessments of von Willebrand Factor ristocetin cofactor activity and VWF antigen. Blood samples for analysis of VWF comprehensive panel will be collected prior to any BIVV001 dosing.

s Adverse events (AEs) and serious adverse events (SAEs) occurring after signing of the ICF through the Safety Follow-Up Call or Visit will be recorded on the eCRF.

t Prior medications from up to 30 days prior to Screening and concomitant therapies and procedures from signing of ICF through the Safety Follow-Up Call or Visit will be recorded on the eCRF. Pain medication related to Hemophilia and administered within 2 weeks prior to the visit will be recorded on the eCRF.

u In addition to scheduled clinic visits, telephone calls are planned approximately once a month, after Week 4, for the site staff to check on each participant's status. During the monthly telephone call, the participant's parent/caregiver will also be reminded about the requirement for timely ePD data entry, and assessments of "spontaneous" and "traumatic" bleeding episodes will be noted.

v Investigator will examine each participant's joints per the Haemophilia Joint Health Score (HJHS). At baseline, the Investigator will assess the presence of any target joints according to the International Society on Thrombosis and Haemostasis (ISTH) criteria.

w For bleeding episodes initially treated at the study sites, the Investigator will contact the caregiver approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode at the study site and record the caregiver's assessment of response to BIVV001 treatment on the eCRF using a 4-point bleeding response scale. For bleeding episodes that are treated at home, caregivers will record response to bleeding episodes in the ePD.

x Samples will be collected prior to any BIVV001 dosing and will be archived by the central laboratory (if required) for future research, eg, immunology assays, further coagulation assays, or clarification of any clinical or laboratory AE, etc. This is optional and participants/caregivers will sign an additional consent for this research.

y At the screening visit, caregivers will be shown and trained on the ePD device to ensure understanding of obligation to enter data during the trial. Devices will be given to caregivers at the baseline visit.

z Caregivers will record all bleeding episodes in the ePD beginning at Baseline. Assessment of response to bleeding episodes will be performed using a 4-point bleeding response scale. The caregiver should record response approximately 72 hours from the time the first BIVV001 injection was administered to treat the bleeding episode, unless treatment of the bleed was administered in the clinic. In that case, the investigator will report the caregiver's response to treatment via the eCRF.

aa The first 12 participants in each age cohort will undergo PK sampling after the first dose of BIVV001 (Baseline). Thereafter, PK sampling at Baseline will be optional. See PK sampling details in Table 2.

bb Trough and peak samples are collected within 30 minutes prior to rFVIIIFc-VWF-XTEN dosing and 15 (±3) minutes post-injection, respectively. This trough sample should be collected at the same time point as the trough inhibitor and ADA samples taken predose.

cc Patient-Reported Outcomes Measurement Information System (PROMIS) Assessments to include Pain Intensity, Pain Interference (PROMIS Pediatric-SF Pain Interference <18 years old), and Physical Function (PROMIS Pediatric-SF Physical Activity <18 years old). The PROMIS instruments will be administered to participants ≥8 years old and to parent proxy for participants aged 5-12 years.

dd The Haemo-QoL children version will be administered to participants ≥4 years old and the parent will be administered a parent proxy version (≥4 years old).

ee The EQ-5D-Y children version will be administered to participants ≥8 years old and the parent version will be administered to parent proxy (for participants 4-7 years old).

Table 2 - PK sampling schedule of activities (PK subgroup)

Assessments[a]	Pre-dose	Post-dose[c]				
	Day 1 Week 1[b]	Day 1 Week 1		Day 2	Day 4	Day 8[d]
		15 minutes (±3) minutes	3 hours (±15 minutes)	24 hours (±2 hours)	72 hours (±5 hours)	168 hours (±5 hours)
FVIII activity (measured by one-stage clotting aPTT and two-stage chromogenic assays)[e]	X	X	X	X	X	X

Abbreviations: aPTT = activated partial thromboplastin assay; FVIII = Factor VIII; PK = pharmacokinetics.

NOTE: Initial dosing of BIVV001 is in the clinic on Day 1 Week 1.

a For a subset of participants who are in the PK subgroup (n=24). Baseline PK sampling can be conducted optionally after full enrollment of the PK subgroup in other participants at the discretion of investigator through central laboratory.

b Washout of at least 96 hours (4 days) for 6 to <12 years participants and at least 72 hours (3 days) for <6 years participants prior to sample collection is required. Pre-dose samples are collected within 30 minutes prior to dosing. The washout period may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor.

c All sampling times are relative to the start of injection.

d Before injection of the next dose of BIVV001. Study drug can be taken after assessments on Day 8.

e Details regarding sample handling and volume in relation to body weight are provided in the Central Laboratory Manual.

Table 3 - Surgical schedule of activities

Tests and assessments	Pre-operative assessment 4 weeks prior to surgery[a] (±7 days)	Day of surgery	Post-operative follow-up 24 hours (±6 hours)[b]	End of perioperative period follow-up phone call[c] Minor surgery: at least 1 week post-surgery Major surgery: at least 2 weeks post-surgery
Physical exam	X[d]			
Weight	X[d]	X		
Vital signs[e]	X[d]	X		
Laboratory safety panels[f]	X[d]	X[h]		
FVIII activity (1-stage clotting aPTT and 2-stage chromogenic assays)[g]	X[d]	X[i]	X[i]	
Nijmegen-modified Bethesda Assay (inhibitor assay)	X[d]	X[h]		
Anti-rFVIIIFc-VWF-XTEN Antibody (ADA)	X[d]	X[h]		
BIVV001 surgical administration		X[j]	X[j]	
BIVV001 between-clinic visit administration(s)	<continued>			
ePD training review	X[d]			
Participant's assessment of response in ePD including assessment of response to a bleed[k]	<<ongoing as applicable>>			
Surgeon's/Investigator's assessment of response to surgery[l]			X	
Investigator's assessment of response to a bleeding episode[m]	<<ongoing as applicable>>			
Adverse events/serious adverse event recording	<<continuous>>			

Tests and assessments	Pre-operative assessment 4 weeks prior to surgery[a] (±7 days)	Day of surgery	Post-operative follow-up 24 hours (±6 hours)[b]	End of perioperative period follow-up phone call[c] Minor surgery: at least 1 week post-surgery Major surgery: at least 2 weeks post-surgery
Concomitant medications, therapies, and procedures	<<continuous>>			

Abbreviations: ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin assay; AST = aspartate aminotransferase; BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation Factor VIII Fc - von Willebrand factor - XTEN fusion protein); BUN = blood urea nitrogen; eCRF = electronic Case Report Form; EOS = end of study; ePD = electronic patient diary; FVIII = Factor VIII; GGT = gamma glutamyl transferase; Hct = hematocrit; Hgb = hemoglobin; RBC = red blood cell; VWF = von Willebrand; WBC= white blood cell.

NOTE: In addition to scheduled clinic visits, telephone calls are planned approximately every 2 weeks for study site staff to check on each participant's status. Unscheduled visits may be necessary during the study to repeat safety assessments or to repeat blood sampling if required.

a In the case of emergent surgery, pre-operative assessments 4 weeks prior to surgery are not required. Day of Surgery Assessments must be completed.

b For minor surgeries only, the post-operative follow-up may be conducted via a phone call 24 hours following surgery for the surgeon/investigator's assessment of response to surgery. For major surgeries and if clinically warranted and at the discretion of the surgeon/investigator for minor surgeries, the participant will be brought back into the clinic 24 hours post surgery for BIVV001 activity sampling (pre-dose if an administration of BIVV001 is planned) and for the surgeon/investigator's assessment of response. Following the 24-hour post-operative study assessment, caregivers will follow the recommended postoperative treatment regimen as per Investigator's advice.

c The perioperative period may be extended at the discretion of the Investigator. Reasons include extended hospital stay or other clinical reasons that prohibit resumption of normal prophylactic regimen treatment. At the end of the perioperative period, caregivers will be instructed to resume their child's pre-surgery treatment regimen and to register treatment accordingly in the ePD. For participants who undergo major surgery at the end of the study (EOS), the EOS assessments will be scheduled at least 14 days post surgery, if applicable.

d Assessments do not need to be repeated as part of the Preoperative Assessment if done within 4 weeks prior to surgery at a scheduled study visit. If surgery is delayed ≥4 weeks, preoperative study assessments must be repeated.

e Vital signs include blood pressure, pulse, respiratory rate, and temperature (°C), and should be taken after the participant has been resting supine for 5 minutes.

f Hematology parameters include red blood cell (RBC) count, white blood cell (WBC) count and differential, platelet count, hemoglobin (Hgb), and hematocrit (Hct). Clinical chemistry parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, blood urea nitrogen (BUN), creatinine, glucose, total protein, sodium, potassium, and chloride. The von Willebrand (VWF) comprehensive panel includes assessments of von Willebrand Factor ristocetin cofactor activity and VWF antigen). All blood samples will be collected prior to dosing.

g FVIII activity samples should be taken according to local procedure and as required to monitor the participant's FVIII levels during surgery and post-surgery until discharge from the hospital. It is requested that a portion of the plasma from any FVIII activity samples also be sent to the central laboratory. As a minimum requirement, at least 1 FVIII activity sample should be taken each day the participant is hospitalized. If FVIII activity is not sampled daily per local requirements, sampling must occur specifically for study central laboratory analysis. The FVIII activity at the 24h follow up will be done only for patient with major surgery (for minor surgery it will be done only if clinically warranted).

h It is not necessary to wait for central laboratory result before proceeding with surgery.

i FVIII levels, tested during surgery, via local laboratory for immediate reference. A portion of any FVIII activity sample to be sent to the central laboratory for reporting purposes.

j Guidelines for perioperative management are provided in Section 6.1.4. The 24h post-operative BIVV001 dosing will be performed only if clinically needed (based on FVIII activity level).

k Assessment of response to bleeding episodes using a 4-point bleeding response scale. The participant's caregiver should record response in the ePD, including assessment of response to a bleed, approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode.

l Investigator's/surgeon's assessments of participant's response to surgery with BIVV001, using a bleeding response scale when participant has completed the surgical period, which includes the 24-hour postoperative time period.

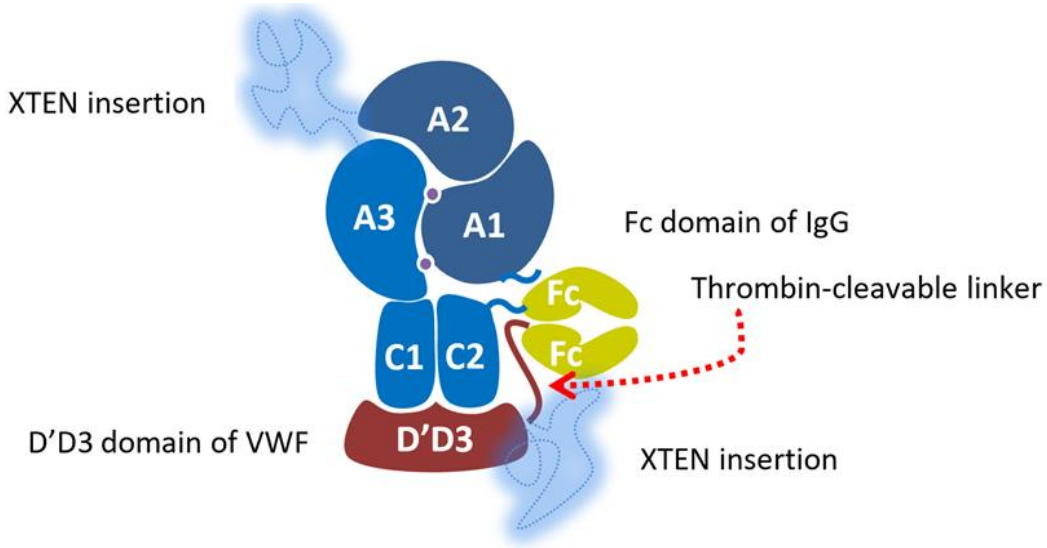
m For bleeding episodes treated in-clinic/hospital, the investigator will contact the caregiver approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode and record the caregiver's assessment of response to BIVV001 treatment on the eCRF using a 4-point bleeding response scale.

2 INTRODUCTION

Recombinant coagulation Factor VIII Fc - von Willebrand factor - XTEN fusion protein (rFVIIIFc-VWF-XTEN) (BIVV001; BIIB073) is designed to be a new class of blood clotting FVIII product. As with existing FVIII products, BIVV001 temporarily replaces the missing FVIII needed for effective hemostasis in hemophilia A patients.

BIVV001 is a novel fusion protein consisting of single-chain B-domain deleted (BDD) human FVIII, the Fc domain of human immunoglobulin G1 (IgG1), FVIII-binding D'D3 domain of human von Willebrand factor (VWF), and 2 XTEN polypeptide linkers (Figure 2) (1). The Fc, VWF, and XTEN linker portions of the molecule are each designed to extend the $t_{½}$ of the FVIII molecule in plasma.

Figure 2 - Overall design and components of BIVV001



2.1 STUDY RATIONALE

BIVV001 is designed to be a new class of blood clotting FVIII. Preclinical and clinical experience indicate that BIVV001 has an extended half-life, which can achieve and maintain higher sustained factor activity levels than currently available treatments, with less frequent administration.

This study is being conducted to determine the safety, efficacy, and PK of BIVV001 administered as QW prophylaxis treatment in PTPs <12 years of age with severe hemophilia A.

2.2 BACKGROUND

Hemophilia A is a congenital X-linked bleeding disorder that occurs predominantly in males and is characterized by deficiency of functional FVIII. It is caused by any of a variety of mutations of the coagulation FVIII gene, including missense or nonsense mutations, gene deletions, inversions, and splice junction mutations (2, 3). The worldwide prevalence of hemophilia A is estimated to be 1 in 10,000 and worldwide incidence is approximately 1 in 5000 male births (4). Hemophilia A appears to be equally distributed across the world (5, 6, 7). The severity of disease is characterized by the endogenous level of FVIII measured in the plasma. Severe hemophilia A (<1% endogenous FVIII activity level [ie, <1 IU/dL]) accounts for approximately 30% to 50% of all cases of hemophilia A (8, 9, 10).

Individuals with severe hemophilia experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following minor trauma. The disease can be acutely life-threatening. Repeated bleeding can lead to debilitating long-term complications, including hemophilic arthropathy from bleeding into the joints (7). Another severe complication is the development of target joints from inflammation due to prior bleeding. Intracranial hemorrhage can result in disability and death and is the leading cause of hemorrhagic death in individuals with hemophilia (11). Significant effects on physical and psychosocial well-being and quality of life (QoL) and substantial financial burden have been reported in patients with severe hemophilia (12).

2.2.1 Current therapies for Hemophilia A

The use of cryoprecipitate in the 1960s and the large-scale production of commercial freeze-dried FVIII concentrates from plasma in the 1970s allowed for outpatient treatment of hemorrhages and reduced the risk during surgeries in patients (13, 14). In the 1970s and 1980s, techniques were developed to eliminate infectious agents, including treatment with heat and detergent, as well as immunoaffinity chromatography (15).

Observations of a milder bleeding phenotype and superior joint health in patients with moderate hemophilia (FVIII activity 1% to 5%) compared to severe hemophilia prompted physicians to investigate the effect of regular injections of FVIII concentrate (16). Significant decreases in the frequency of bleeding and progression of arthropathy, as compared to historical data, were observed. These findings were confirmed by subsequent large cohort studies (17) and randomized clinical trials (18, 19, 20) comparing prophylactic treatment regimens with episodic (on-demand) treatment. Patients with hemophilia A treated episodically have been estimated to have from 20 to more than 40 bleeding episodes per year (21, 22). With prophylactic treatment, annual median bleeding rates of less than 10 to as low as 1 bleeding episode per year have been reported (21). As a result, prophylaxis treatment regimens are being adopted as the standard of care in many countries, with episodic treatment as an alternative option.

The use of a prophylaxis regimen in young children with hemophilia improves their long-term clinical outcome by preventing joint bleeding in the early years of life and subsequent hemophilic arthropathy (18, 23, 24). This was confirmed by a prospective, randomized controlled study comparing the joint outcome between episodic and prophylactic regimens in children. At 6 years of age, children on a prophylaxis regimen had significantly less joint damage than children treated with an on-demand regimen (18).

However, it is well recognized that there are still many hemophilia patients throughout the world that continue with on-demand treatment regimens for a multitude of reasons, including high treatment burden of current prophylactic FVIII replacement therapies (25). This also includes newer generation extended half-life FVIII therapies that still require 2 to 3 injections per week to maintain activity levels ≥1% (26). The administration of FVIII is challenging, particularly in children due to the requirement for venous access, dosing compliance due to time commitment, and the cost associated with frequent administration. Intravenous access may be impaired in children, and central venous access comes with its own set of complications including infection, sepsis, and catheter-related thrombosis. While overall prophylactic treatment continues to become more prevalent, many hemophilia patients continue with on-demand treatment as their standard-of-care, even with the current extended half-life FVIII products as the burden of current regimens remains an obstacle to adoption of and adherence to prophylaxis (27).

Next-generation FVIII products that prevent and control bleeding episodes for longer periods of time potentially reduce the burden of frequent IV administration, and in turn may improve the QoL for hemophilia patients. Products with a longer $t_{½}$ would also offer the opportunity for reduced time below the threshold of FVIII activity levels at which there may be an increased risk of bleeding events (28). Indeed, it is well established that the accepted minimum target of FVIII activity trough level (1%-3%) of current prophylactic treatment regimens is not adequate to protect patients from all bleeds and the resulting morbidity associated with such bleeding episodes. Joint bleeds still occur at these levels, leaving patients susceptible to long-term morbidity, especially joint damage (26, 29, 30). The ability to increase patient protection by achieving higher sustained levels of factor activity remains a critical need for patients (31) and follows recommendations from World Federation of Hemophilia (WFH) (5).

2.2.2 BIVV001

BIVV001 is a recombinant fusion protein consisting of single-chain FVIII, the Fc domain of IgG1, the FVIII-binding D'D3 domain of VWF, and 2 XTEN linkers. It is believed that the plasma $t_{½}$ of FVIII is prolonged by its interaction with VWF. All current extended half-life recombinant FVIII (rFVIII) products interact with VWF and have comparable circulating $t_{½}$, owing to the approximate 15-hour $t_{½}$ of endogenous VWF (32, 33). BIVV001 is the first rFVIII engineered to be independent of VWF, theoretically extending its $t_{½}$. Nonclinical and clinical studies of BIVV001 have demonstrated that its $t_{½}$ is significantly prolonged compared with current FVIII products.

BIVV001 was engineered to include an rFVIIIFc containing a BDD human FVIII covalently linked to the Fc domain of human IgG1 that is currently approved for individuals with hemophilia A (34). The rFVIIIFc binds to the neonatal Fc receptor, utilizing a naturally occurring pathway by which the receptor binds the Fc region of IgG1 and protects immunoglobulins from lysosomal degradation. The rFVIIIFc fusion thereby allows for longer plasma $t_{½}$ than endogenous FVIII. The fusion of Fc to human FVIII utilized a proven approach for increasing the $t_{½}$ of therapeutic proteins, including several approved drugs (35, 36). Additionally, the rFVIIIFc in BIVV001 has been appended to the D'D3 domain of VWF, which not only provides protection and stability to FVIII but also prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII $t_{½}$ imposed by VWF (33, 37). The D'D3 domain has not been reported to interact with

other targets. Additionally, in silico tools were utilized in the design and preparation of BIVV001 to assess and reduce the immunogenic potential of this fusion protein. Finally, the XTEN linkers (unstructured polypeptides composed exclusively of natural amino acids) extend the $t_{½}$ of the fusion protein by altering the hydrodynamic radius of the molecule, which in turn reduces its clearance (38).

2.2.3 Brief summary of clinical data of BIVV001

The BIVV001 clinical development program includes two completed studies: a Phase 1/2a study (242HA101) and a Phase 1 study (242HA102) evaluating the safety, tolerability, and PK of BIVV001 administered as single and repeat IV doses, respectively. In Study 242HA101, 15 participants received a single dose of BIVV001 and in Study 242HA102, 24 participants received a total of 4 doses of BIVV001.

A Phase 3 open-label, multicenter study of the safety, efficacy and PK of BIVV001 in previously treated adults and adolescents ≥12 years of age with severe hemophilia A (EFC16293) is currently on-going.

2.2.3.1 Study 242HA101

Study 242HA101 was a First in Human Phase 1/2a, open-label, dose-escalation, multicenter study to assess the safety, tolerability and PK of a single IV dose of BIVV001 in adult male PTPs with severe hemophilia A. Participants received a single IV dose of 25 IU/kg or 65 IU/kg rFVIII comparator (Advate) followed by a washout period and a single IV dose of 25 IU/kg or 65 IU/kg of BIVV001 in the low and high dose cohorts, respectively. Of the 16 participants enrolled in the study, all received a single dose of Advate (25 IU/kg, n=7; 65 IU/kg, n=9) and 15 received a single dose of BIVV001 (25 IU/kg, n=6; 65 IU/kg, n=9).

Safety results

Of the 16 participants enrolled, all 16 received a single dose of Advate and were included in the safety analysis. During the Advate treatment period, 8 treatment-emergent adverse events (TEAEs) were reported in 3 participants. This included 4 treatment-emergent serious adverse events (TESAEs) that occurred in 1 participant in the setting of a motor vehicle accident after which the participant was withdrawn from the study. The most common TEAE during the Advate treatment period was Thrombin-antithrombin III complex increased (2 participants, 1 from each cohort).

Of the 16 participants enrolled, 15 received a single dose of BIVV001 and were included in the safety analysis. During the BIVV001 treatment period, 18 TEAEs were reported in 9 participants. This included 1 TESAE of a small intestinal obstruction; the Investigator attributed the event to complications from a prior appendectomy. The most common TEAEs during the BIVV001 treatment period were Thrombin-antithrombin III complex increased and headache (2 participants each, 1 from each cohort). No inhibitor development to FVIII was detected and there were no reports of hypersensitivity or anaphylaxis. Overall, single dose BIVV001 was well tolerated and no safety concerns were identified.

Pharmacokinetic results

In the low-dose (25 IU/kg) cohort, 6 participants had evaluable PK data for BIVV001 treatment. The average FVIII activity level as measured by the one-stage aPTT assay in the low-dose cohort was 26.2% after 72 hours for BIVV001 as compared to 0.7% for Advate. The extended PK profile for BIVV001 showed average FVIII activity levels of 12.2% at 5 days, 5.3% at 7 days, and 1.3% at 10 days, based on the one-stage aPTT assay. The geometric mean $t_{1/2}$ was 37.6 hours for BIVV001 compared with 9.1 hours for Advate based on FVIII activity measured by the one-stage aPTT assay (geometric mean ratio [GMR]=4.1 [95% CI: 2.9, 5.8]; p <0.001) in the low-dose cohort.

In the high-dose (65 IU/kg) cohort, 8 participants had evaluable PK data for BIVV001 treatment. The average FVIII activity level as measured by the one-stage aPTT assay was 78.2% after 72 hours for BIVV001 as compared to 2.3% for Advate. The extended PK profile for BIVV001 showed average FVIII activity levels of 37.8% at 5 days, 17.0% at 7 days and 1.1% at 14 days, based on the one-stage aPTT assay. The geometric mean $t_{1/2}$ was 42.5 hours for BIVV001 compared with 13.2 hours for Advate based on FVIII activity measured by the one-stage aPTT clotting assay (GMR=3.2 [95% CI: 2.8, 3.8]; p <0.001) in the high-dose cohort.

2.2.3.2 Study 242HA102

Study 242HA102 was a Phase 1, open-label, single-site study to assess the safety, tolerability, and PK of repeat-dose BIVV001 in adult male PTPs with severe hemophilia A. Participants were enrolled into either Cohort 1 or Cohort 2 and received a total of 4 once-weekly doses (Days 1, 8, 15, and 22) of BIVV001 at 50 IU/kg or 65 IU/kg, respectively. A predose PK sample was taken on Day 1. In addition, there were multiple PK samples taken after dosing on Days 1 and 22, and a trough (168 hours) sample taken prior to dosing on Days 8, 15, and 22. Of the 24 participants enrolled in the study, all 24 received a total of 4 doses of BIVV001.

Safety results

Repeat doses of BIVV001 were well tolerated and no safety concerns were identified. No inhibitor development to FVIII was detected and there were no reports of hypersensitivity, anaphylaxis, or vascular thrombotic events. Of the 24 participants included in the Safety Analysis Set, 12 participants (50.0%) were reported to have experienced at least 1 TEAE, with a total of 25 TEAEs reported. No study drug-related TEAEs, TEAEs leading to study discontinuation, TESAEs or deaths were reported during the study. The most common (≥2 subjects overall) TEAEs reported were rhinitis (4 subjects [16.7%]), arthralgia (2 subjects [8.3%]), upper respiratory tract infection (2 subjects [8.3%]), and headache (2 subjects [8.3%]). All other TEAEs were reported in 1 subject (4.2%), each. The reported TEAEs were generally consistent with those anticipated in a population of adult subjects with severe hemophilia A.

Pharmacokinetic results

The mean $t_{1/2}$ based on one-stage clotting and chromogenic assays, respectively, was 41.25 and 43.87 hour following 50 IU/kg; and 37.31 and 42.51 hour following 65 IU/kg. The C_{max} and Incremental Recovery [IR] for one-stage and chromogenic assay were comparable on Days 1 and 22 indicating consistent recovery within dose level (50 and 65 IU/kg QW treatment). Following 4 weekly doses of BIVV001, no accumulation of BIVV001 was observed. The one-stage FVIII C_{trough} was 9.16% with 50 IU/kg and 10.8% with 65 IU/kg whereas chromogenic FVIII activity C_{trough} was 6.51% with 50 IU/kg and 7.37% with 65 IU/kg dosing. On Day 22 with QW dosing, the one-stage and chromogenic FVIII activity was maintained above 10% for 162.75 and 141.16 hour, respectively at 50 IU/kg; and 172.53 and 146.70 hour, respectively at 65 IU/kg. The results of this study confirm a prolonged $t_{1/2}$ of BIVV001, between 37-44 hours, with minimal accumulation for weekly dosing regimens of 50 IU/kg and 65 IU/kg. After the weekly 50 IU/kg dose, mean steady state FVIII activity levels 3, 5 and 7 days following drug administration were 46%, 22%, and 9%, respectively (one-stage clotting assay). After the weekly 65 IU/kg dose, mean steady state FVIII activity levels 3, 5, and 7 days following drug administration were 69%, 27% and 12%, respectively (one-stage clotting assay).

A more detailed description of the chemistry, pharmacology, and safety of BIVV001 is provided in the BIVV001 Investigator's Brochure (IB).

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Benefit assessment

BIVV001 is designed to be a new class of blood clotting FVIII engineered to be independent of VWF. New classes of extended half-life FVIII products that prevent and control bleeding episodes for longer periods of time potentially reduce the burden of frequent IV administration and in turn, may improve adherence and outcomes, including QoL for individuals with hemophilia A. In addition to the patient burden that results from frequent administration (25) it is well established that the currently accepted FVIII activity trough level (1%-3%) is not adequate to protect patients from all bleeds and the resulting morbidity associated with such bleeding episodes. Joint bleeds still occur at these levels, leaving patients susceptible to long-term morbidity (18, 26, 30). The ability to increase patient protection by achieving higher sustained levels of factor activity remains a critical need for patients (31) and follows recommendations from the World Federation of Hemophilia (5). BIVV001 has the potential to achieve and maintain substantially higher factor activity levels than currently available therapies, with less frequent administration, which would represent a major advance in hemophilia management.

2.3.2 Risk assessment

There is a long history of therapeutic use of rFVIII products in the treatment of hemophilia A, with a well-recognized and understood safety profile. Patients treated with other rFVIII products have reported adverse reactions that include hypersensitivity, anaphylaxis, and development of inhibitors. Based on the currently available non-clinical (*in vivo* and *in vitro*) and clinical data, it is expected that BIVV001 will have a safety profile similar to other rFVIII products.

The safety and tolerability of BIVV001 in previously treated adults with severe hemophilia A was evaluated in a single dose Phase 1/2a study (Study 242HA101) and in a repeat dose Phase 1 study (Study 242HA102). Single and repeat doses BIVV001 were well tolerated and no safety concerns were identified.

2.3.3 Overall benefit: risk conclusion

Overall, the clinical development program for BIVV001 is supported by the available nonclinical and clinical data as well as the potential benefits associated with development of a rFVIII product with an extended $t_{1/2}$ that offers increased protection in the treatment of individuals with hemophilia A.

3 OBJECTIVES AND ENDPOINTS

Table 4 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A	• The occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen modified Bethesda assay
Secondary	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) (for treated, for untreated, for all bleeding episodes) and by type and location • Percentage of participants who maintain FVIII activity levels over 1%, 3%, 5%, 10%, 15%, and 20% at Day 7
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• Number of injections and dose of BIVV001 to treat a bleeding episode • Percentage of bleeding episodes treated with a single injection of BIVV001 • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale • Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale
• To evaluate BIVV001 consumption for prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• Annualized joint bleeding rate (AJBR) • Target joint resolution at Week 52, based on ISTH criteria • Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS)
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score and physical health domain score from baseline to Week 52 (≥4 years old) and via parent proxy version (≥4 years old)
• To evaluate the efficacy of BIVV001 for perioperative management	• Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment on the ISTH 4-point response for surgical procedures scale • Number of injections and dose to maintain hemostasis during perioperative period for major surgery • Total BIVV001 consumption during perioperative period for major surgery • Number and type of blood component transfusions used during perioperative period for major surgery • Estimated blood loss during perioperative period for major surgery

Objectives	Endpoints
• To evaluate the safety and tolerability of BIVV001 treatment	• The occurrence of adverse events (AEs) and serious adverse events (SAEs) • The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests • The occurrence of embolic and thrombotic events
• To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	• PK parameters including, but not limited to, maximum activity (C_{max}), elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}), area under the activity time curve (AUC), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels
Tertiary/Exploratory	
• To assess the impact of BIVV001 treatment on caregiver- and/or patient-reported clinical outcome assessments measurements and health resource utilization	• Changes in PROMIS-SF Physical Function measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in PROMIS Pain Intensity measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in PROMIS Pediatric-SF Pain Interference measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥ 5 years old) • Changes in EuroQoL 5-dimension 5-level Youth (EQ-5D-Y) from Baseline to Week 52 (≥8 years old) and via parent proxy version (4-7 years old) • Caregiver interviews at Week 52 (or subsequent post-study follow-up visit) • Changes in healthcare resource utilization and productivity

Abbreviations: ABR = annualized bleeding rate; AE = adverse event; AJBR = annualized joint bleeding rate; aPTT = activated partial thromboplastin time; AUC = area under the activity time curve; CL = total clearance; CL_{ss} = total clearance at steady state; C_{max} = maximum activity; C_{trough} = trough activity; DNAUC = dose-normalized area under the activity-time curve; EQ-5D-Y = EuroQoL-Youth; FVIII = factor VIII; Haemo-QoL = Haemophilia Quality of Life Questionnaire for Children and Adolescents; HJHS = Hemophilia Joint Health Score; IR = incremental recovery; ISTH = International Society on Thrombosis and Haemostasis; MRT = mean residence time; PGA = Physician's global assessment; PROMIS = Patient-Reported Outcomes Measurement Information System, QoL = Quality of Life; SAE = serious adverse event; $t_{1/2}$ = half-life; V_{ss} = volume of distribution at steady state.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the safety and efficacy assessments chosen for use in this study are considered well established and relevant in hemophilia. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy to minimize risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multinational, multicenter, open-label Phase 3 study of the safety, efficacy, and PK of IV BIVV001 in PTPs <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). The study is comprised of one arm where participants will receive BIVV001 at a dose of 50 IU/kg IV QW for 52 weeks.

Overall, approximately 65 participants will be enrolled to achieve at least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 EDs.

Following a washout period (at least 3 to 4 days, depending on age), the first 24 participants from 2 age cohorts (at least 12 participants <6 years of age and at least 12 participants 6 to <12 years of age) will undergo PK sampling after their first dose of BIVV001 (Baseline). For all participants included in the PK subgroup, existing PK information with the participant's pre-study FVIII product ($t_{1/2}$ and IR) should be available.

Participants who undergo major surgery during the study will be included in the surgery subset to assess control and prevention of bleeding during use of BIVV001 in the surgical setting. The definition of major surgery is included in Appendix 7, Section 10.7.1.

Enrollment in a planned open-label extension study will be offered to participants after completion of this study.

Screening

Participants will come to the clinic for determination of eligibility. All screening evaluations must be completed within 8 weeks and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and rescreened, to confirm eligibility or record reasons for screening failure, as applicable. If a participant is considered a screen failure, the reasons for exclusion must be documented in his source documents and on the Screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any AEs. Participants who rescreen will sign the informed consent form (ICF) again and repeat all assessments.

Participants will undergo a washout period of at least 48 hours prior to the Screening inhibitor test to obtain interpretable test results. Washout prior to BIVV001 Day 1 dose administration (Baseline Visit) is at least 96 hours (4 days) for 6 to <12 years participants and at least 72 hours (3 days) for <6 years participants. The washout prior to the Day 1 BIVV001 dose administration may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor.

Participants will be registered as screened in the Interactive Response Technology (IRT) system and will be assigned a unique identification number that will be used on study-related documents pertaining to the participant.

Enrollment and baseline (Day 1)

Participants will be enrolled via IRT, after all screening assessments have been successfully completed and after the Investigator has verified that the participant is eligible to participate in the study per criteria detailed in Section 5.1 and Section 5.2. Approximately 65 patients will be enrolled.

Participants will receive BIVV001 as weekly prophylaxis for 52 weeks. Additional doses will be given as necessary to treat breakthrough bleeding episodes according to Section 6.1.3. Selected doses will be given in clinic according to the Schedule of Activities ([SoA]; Table 1). Other doses will be administered by the participant or caregiver at home, or in clinic.

Participant's caregivers will be supplied with an electronic patient diary (ePD) at the Baseline visit to record all bleeding episodes and doses of BIVV001 administered after the Baseline visit. Entries are to be made in a timely manner and it is preferred that details of doses are entered immediately upon administration or within 7 days. Participant's caregivers will be prompted to enter bleeding location, type (spontaneous or traumatic), reasons for dosing (prophylaxis or treatment of a bleeding episode), symptoms and response to treatment. An ePD training will be completed at the study site at the Baseline visit. Training of caregivers should be documented in the appropriate source record. The ePD refresher training should also be provided at any point during the study.

The first 12 participants in each age cohort (<6 years of age to 12 years and 6 to <12 years of age) will undergo PK sampling after the first dose of BIVV001 (Baseline) (see Table 2 for details). After full enrollment of the PK subgroup, optional participation in the PK subgroup is offered. All other participants will have trough and peak samples only (collected within 30 minutes prior to BIVV001 dosing and 15 (±3) minutes post injection).

Participants who undergo major surgery during the study will be included in the surgery subgroup.

Study clinic visits

All enrolled participants will come in to scheduled visits at the following time points: Baseline (Day 1), Week 4, Week 13, Week 26, Week 39, and Week 52. Details of each visit are provided in Table 1.

For all participants each scheduled study visit subsequent to BIVV001 Day 1 is to be arranged 7 days (±1 day) after the preceding prophylaxis dose. The participant should withhold the weekly prophylaxis dose on the day of the study visit, so that it can be administered at the study visit.

The first 12 participants in each age cohort (<6 years of age to 12 years and 6 to <12 years of age) will undergo PK sampling after the first dose of BIVV001 (Baseline), including samples at Day 1, Day 2, Day 4 and Day 8 (Table 2). All other participants will have trough and peak sample only (collected within 30 minutes prior to BIVV001 dosing and 15 (±3) minutes post-injection at each visit where a BIV001 injection is scheduled.

Participants will undergo efficacy and safety assessments throughout their participation in the study. Safety assessments will include testing for inhibitor development to FVIII. A Follow-up Safety Visit or Telephone Call will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study. Participants will complete their End of Study (EOS) Visit 52 (±7) days post-Baseline, or earlier if EOS has been declared.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

BIVV001 is designed to be a new class of blood clotting FVIII. Preclinical and clinical experience indicate that BIVV001 has an extended $t_{1/2}$, which can achieve and maintain higher sustained factor activity levels than currently available treatments, with less frequent administration.

This study is being conducted to determine the safety, efficacy, and PK of BIVV001 administered as prophylaxis treatment in PTPs <12 years of age with severe hemophilia A at a weekly dose of 50 IU/kg.

The study will enroll PTPs with severe hemophilia A aged <12 years. The study design takes into consideration the published guidelines for the clinical investigation of recombinant and human plasma-derived FVIII products per the European Medicines Agency (EMA) guidelines (39).

Participants should have been treated with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6-11 years and at least 50 EDs for patients aged <6 years.

Participants will receive prophylactic BIVV001 at QW dosing interval for 52 weeks.

The primary endpoint is the occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen-modified Bethesda assay. The incidence of inhibitor formation for all (≥0.6 BU/mL), “high (≥5.0 BU/mL)” and “low (≥0.6 BU/mL and <5.0 BU/mL)”, titer inhibitors from the central laboratory will be summarized for each age cohort and overall; a 95% CI using Clopper-Pearson method will be calculated for each incidence.

The efficacy of BIVV001 as a prophylactic treatment will also be assessed and the secondary efficacy endpoints will include ABR. The ABR has traditionally been used to assess efficacy of FVIII products in the clinical trial setting and is considered an objective and measurable endpoint consistent with current EMA guidance and established regulatory precedents.

4.3 JUSTIFICATION FOR DOSE

The dose of 50 IU/kg IV QW was selected as the prophylactic dose in both age cohorts (6 to <12 years and <6 years). The dosing regimen was chosen to optimize protection against bleeds and reduce the treatment burden on participants and their families. The dose was selected based on data from Study 242HA101, which assessed the PK of 2 single dose levels of BIVV001 (25 IU/kg and 65 IU/kg) and Study 242HA102, which assessed the PK of 2 QW dose levels of BIVV001 (50 IU/kg and 65 IU/kg). A population PK model was built with data from the single dose Study 242HA101 and multiple dose Study 242HA102. The population PK model with adult data was extrapolated to pediatric subjects with allometric exponents driven by body weight ([redacted]). Pediatric simulations with body weight ranges from historical hemophilia trials were performed to understand steady state kinetics of BIVV001 in 6-12 years and <6 years age cohorts. Physiologically-based pharmacokinetic model were also evaluated to understand the effect of age ontogeny on BIVV001 PK profile in younger subjects.

At a dose of 50 IU/kg QW in the 6 to <12 years age cohort, the population PK model predicted a mean time above 40% (normal or near-normal FVIII activity levels) for [redacted] days with the one-stage aPTT assay and for [redacted] days with the chromogenic assay, providing a sustained level of protection. The population means for C_{max} were in the upper physiological range of FVIII activity with [redacted] and [redacted] IU/dL for the one-stage aPTT assay and the chromogenic assay, respectively. The population means for C_{trough} were [redacted] and [redacted] IU/dL [redacted] days post-dose, for the one-stage aPTT assay and the chromogenic assay, respectively.

At a dose of 50 IU/kg QW in the <6 years cohort, the population PK model predicted a mean time above 40% (normal or near-normal FVIII activity levels) for [redacted] days with the one-stage aPTT assay and for [redacted] days with the chromogenic assay, providing a sustained level of protection. The population means for C_{max} were in the upper physiological range of FVIII activity with [redacted] and [redacted] IU/dL for one-stage aPTT assay and chromogenic assay, respectively. The population means for C_{trough} were [redacted] and [redacted] IU/dL for one-stage aPTT assay and chromogenic assay, respectively.

The Sponsor's proposed dosing regimen was selected taking into consideration the potential increased protection conferred by sustained FVIII activity levels in the normal to mild range along with the decreased treatment burden of once weekly dosing. This combined level of FVIII activity protection and dosing interval is not possible with current intravenous FVIII replacement therapies (40). BIVV001 is the first FVIII replacement therapy to overcome the $t_{1/2}$ limitations of VWF (32) and could thus allow for higher sustained levels of protection. Therefore, BIVV001 is the first FVIII replacement therapy that allows prospective testing of the hypothesis that higher sustained factor levels will further reduce or eliminate joint bleeds and potentially provide other clinical benefits, while decreasing the burden of treatment.

Development of a new class of FVIII replacement therapy whose $t_{1/2}$ extension is independent of VWF and can be administered less frequently while achieving higher factor levels would represent a major advance in hemophilia management. Historically, prophylactic therapy for pediatric patients with hemophilia A targeted FVIII activity levels of ≥1% with 2 or 3 times dosing weekly (19). However, it has become clear that the currently defined FVIII activity threshold of 1%-3% trough for prophylactic therapy is insufficient to prevent all bleeding and

does not eliminate the considerable long-term joint damage associated with severe hemophilia A, albeit it does delay its onset (26, 41). Manco-Johnson and colleagues recently evaluated prophylaxis use in the United States in relation to bleeding rates and joint health outcomes (29). Despite increasing rates of prophylaxis usage in this population, patients on prophylaxis continued to suffer from joint bleeds and experience target joints. This trend is also noted in the pediatric population where despite prophylactic treatment regimens, pediatric patients also develop joint damage as evidenced on magnetic resonance imaging at an early age (18) when the burden and incidence would likely increase over time. The development of joint damage is also impacted by the time at which prophylaxis therapy is initiated (42). Thus, the continued development of joint damage despite prophylactic treatment suggests that current treatment regimens targeting FVIII activity trough levels of ≥1% are inadequate (31). Recommendations from World Federation of Hemophilia have supported the maintenance of higher FVIII activity levels (5).

The dose of BIVV001 recommended for treating bleeding episodes and surgical management follows published treatment guidelines to achieve minimum FVIII activity levels (6). Simulations were conducted using the population PK model mentioned above and scenario testing indicated that these dosing paradigms would achieve the minimum FVIII activity levels for treatment of bleeding episodes and surgery as defined by the WFH guidelines (6).

A dose 50 IU/kg of BIVV001 is recommended for treating bleeding episodes. This dose maintains the mean FVIII activity levels in the normal to low normal range (more than 40%) for up to 3 to 4 days post-dose. Using the same dose for treatment of bleeding episodes as for the prophylactic treatment regimen is recommended to avoid complexity and dosing errors. It is anticipated that most bleeding episodes will require treatment with 1 dose of BIVV001. Based on the investigator's judgement, additional doses of 30 or 50 IU/kg can be considered every 2 to 3 days. For minor/moderate bleeding episodes that occur within 2 to 3 days after a prophylaxis dose and require treatment, the investigator has the option to choose a lower initial dose of 30 IU/kg. The Sponsor has defined minor/moderate/major bleeding episodes in Appendix 7, Section 10.7.2 of the protocol.

A loading dose of 50 IU/kg of BIVV001 is recommended for perioperative management. Simulations were conducted using the population PK model mentioned above and scenario testing indicated that for minor surgery, mean factor levels in the range suggested by WFH are obtained with a single dose. Alternatively, the procedure may be planned around a standing prophylactic dose without the need for additional dosing. For major surgeries that require target FVIII activity levels in the normal range that decrease over time from surgery, repeated doses of 30 or 50 IU/kg are recommended.

4.4 END OF STUDY DEFINITION

End of Study will occur when both of the following criteria have been met:

- At least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) have reached 50 EDs and have completed a valid inhibitor test after the 50th ED.

- 24 participants (12 participants <6 years of age and 12 participants 6 to <12 years of age) in the PK subgroup have completed the BIVV001 PK profile with adequate estimate of terminal $t_{1/2}$.

Once this milestone has been achieved, all ongoing study participants will return to the study center for the EOS/Early Termination (ET) visit assessments.

At the EOS, eligible patients will have the option to participate in a long-term extension study.

4.5 STUDY STOPPING RULES

The Sponsor may terminate the study at any time, after informing Investigators, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and applicable regulatory agencies. Investigators will be notified by the Sponsor (or designee) if enrollment and dosing are suspended, completed, or closed.

At the EOS, eligible patients will have the option to participate in a long-term extension study.

4.5.1 Criteria for dose and/or enrollment suspension

The occurrence of specific study events will require that further enrollment in the study and further dosing be suspended. In this situation, the event(s) will be investigated prior to enrollment and dosing of any additional participants.

In this study, events requiring dose and/or enrollment suspension are as follows:

- Inhibitor development in 2 or more participants following administration of BIVV001 (See Section 8.3.7 for definition of inhibitor development).
- The Investigator and Sponsor (or Sponsor alone) determine that an event or current data warrant further evaluation.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be younger than 12 years of age, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII as documented either by central laboratory testing at Screening or in historical medical records from a clinical laboratory demonstrating <1% FVIII coagulant activity (FVIII:C) or a documented genotype known to produce severe hemophilia A.

I 03. Previous treatment for hemophilia A (prophylaxis or on-demand) with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6-11 years and above 50 EDs for patients aged <6 years.

I 04. For the PK subgroup only: existing PK information with the participant's pre-study FVIII product ($t_{1/2}$ and IR) should be available, or alternatively, historic PK assessments deemed adequate for calculating $t_{1/2}$ and IR PK by the Sanofi PK scientist.

I 05. Platelet count ≥100 000 cells/µL at Screening.

I 06. A participant known to be human immunodeficiency virus (HIV) antibody positive, either previously documented or identified from screening assessments, must have the following results prior to enrollment.

a) CD4 lymphocyte count >200 cells/mm³

b) Viral load of <400 copies/mL

Documented results of CD4 lymphocyte count and viral load will be accepted if samples were collected within 26 weeks prior to Screening or if samples were collected during Screening and evaluated by the central laboratory. Participants who have previously tested negative for HIV must have a repeat test by the central laboratory during Screening.

I 07. Willingness and ability of the caregiver to complete training in the use of the study ePD and to use the ePD throughout the study.

Weight

I 08. Weight above or equal to 10 kg.

Sex

I 09. Male

a) Male participants

No contraceptive measures required for this study.

Informed Consent

I 10. Ability of the participant or his legally authorized representative (eg, parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent or assent (as applicable) and authorization to use protected health information in accordance with national and local participant privacy regulations.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Serious active bacterial, viral or fungal infection (other than chronic hepatitis or HIV) present within 30 days of Screening.

E 02. Other known coagulation disorder(s) in addition to hemophilia A.

E 03. History of hypersensitivity or anaphylaxis associated with any FVIII product.

E 04. History of a positive inhibitor (to FVIII) test defined as ≥0.6 BU/mL, or any value greater than or equal to the lower sensitivity cut-off for laboratories with cut-offs for inhibitor detection between 0.7 and 1.0 BU/mL, or clinical signs or symptoms of decreased response to FVIII administrations. Family history of inhibitors will not exclude the participant.

E 05. Positive inhibitor test result, defined as ≥0.6 BU/mL at Screening.

E 06. Active renal disease (per the discretion of the Investigator and medical records) at Screening.

E 07. Active hepatic disease (per the discretion of the Investigator and medical records) at Screening.

Prior/concomitant therapy

E 08. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) above the maximum dose specified in the regional prescribing information within 2 weeks prior to Screening.

E 09. Treatment with acetylsalicyclic acid (ASA) or other non-NSAIDs anti-platelet therapies within 2 weeks prior to Screening.

E 10. Systemic treatment within 12 weeks prior to Screening with chemotherapy and/or other immunosuppressive drugs (except for the treatment of hepatitis C virus [HCV] or HIV). Use of corticosteroids is allowed, except for systemic corticosteroid treatment given daily or on alternate days for >14 days. Local, topical, and/or inhaled steroid use is permitted.

E 11. Emicizumab use within the 20 weeks prior to Screening.

Prior/concurrent clinical study experience

E 12. Previous enrolment in this study; participants who fail Screening may rescreen (maximum of 2 rescreenings).

E 13. Treatment with an investigational product within 30 days or 5.5 half-lives prior to Screening, whichever is longer. For investigational products with a pharmacodynamic effect that persists longer than the half-life, the maximal pharmacodynamic effect must return to baseline prior to Screening.

Other exclusions

E 14. Major surgery within 8 weeks prior to Screening. Major surgery is defined as any surgical procedure (elective or emergent) that usually, but not always, involves general anesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (eg, laparotomy, thoracotomy, craniotomy, joint replacement, or limb amputation).

E 15. Any country-related specific regulation that would prevent the participant from entering the study.

E 16. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 17. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 18. A Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

Participants who routinely administer an additional dose of FVIII prior to a sports activity or increased physical activity will not be allowed to do so in this study. However, the day of BIVV001 dosing could be chosen prior to a weekly recurring physical activity.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent/assent, demography, screen failure reasons, eligibility criteria, and any AEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice maximum. Rescreened participants should be assigned the same participant number as for the initial screening. If a participant is considered a screen failure, the reasons for exclusion must be documented in his source documents and on the Screening log. Reasons for screen failure will be captured in the Interactive Response System.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 5 - Overview of study interventions administered

ARM name	Prophylaxis
Intervention name	rFVIIIFc-VWF-XTEN (BIVV001)
Type	Drug
Dose formulation	Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent)
Unit dose strength(s)	250, 500, 1000, 2000 IU per vial
Dosage level(s)	50 IU/Kg every week
Route of administration	Intravenous
IMP and NIMP	IMP
Packaging and labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement
[Current/Former name(s) or alias(es)]	---

Abbreviations: IMP = Investigational medicinal product; NIMP = noninvestigational medicinal product.

6.1.1 Investigational medicinal product(s)

BIVV001 drug product will be supplied as a lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent), which will also be supplied by Sanofi. For this study, each vial of drug product nominally contains 250, 500, 1000, 2000 IU of BIVV001 in the formulation buffer (10 mM L-histidine, 250 mM L-arginine-HCl, 5mM CaCl2, 5% (w/v) sucrose, 0.05% (w/v) polysorbate 80, pH 7.0). Please refer to the BIVV001 Pharmacy Manual, or the BIVV001 IB for additional details.

BIVV001 must be dispensed only by the Pharmacist or appropriately qualified staff. BIVV001 is to be dispensed only to the caregivers and/or legal guardians of participants enrolled in this study. Once BIVV001 is prepared for a participant, it can only be administered to that participant. The first dose of BIVV001 must be administered at the Baseline visit by the Investigator or qualified delegate at each study site, where medication and resuscitation equipment for the emergent management of an allergic reaction are readily available. BIVV001 preparations are for one-time study use only; the study site staff should not use any leftover BIVV001 remaining in the vial for another participant.

6.1.2 Study treatment schedule and administration

Instructions for the preparation and administration of BIVV001 are provided in the Pharmacy Manual and the Information for Patients.

The prophylactic treatment regimen is QW (every 7 days) dosing with 50 IU/kg BIVV001. This dose was determined based on population PK model and appropriate simulations to understand steady state kinetics of BIVV001. The aim of the 50 IU/kg QW treatment regimen is to provide sustained FVIII activity levels in the normal to mild hemophilic range and to decrease treatment burden with QW dosing.

The dosing interval in the younger age cohort (<6 years) may be reduced by 1 or 2 days if clinically warranted at the discretion of the investigator and only after consultation with the study medical monitor. For participants who have their BIVV001 dosing interval reduced, the washout period prior to inhibitor tests must be adjusted accordingly.

BIVV001 will be delivered via a slow push IV injection at a rate of administration listed in Table 6 and determined by the participant's comfort level. BIVV001 formulation contains sucrose and the injection durations listed in Table 6 are consistent with recommendations on infusion rates. Overall, the recommended maximum total injection time should be ≤15 minutes for all doses.

Table 6 - BIVV001 weight-based vial and injection rate recommendations

Participant weight	Minimum injection duration per vial	Maximum total injection time
10-<20 kg	6 minutes per vial	15 min
20-<30 kg	3 minutes per vial	15 min
≥30 kg	2 minutes per vial	15 min

Any missed of BIVV001 doses should be taken as soon as possible or according to the instructions of the Investigator, taking into account that 2 consecutive prophylactic doses of 50 IU/kg should be separated by a period of at least 72 hours.

6.1.3 Treatment of bleeding episodes during prophylactic treatment regimen

The participant's caregiver will be instructed by the clinic on how to treat a bleeding episode at home and record this in the ePD (for a definition of bleeding episode refer to Section 8.1.2). Bleeding episodes requiring treatment will be treated with a single dose of 50 IU/kg, as described in Table 7.

Major bleeding episodes will be treated in the hospital/clinic or at home, as applicable. The participant's caregivers will be instructed to consult the investigational site prior to dosing any follow-up injection. Administration of a second dose of BIVV001 as follow-up treatment will be determined by the Investigator and participant's caregivers based on the participant's clinical condition. If a bleed does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may

be considered. For mild/moderate bleeds within 2-3 days of a recent prophylactic dose, a 30 IU/kg dose may also be used. Treatment of any bleeding reported within 72 hours of a previous episode at the same location should be considered a follow-up injection and the event should not be recorded as a new bleeding episode. If a bleeding episode occurs at the time when a regular prophylaxis dose of BIVV001 is due, the participant will inject with a dose of 50 IU/kg.

Resumption of prophylaxis dosing following treatment for bleeding episodes is outlined below:

If the bleeding episode is stopped with a single dose of 50 IU/kg BIVV001, the participant will continue with the schedule of weekly prophylaxis dosing he was on prior to the bleeding episode, unless the next scheduled prophylaxis dose is within 72 hours of the treatment of the bleeding episode. In this case, the prophylaxis dose should be delayed until 72 hours after last 50 IU/kg dose for treatment of the bleeding episode. Thereafter, the participant should return to the schedule of weekly prophylaxis dosing that he/she was on prior to the bleeding episode. If the participant needs additional doses of 30 IU/kg after the first 50 IU/kg dose to treat a bleeding episode, these additional doses will not require any further delay of the next prophylaxis dose.

6.1.4 Surgical dosing

Minor surgeries can be performed while participating in this trial by administering a dose of 50 IU/kg BIVV001 (Table 7).

Participants who undergo major surgery during the study will be included in the surgery subset. Definitions for major and minor surgery are listed in Appendix 7, Section 10.7.1.

Prior to surgery, the Investigator will plan the perioperative treatment regimen of FVIII replacement therapy generally required for the type of planned surgery in accordance with the dosing guidance in Table 7. Recommendation for the appropriate dosing of BIVV001 in the surgical treatment period, including any rehabilitation time, will be discussed among the Investigator, Surgeon, and Sanofi BIVV001 Medical Monitor. No continuous infusion of BIVV001 will be allowed for this study.

For all participants in the surgery subgroup, the surgical period will begin with their first dose of BIVV001 given for the surgery (ie, the pre-operative loading dose) of 50 IU/kg IV. If needed, the dose level of BIVV001 should be adjusted to aim for a FVIII activity level of at least 100% and maintained during the surgery according to the WFH Guidelines.

Post-operatively, FVIII activity levels should be monitored by daily measurements of FVIII activity locally as long as the patient is hospitalized. FVIII levels should be maintained at recommended levels and duration according to WFH Guidelines. Depending on the targeted FVIII activity level this likely means a need to administer a second dose approximately 48-72 hours after the pre-operative loading dose. Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered depending on the desired FVIII activity levels and the severity of the procedure. Due to the long $t_{1/2}$ of BIVV001, the frequency of dosing in the post-surgical period may be extended after the first week post-surgery.

Table 7 - Intravenous BIVV001 treatment

Indication	Dosage	Frequency
Prophylaxis	50 IU/kg	Once weekly
Bleeding episode[a]	50 IU/kg	Single dose for all bleeding episodes. Additional and adjusted doses only after consultation with the Investigator: If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. For minor/moderate bleeding episodes within 2 to 3 days of a recent prophylactic dose, a 30 IU/kg dose may also be used.
Minor surgery	50 IU/kg	Single dose prior to surgery
Major surgery, only allowed after 6 EDs	50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered.

a Refer to Appendix 7 (Section 10.7.2) for definitions of minor, moderate, and major bleeding episodes.

6.1.5 Bleeding episodes that occur prior to the baseline and during PK sampling period

If a participant experiences a bleeding episode during the washout period before PK sampling in conjunction with their first dose of BIVV001, the participant should treat the bleeding episode with their pre-study FVIII product. A participant who experiences a bleeding episode in the dosing interval prior to a scheduled visit to monitor trough PK levels should be treated with BIVV001 using the treatment guidelines described in Table 7.

Detailed guidelines for washout and sampling details are provided in Appendix 7, Section 10.7.4.

6.1.6 BIVV001 dosing calculations

This section explains when the actual potency or nominal strength is to be used for dose calculations. The definitions of these terms and the types of dose calculations in this study are described below.

6.1.6.1 Definitions of nominal strength versus actual potency

The nominal strength is the target potency of the vial (that is, 250 IU, 500 IU, 1000 IU, 2000 IU per vial).

The actual potency is the true potency of the vial as measured by a validated potency assay. (Actual potency may vary between 80% to 125% of nominal strength.)

6.1.6.2 Calculation and recording of actual versus nominal dosing

Actual potency must be used for dose calculations for the following:

Baseline PK and Peak/Trough at Week 4*:* Dose for PK is 50 IU/kg. The ***actual*** potency shown on the vial must be used to calculate the volume of BIVV001, using partial vial(s). The instructions provided in the Pharmacy Manual must be used to calculate the *volume for administration based on actual potency.*

Nominal strength can be used for dose calculations for the following:

Peak/Trough after Week 4 and dosing for prophylactic treatment or treatment of bleeds. The ***nominal*** strength should be used for calculations and rounded up to the nearest whole vial. Note: The instructions provided in the Pharmacy Manual must be used to calculate the *number of vials for administration based on nominal strength* (unless an equivalent alternative site-specific template is approved by the clinical research associate [CRA] prior to use).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must maintain accurate records of receipt and the condition of the study drug supplied for this study including dates of receipt. They must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. Accurate records must be kept of when and how much study drug is dispensed and administered to each participant in the study. Any reasons for departure from the protocol dispensing treatment regimen must also be recorded. BIV001 may be supplied at the site or from the site to the participant via a Sponsor-approved courier company, where allowed by local regulations and approved by the participant.

All drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information about drug accountability and the final disposition of unused study drugs are provided in the Pharmacy manual.

Any quality issue noticed with the receipt or use of an investigational medicinal product (IMP) deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be participant to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP/NIMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP/NIMP to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP in any other manner.

6.2.1 Study drug packaging and labelling

BIVV001 will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP). BIVV001 vials will be labeled according to the requirements of local law and legislation. Label text will be approved according to Sanofi procedures, and copies of the labels will be made available to the study site upon request.

6.2.2 Study drug storage

The study site staff should follow the BIVV001 Pharmacy Manual for specific instructions on its storage.

6.2.3 Study drug preparation

The study site staff should follow the BIVV001 Pharmacy Manual for specific instructions on its preparation.

6.2.4 Study drug administration

The study site staff should follow the BIVV001 Pharmacy Manual for specific instructions on its administration. During study visits, for reliable PK assessment, PK sampling should not be done via the same intravenous access route as used for the BIVV001 administration.

6.2.5 Study drug accountability

Accountability for BIVV001 is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of BIVV001 received, to whom dispensed (participant-by-participant accounting), and accounts of any BIVV001 accidentally or deliberately destroyed or lost. The study site staff should follow the BIVV001 Pharmacy Manual for specific instructions on its accountability.

6.2.6 Study drug handling and disposal

Unless otherwise notified, all BIVV001 vials (used and unused) must be saved for BIVV001 accountability. Participants should bring in all used and unused vials to the clinic during their scheduled visits. Reconciliation must be made between the amount of BIVV001 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation

must be provided for any discrepancies. The study site staff should follow the BIVV001 Pharmacy Manual for specific instructions on its disposal.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable as this is an open-label study.

6.4 STUDY INTERVENTION COMPLIANCE

The Investigator or pharmacist will keep accurate records of the quantities of the IMP dispensed, used, and unused. The product accountability and inventory form is to be updated each time investigational product is dispensed. The study monitor will periodically check the supplies of the IMP held by the Investigator or pharmacist to verify accountability.

Treatment kit number has to be recorded on the appropriate page of the electronic Case Report Form (eCRF) and also on the product accountability and inventory form.

All used, partially used, or unused treatments will be destroyed according to the standard practice at the site or per local regulations. A detailed treatment log of the IMP will be established with the Investigator or other personnel designated by the Investigator and countersigned by the Investigator and the Monitoring. Confirmation of destruction will be provided to the Sponsor.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from the time of signature of the ICF through the Safety Follow-Up Call or Visit will be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Permitted concomitant therapy

Participants taking medication routinely for a pre-existing condition should be on a treatment regimen that has been stable for at least 3 weeks prior to enrollment, and dosage changes should not be anticipated during the observation period for this study. Pre-study stable NSAID doses below the maximum dose specified in the local prescribing information at the time of enrollment are permitted. All concurrent prescription and nonprescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements) should be recorded from the time of signature of the ICF throughout the treatment and follow-up periods.

Prohibited concomitant therapy

No premedication for pain or pyrexia relief is to be given for administration of BIVV001. Should pre-medications be contemplated, this will be discussed on a case-by-case basis with the Sanofi Study Medical Monitor or designee and before administration.

Medications prohibited during the study include:

1. NSAIDs at doses above the maximum dose specified in local prescribing information.
2. Acetylsalicyclic acid (ASA) or other non-NSAIDs anti-platelet therapies.
3. Systemic treatment with chemotherapy and/or other immunosuppressive drugs (except for the treatment of HCV or HIV). The use of systemic steroids for the treatment of acute respiratory illness (eg, asthma), acute allergic episodes, or otherwise life-threatening episodes is allowed. Treatment in these circumstances should not exceed a14-day duration. Local, topical, and/or inhaled steroid use is permitted.
4. Any other FVIII product.
5. Emicizumab.
6. Anticoagulant agents, excluding the use of heparin for intermittent flushing for maintenance of patency of intravenous catheters, and short-term thromboembolic prophylaxis during immobilization and/or perioperatively.

Participants who routinely administer an additional dose of FVIII prior to a sports activity or increased physical activity will not be allowed to do so in this study. However, the day of dosing BIVV001 could be chosen prior to a weekly recurring physical activity.

6.6 DOSE MODIFICATION

Not applicable.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The Sponsor plans to perform a long-term safety trial. Enrollment in this open-label extension study will be offered to participants after completion of this study based on eligibility criteria. No other post study treatment access will be offered.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants or their caregivers are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or withdrawal from the study must be fully documented in the eCRF and should be followed up by the Investigator. The Investigator or sponsor may withdraw a participant at any time if it is considered to be in the participant's best interest.

Discontinuation of study drug and withdrawal from the study are described in Section 7.1 and Section 7.2, respectively.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

Participants who discontinue study drug for any reason should have every effort made to conduct the assessments at the EOS/ET visit as specified in the SoA (Table 1).

The Investigator, Sponsor, or designee may discontinue dosing in a participant if the participant:

- Is in significant violation of the protocol
- Is non-adherent to treatment regimen
- Experiences a serious or intolerable AE
- Requires a prohibited medication

A participant must permanently discontinue study treatment if any of the following occur:

- Participant develops an inhibitor (see Section 8.3.7 for definition of inhibitor development)
- Participant experiences a Grade 3 or greater allergic reaction per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or an anaphylactic reaction in association with BIVV001 administration
- The participant or his caregivers withdraws consent

The Investigator may confer with the Sponsor or Study Medical Manager before discontinuing dosing in the participant.

Participants or their caregivers may decide that IMP be discontinued.

If a participant discontinues dosing due to an AE or SAE, the event should be followed as described in Section 8.3.3. When a participant discontinues IMP dosing, the primary reason must be recorded in the appropriate section of the eCRF.

See the SoA (Table 1) for data to be collected at the time of study drug discontinuation and follow-up, and for any further evaluations that need to be completed.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of study drug, the participants will be assessed using the procedures in the ET/EOS visits. All participants should also complete the Safety Follow-up Call or Visit, refer to Section 1.3.

All cases of definitive study drug discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary study drug discontinuation may be considered by the Investigator because of a suspected adverse reaction. For all temporary study drug discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF and AEs should be reported according to Section 8.3.

7.1.2.1 Rechallenge

Re-initiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 5)

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- Participants may withdraw from the study at any time at their own or their caregiver's request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 1).
- See SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant or his parents withdraw consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he or his parents may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Participants who withdraw from the study intervention or their caregivers should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant or his caregivers may withdraw consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

Participants who have withdrawn from the study cannot be re-treated in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant/caregiver and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant/caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant/caregiver continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1, Section 10.1.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA (Table 1).

8.1.1 Electronic patient diary supply and training

Participant's caregiver will be supplied with an ePD at the Baseline visit to record all bleeding episodes and doses of BIVV001 administered after the Baseline visit. Entries are to be made in a timely manner and it is preferred that details of doses are entered immediately upon administration or within 7 days. Participant's caregiver will be prompted to enter bleeding location, type (spontaneous or traumatic), reasons for dosing (prophylaxis or treatment of a bleeding episode), symptoms and response to treatment. An ePD training will be completed at the study site at the Baseline visit. Training of caregivers should be documented in the appropriate source record. The ePD refresher training should also be provided at any point during the study.

8.1.2 Bleeding episodes data

In this study, a standardized definition of a bleeding episode based on International Society on Thrombosis and Haemostasis (ISTH) criteria will be used (43). A bleeding episode is defined as an episode that starts from the first sign of bleeding and ends no more than 72 hours after the last injection to treat the bleeding episode. Any subsequent bleeding at the same location and injections administered ≤72 hours from the previous injection will be considered as the same bleeding episode. Multiple bleeding locations treated with a single injection will also be considered a single bleeding episode. Any injection to treat the bleeding episode that is administered >72 hours after the preceding one will be considered the first injection to treat a new bleeding episode in the same location. Any injection used to treat subsequent bleeding at a different location will be considered a separate bleeding episode, regardless of the time from the last injection to treat a bleeding episode.

If a bleeding episode occurs on the same day as a regularly scheduled prophylaxis dose, participants are instructed to record in their diary:

- Treatment for bleeding episode: if the bleeding episode required BIVV001 treatment on the regular prophylaxis day.
- Follow up injection: if an additional injection is required to treat the bleed on the regular prophylaxis day.

OR

- Prophylaxis dose: if the bleeding episode did not require BIVV001 treatment on the regular prophylaxis day. In this case, the bleeding episode should be recorded and considered as an untreated bleeding episode.

Bleeding episodes or hemorrhages will be classified as either spontaneous or traumatic. The participant's ePD will serve as the primary source document for bleeding episodes while the participant is enrolled in the study. Spontaneous and traumatic bleeding episodes are further defined as follows:

- Spontaneous bleeding episodes: Bleeding episodes are classified as spontaneous if a participant or caregiver records a bleeding episode when there is no known contributing factor, such as a definite trauma or antecedent "strenuous" activity. The determination of "strenuous" is at the discretion of the Investigator, and the parent/caregiver/participant needs to be instructed by the Investigator on the proper categorization.
- Traumatic bleeding episodes: Bleeding episodes are classified as traumatic if the participant or caregiver records a bleeding episode when there is a known or believed reason for the bleed. For example, if a participant exercised strenuously and then had a bleeding episode in the absence of any obvious injury, the bleeding episode is still recorded as traumatic. Target joint bleeding episodes can be traumatic if a known action led to bleeding into the joint.

During the clinic visits and telephone calls with the participant's caregiver, the Investigator will review the bleeding episode data in the ePD. If the Investigator judges that the classification by the participant's caregiver was incorrect, the Investigator will document it in the participant's medical records with the rationale for the new classification, and in the eCRF, documenting the new classification of the bleeding episode according to the Investigator and whether or not the participant's caregiver agreed with this new classification.

Bleeding episodes will be reported for each participant during the treatment period, either in the ePD or the eCRF, as follows:

- Bleeding episodes and doses to treat bleeding episodes outside the clinic: Participant's caregiver completion and Investigator review of the participant's ePD are captured by the participant's caregiver using the ePD. The date and details of injection and bleeding episodes will be recorded by the participant's caregiver in the ePD within 7 days of the episode.
- Bleeding episodes in-clinic/hospital and doses to treat bleeds given at the clinic/hospital are captured by the Investigator in the eCRF.

- Electronic patient diary (ePD) Review and Training: Investigator or designee to review ongoing ePD data and perform participant retraining as necessary.
- Assessment of response to treatment of a bleeding episode, using 4-point bleeding response scale based on ISTH definitions:
  - Bleeding episodes that occur outside the clinic/hospital: assessment of response will be recorded in ePD for each bleeding episode.
  - Bleeding episodes treated in the clinic/hospital: assessment of response will be obtained from the participant by the Investigator and recorded in the eCRF.

8.1.3 Assessment of clinical response to BIVV001 treatment for bleeding episodes

The ISTH 4-point assessment scale of treatment of acute bleeds will be used throughout the study for the assessment of response to treatment with BIVV001 for bleeding episodes (43) (Table 8). The assessment should be performed approximately 72 hours after the initial treatment for the bleeding episode.

Table 8 - ISTH assessment of treatment of acute bleeds

Excellent	Complete pain relief within 8 h and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy for relief of persistent symptoms and signs in the same joint within 72 h
Good	Significant pain relief and/or improvement in signs of bleeding within approximately 8 h after a single injection, but requiring more than one dose of replacement therapy within 72 h for complete resolution
Moderate	Modest pain relief and/or improvement in signs of bleeding within approximately 8 h after the initial injection and requiring more than one injection within 72 h but without complete resolution
None	No or minimal improvement, or condition worsens, within approximately 8 h after the initial injection

8.1.4 Physician's global assessment (PGA)

The Physician's global assessment (PGA) is an assessment of the participant's response to treatment using a 4-point response scale (Table 9).

Table 9 - Physician's global assessment

Excellent	• Bleeding episodes responded to fewer than or the usual number of injections or less than or the usual dose of FVIII, **OR** • The rate of breakthrough bleeding during prophylaxis was less than or equal to that usually observed.
Effective	• Most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, **OR** • There was a minor increase in the rate of breakthrough bleeding.
Partially effective	• Bleeding episodes most often required more injections and/or higher doses than expected, **OR** • Adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.
Ineffective	• Routine failure to control hemostasis or hemostatic control required additional agents.

8.1.5 Hemophilia joint health score (HJHS)

Joint function assessed by physical joint examination performed by an experienced health care professional is often used as the primary outcome for haemophilic arthropathy. The HJHS is a functional measure of joint health assessing ankles, knees and elbows (flexion, extension, range of movement, muscle strength, swelling, duration of swelling, crepitus, pain, and muscle atrophy) and general gait (Section 10.7.3). The assessment is administered by a healthcare professional trained in the use of anthropometric measures. Ideally, HJHS should be performed and assessed by the same Investigator or designee at each time point. The HJHS will be used in children aged ≥4 years at Baseline, Week 26 and Week 52.

8.1.6 Investigator's target joint assessment

The Investigator will assess target joints at Baseline according to the ISTH criteria. A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) into which ≥3 spontaneous bleeding episodes occurred in a consecutive 6-month period. Target joint resolution is defined as ≤2 bleeding episodes in the target joint over 12 months of continuous exposure.

8.1.7 Assessment of response to surgery

The Investigators/Surgeons who complete the surgical procedures will assess the participant's response to surgery with BIVV001 treatment using a 4-point scale as described below. This includes observations during surgery and the 24-hour post-operative time period. This assessment will be performed 24 hours after the surgery.

Participants must have 6 EDs to BIVV001 and a negative inhibitor test within 4 weeks prior to surgery to be eligible for the surgery subgroup. Prior to surgery, the Investigator will plan the perioperative treatment regimen of FVIII replacement therapy generally required for the type of surgery in accordance with the dosing guidance in Table 7. Recommendation for the appropriate dosing of BIVV001 in the surgical treatment period, including any rehabilitation time, will be discussed among the Investigator, Surgeon, and Sanofi BIVV001 Medical Monitor. Continuous infusions will not be allowed for this study.

Guidelines on surgical dosing are found in Section 6.1.4. Pharmacokinetic samples taken during surgical procedures will be analyzed locally, but the site is requested to split the plasma and send an aliquot to the central laboratory for analysis.

Following a 24-hour post-operative study assessment, participants will follow the recommended postoperative treatment regimen as per Investigator's advice.

Data collected during the surgical/rehabilitation period for major and minor surgeries will be excluded from the analysis, including all bleeding episodes as well as the follow-up time during this period. The surgical/rehabilitation period will typically begin with the first dose of BIVV001 given for the surgery (ie, the pre-operative loading dose). The end of the surgical/rehabilitation period will occur with the latest of one of the following dates: 1) the date of discharge from the hospital; 2) the date of the perioperative period follow-up phone call; or 3) the end of a two-week period (one-week for minor surgeries) after the resumption of the participant's pre-surgery treatment regimen.

The perioperative period may be extended at the discretion of the Investigator. Reasons include extended hospital stay or other clinical reasons that prohibit resumption of normal prophylactic regimen. At the end of the perioperative period, participants will be instructed to resume their pre-surgery treatment regimen and register their treatment accordingly in the ePD. For participants who undergo major surgery at the end of the study, the EOS assessments will be scheduled at least 14 days post surgery, if applicable.

In the case of minor surgery (eg, simple tooth extractions, incision and drainage of abscess, or simple excisions), participants will be treated with BIVV001 during the minor intervention according to the guidelines on surgical dosing found in Section 6.1.4. A post-operative follow-up call should occur 24 hours following minor surgery for the surgeon/investigator's assessment of response to surgery. If clinically warranted and at the discretion of the surgeon/investigator, the participant will be brought back into the clinic 24 hours post-minor surgery for BIVV001 activity sampling (pre-dose if an administration of BIVV001 is planned) and for the surgeon/investigator's assessment of response.

All doses administered in the hospital will be captured in the eCRF. Any doses administered outside of the clinic/hospital prior to returning to the pre-surgical treatment regimen will be captured in the ePD. At the final post-operative visit, participants will be instructed to return to their pre-surgical treatment regimen.

Participants will remain on the dose and schedule prescribed for the post-operative surgical prophylaxis until the Investigator deems that it is appropriate for the participant to return to his pre-surgery treatment regimen. Participants who undergo major surgery within 2 weeks before the end of study should have their end of study visit performed no earlier than 14 days post-surgery.

The Investigator/Surgeon who completed the surgical procedures will assess the participant's response to surgery with BIVV001 treatment using a 4-point clinical scale: Excellent, Good, Fair, and Poor (Table 10). This includes observations during surgery and the 24-hour post-operative time period so this assessment will be done 24 hours after the surgery.

Table 10 - ISTH hemostatic response for surgical procedures scale

Excellent	Intraoperative and postoperative blood loss similar (within 10%) to the non-hemophilic patient with no extra (unplanned) doses of FVIII/FIX/"bypassing agents" needed and blood component transfusions are similar to the non-hemophilic patient
Good	Intraoperative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10% and 25% of expected), but the difference is judged by the involved surgeon/anesthetist/relevant healthcare professional to be clinically insignificant as evidenced by no extra (unplanned) doses of FVIII/FIX/'bypassing agents" needed and blood component transfusions are similar to the non-hemophilic patient
Fair	Intraoperative and/or postoperative blood loss increased over expectation (25%-50%) for the non-hemophilic patient and additional treatment is needed such as extra (unplanned) doses of FVIII/FIX/"bypassing agents" or increased blood component use (within two-fold) of the anticipated transfusion requirement
Poor	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia, unexpected hypotension or unexpected transfer to an Intensive Care Unit due to bleeding or substantially increased blood component use (>2 fold) of the anticipated transfusion requirement

8.1.8 Samples for future scientific research

Additional serum and plasma samples will be collected and archived (along with unused backup samples) for testing by the central laboratory for future scientific research.

This research will enable a better understanding of the factors contributing to clinical outcomes and immunological responses during treatment with BIV001 in patients with Hemophilia A and may include the following investigations: clotting experiments (thrombin generation assays, fibrin generation assay and clotting assays with additional clotting reagents), tests to clarify any clinical or laboratory AE and viral analyses. [redacted]

This is optional, and only participants who provided assent and who had their parent's consent for sample collection and use of unused samples for future research will have their samples archived.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical examinations

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, Neurological, Dermatological and Musculoskeletal systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

For participants with a central or peripheral indwelling venous access, the physical examination should include an assessment of the device.

Any new finding or worsening of a previous finding should be reported as a new AE.

8.2.2 Vital signs

- Oral, tympanic, axillary or temporal temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.
- Vital signs will be measured pre-injection (before blood collection for laboratory tests) and 30 (±15 minutes) from the start of injection at clinic visits. Refer to Section 1.3 for vital sign collection timepoints.

8.2.3 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Table 1) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered abnormal and clinically significant during participation in the study or within 3 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE and SAE can be found in Appendix 3 (Section 10.3).

Adverse events and SAEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the safety follow-up call or visit at the time points specified in the SoA (Section 1.3).

All SAEs and adverse events of special interest (AESIs) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE and AESI data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, and non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (IB).
- Suspected unexpected serious adverse reactions (SUSARs) are reported to regulatory authorities, Investigators, and IRBs/IECs as follows:
  - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days
  - For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor
- An Investigator who receives an Investigator safety report describing a SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The following disease related events (DREs) are common in participants with hemophilia A and can be serious/life threatening:

- Bleeding

Bleeding episodes in this patient population are not considered AEs. Bleeding episodes that meet a serious criterion (see Section 10.3) should be reported as an SAE. All bleeding episodes after signature of the ICF will be captured in the ePD that the participant's caregivers will be maintaining throughout the study period.

8.3.7 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Symptomatic overdose (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as follows: any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol.
- **Other project specific AESI(s)**
  - A participant develops an inhibitor (defined as an inhibitor result of $\geq$0.6 BU/mL that is confirmed by a second test result of $\geq$0.6 BU/mL from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay).
  - A participant develops a Grade 3 or higher allergic reaction per CTCAE version 5.0 or an anaphylactic reaction in association with BIVV001 administration.
    - Grade 3 allergic reaction: bronchospasm or hospitalization indicated for clinical sequelae or intravenous intervention indicated
    - Grade 4 allergic reaction: Life-threatening consequences or urgent intervention indicated
    - Grade 5 allergic reaction: Death
  - A participant develops an embolic or thrombotic event, except for injection site thrombophlebitis.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for any AE/SAE and laboratory abnormalities as applicable.
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document appropriately in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Pharmacokinetic sampling will be conducted as outlined in the sections that follow. Detailed guidelines of washout and PK sampling requirements for baseline and bleeding scenarios are provided in Appendix 7, Section 10.7.4. If a participant has a bleed during the PK time period (Table 2), the participant's caregiver should enter the bleed into the ePD, contact the Investigator as soon as possible and follow the criteria given in Appendix 7, Section 10.7.4.

The first 24 participants from the 2 age cohorts (12 participants <6 years of age and 12 participants 6 to <12 years of age) will undergo an evaluation of the PK profile of BIVV001 and will be included in the PK subgroup. After completing the baseline PK assessments, these 24 participants will begin QW 50 IU/kg prophylactic treatment with BIVV001. Any participant who does not have adequate PK data will be excluded from the PK analysis. Additional participants may be enrolled to ensure that at least 24 participants have adequate PK data for analysis. The remaining participants will proceed directly to QW prophylactic treatment. Baseline PK sampling can be conducted in other participants at the discretion of investigator through the central laboratory.

During study visits, for reliable PK assessment, PK sampling should not be done via the same intravenous access route as used for the BIVV001 administration.

PK Subgroup: At least 12 participants <6 years of age and at least 12 participants 6 to <12 years of age will undergo PK sampling (up to 168 hours) for BIVV001 activity as follows:

- Dosing at Day 1: single dose of BIVV001 50 IU/kg administered under medical supervision (using a partial vial and actual potency dosing, see Section 6.1.6.1)
- Baseline PK sampling at BIVV001 Day 1: Pre-injection and 15 (±3) minutes, 3 hours (±15 minutes), 24 (±2) hours [Day 2], 72 (±5) hours [Day 4], and 168 (±5) hours [Day 8] from the start of the injection

See Table 2 for details of PK sampling of first 12 participants in each age cohort. If a participant has a bleed during the PK time period above, the participant's caregiver should enter the bleed into the ePD and contact the Investigator as soon as possible.

Peak and trough sampling: Participants in the PK subgroup in both age cohorts will have trough and peak sampling at all scheduled visits subsequent to Day 1. Participants not included in the PK subgroup in both age cohorts will have trough and peak sampling at all scheduled visits including Day 1.

PK assessments will be based on FVIII activity levels determined by one-stage aPTT clotting assay and two-stage chromogenic assay performed at all scheduled visits. The first 12 participants in each age cohort will undergo PK sampling at Day 1. Refer to Appendix 7, Section 10.7.4 for PK sampling completion criteria.

Pharmacokinetic sampling will be used to estimate PK parameters, including but not limited to the following: C_{max}, $t_{1/2}$, CL, CL_{ss}, AUC, Vss, MRT, IR, C_{trough} and time above predefined FVIII activity levels.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters will be not evaluated in this study.

8.7 GENETICS

There is 1 target gene for hemophilia A. The name of the target gene is F8. Genotyping may provide information regarding the predisposition of genotypic subpopulations to experience different bleeding frequencies. The development of an inhibitor to treatment with factor concentrates is the single most serious complication of factor replacement. One of the decisive risk factors for the development of inhibitors is the type of mutation (eg, full or missense) that codes for a protein that may be absent, truncated, or present but not functional. There is a correlation between the resultant protein and the likelihood of developing inhibitors to factor replacement (44).

Where local regulations and EC allow approval, for participants whose FVIII genotype is not known, an optional sample will be collected at Week 13 for genotype analysis, including FVIII and human leukocyte antigen (HLA) genotype. The sample will not be needed if previously documented. Genotype will not be a criterion for inclusion or exclusion. The results will be shared with the Investigator.

The DNA samples will be coded with the participant's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. Participants or participant's caregiver may withdraw consent and request to have the participant's sample destroyed at any time and no further genetic data will be generated; any data already generated will not be destroyed.

8.8 BIOMARKERS

There are no planned analyses of biomarkers or pharmacogenetics.

8.9 IMMUNOGENICITY ASSESSMENTS

8.9.1 Inhibitor development

Blood samples will be collected per the schedule in Table 1 for the detection of inhibitors. Samples may also be collected at the time of any clinical event deemed relevant to inhibitor testing. Inhibitor development will be assessed at a central laboratory by the Nijmegen-modified Bethesda assay and is defined as an initial test result of ≥0.6 BU/mL confirmed by a second test result from an independent blood sample collected within 2 to 4 weeks of the first positive sample.

- Low titer inhibitor development is defined as inhibitor test results of ≥0.6 and <5.00 BU/mL.
- High titer inhibitor development is defined as inhibitor test results of ≥5.00 BU/mL.

Participants with discrepant inhibitor test results (initial low titer result followed by high titer result or initial high titer result followed by low titer result) should have repeat inhibitor testing performed by the central laboratory from a separate blood sample collected 2 to 4 weeks following the previous sample.

- If 2 of 3 test results are <5.00 BU/mL, the inhibitor is considered low titer.
- If 2 of 3 test results are ≥5.00 BU/mL, the inhibitor is considered high titer.

8.9.2 Anti-drug antibodies

Blood samples will be collected per the schedule in Table 1 for the detection and analysis of anti-BIVV001 antibodies. Samples may also be collected at the time of any clinical event deemed relevant to anti-BIVV001 antibody testing. Testing for potential antibody formation will be performed at a central laboratory using a validated BIVV001-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to FVIII, Fc, XTEN, or D'D3.

8.10 CAREGIVER- AND/OR PATIENT-REPORTED CLINICAL OUTCOME ASSESSMENTS AND MEDICAL RESOURCE UTILIZATION

8.10.1 Caregiver- and/or patient-reported clinical outcome assessments

Table 11 shows the concepts of clinical outcome assessments (COAs) along with their related questionnaires to be used in the study. The Sponsor or designee will provide the translations for all caregiver- and/or patient-reported COA instruments, where translations are available. Where available, the COAs will be distributed to children <12 years and their caregivers (proxy) as specified in the SoA (Table 1). If an instrument is not available in the participant's language, the instrument will not be completed. All caregiver or Patient Reported Clinical Outcome assessment are collected via an electronic tablet and transmitted to a third-party vendor data server over public networks using encrypted data.

Table 11 - List of caregiver- and/or patient-reported clinical outcome assessments

Concept	Questionnaire	Administered to	Endpoint	Assessment Schedule
Pain and Physical Function (PROMIS Instruments)	PROMIS instruments: 1. PROMIS Pediatric NRS-Pain Intensity (participants ≥8 years old) 2. PROMIS Pediatric-Pain Interference-SF (participants ≥8 years old) 3. PROMIS Pediatric- Physical Activity-SF (participants ≥8 years old) 4. PROMIS Parent Proxy NRS - Pain Intensity (participants 5 to <12 years old) 5. PROMIS Parent Proxy- Pain Interference-SF (participants 5 to <12 years old) 6. PROMIS Parent Proxy- Physical Activity-SF (participants 5 to <12 years old)	Children version for participants ≥8 years old and parent proxy version (participants 5 to <12 years old).	Exploratory	Baseline, Weeks 26, 52
Hemophilia specific	Haemo-QoL 1. Haemo-QoL kids (4-7 years) 2. Haemo-QoL kids (8 to <12 years) 3. Haemo-QoL parent proxy (for participants 4-7 years) 4. Haemo-QoL parent proxy (for participants 8 to <12 years)	Children version for participants (≥4 years old) and via parent proxy version (≥4 years old) Note:There are separate Haemo-QoL versions for participants and parent proxy based on age of participant (for participants 4-7 years and for participants 8 to <12 years)	Secondary (total and physical health score)	Baseline, Weeks 26, 52
Health status	EQ-5D-Y 1. EQ-5D-Y kids (8 to <12 years) 2. EQ-5D-Y parent proxy (for participants 4-7 years)	Children version for participants ≥8 years old and parent version for proxy parent (participants aged 4-7 years).	Exploratory	Baseline, Weeks 26, 52
Experience with treatment and impact	Caregiver interviews (in a subset of caregivers of patients)	Caregivers (all ages)	Exploratory	Week 52 (or subsequent follow-up visit)

Abbreviations: EQ-5D-Y = EuroQoL-Youth; Haemo-QoL = Haemophilia Quality of Life Questionnaire for Children and Adolescents; PROMIS = Patient-Reported Outcomes Measurement Information System.

8.10.1.1 PROMIS instruments

Patient-Reported Outcomes Measurement Information System (PROMIS) is a system of reliable and precise measures of participant-reported heath status (45). The PROMIS initiative is part of the National Institute of Health (NIH) goal to develop systems to support NIH-funded research across all its institutes and centers. PROMIS measures cover physical, mental and social health and can be used for many chronic conditions. These questionnaires use a 5-point Likert response scale or 11-point Numeric Rating Scale with and a recall period of the past 7 days. The PROMIS instruments will be administered at Baseline and Weeks 26 and 52 in children aged 8 to <12 and parent proxy for ages 5-12.

PROMIS Pediatric Numeric Rating Scale Pain Intensity v1.0

The PROMIS Pediatric Numeric Rating Scale Pain Intensity v1.0 is a single item rating scale. (refer Appendix 7, Section 10.7.5.1.1 and Section 10.7.5.1.4 for children and parent version, respectively). The estimated completion time is <1 minute.

PROMIS Pediatric SF v2.0 - Pain Interference 8a

The PROMIS Pediatric-SF v2.0 - Pain Interference 8a is for participants <18 years of age and is used to measure pain interference (refer to Appendix 7, Section 10.7.5.1.2 and Section 10.7.5.1.5 for children and parent version, respectively). The estimated time of completion is 1 minute.

PROMIS Pediatric-SF v1.0 - Physical Activity 8a

The PROMIS Pediatric-SF v1.0 - Physical Activity 8a is used to assess physical activity in participants <18 years of age (refer to Appendix 7, Section 10.7.5.1.3 and Section 10.7.5.1.6 for children and parent version, respectively). The estimated completion time is 1-2 minutes.

8.10.1.2 Hemophilia quality of life questionnaire (Haemo-QoL)

The Hemophilia Quality of Life Questionnaire (Haemo-QoL) questionnaire for children with hemophilia is available for participants <17 years of age. Estimated completion time is less than 10 minutes (46). The instrument (children's short versions by age groups: 4-7 years - 16 items [Section 10.7.5.2.1]; 8 to <12 years - 35 items [Section 10.7.5.2.2] and parent's short versions: 4-7 years - 16 items [Section 10.7.5.2.3]; 8 to <12 years - 35 items [Section 10.7.5.2.4]) will be administered to participants and their caregivers at Baseline and Weeks 26 and 52.

8.10.1.3 EuroQoL-Youth (EQ-5D-Y)

The EuroQoL-5D-Youth (EQ-5D-Y) comprises of 5 dimensions (mobility, looking after myself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy) with 3 levels and a visual analogue scale and is a qualitative measure of health outcomes. The EQ-5D-Y will be administered to children aged 8 to <12 years (Section 10.7.5.3.1) and parent proxy version will be used for children aged 4-7 years (Section 10.7.5.3.2).

8.10.1.4 Caregivers interviews

Semi-structured interviews (Appendix 7, Section 10.7.5.4) will be conducted in a subset of caregivers of children (ie, caregivers from English speaking countries, including but not limited to the USA. Non English-speaking countries may be included based on feasibility) in the study at the last visit or a subsequent follow-up visit to evaluate their expectations from treatment, perception of treatment impact on the daily lives and functioning of children and their caregivers. The interviews will be conducted by trained interviewers based on a structured interview guide.

8.10.2 Healthcare resource utilization

Healthcare resource utilization (HRU) associated with medical encounters and attributable to Hemophilia A will be collected in the eCRF by the Investigator and study-site personnel for all participants at Baseline and Weeks 26 and 52.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number of non-study medical care encounters (outpatient, urgent-care, emergency room).
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit]).
- The full HRU questionnaire is provided in Appendix 7, Section 10.7.6. Medical resource utilization data associated with medical encounters will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

In general, all statistical analyses will be descriptive in nature. No formal comparison is planned and no hypothesis will be formally tested. For the primary endpoint, the proportion of participants who experience any inhibitor during the study will be calculated including an exact (Clopper-Pearson) 2-sided, 95% CI. Continuous endpoints will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum with the 25th and 75th percentiles, where appropriate. Categorical endpoints will be summarized by counts and percentages. All data will be summarized for each age cohort (<6 years and 6 to <12 years) and overall.

9.2 SAMPLE SIZE DETERMINATION

The determination of the number of participants is based on clinical rather than statistical considerations. Taking into consideration the guideline from Committee for Medicinal Products for Human Use (EMEA/CHMP/BPWP/144533/2009 rev.2), approximately 65 PTPs will be enrolled to obtain at least 50 participants with at least 50 EDs at the end of the study. All participants completing or remaining at the end of study will be offered participation in the planned extension trial.

At least 12 participants in each age cohort need to have completed adequate blood sample collection to assess key PK parameters.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined (Table 12):

Table 12 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF
Full Analysis Set	All participants who take at least 1 dose of study intervention
Safety Analysis Set	The safety analysis is the same as the Full Analysis Set and will include all participants who receive at least one dose of study drug
PK Analysis Set	All participants who have completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist.

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

9.4 STATISTICAL ANALYSES

9.4.1 General considerations

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.2 Primary endpoint(s)

The primary endpoint is the occurrence of inhibitor development, defined as an inhibitor result of ≥0.6 BU/mL that is confirmed by a second test result from a separate sample, drawn 2 to 4 weeks following the date when the original sample was drawn. Both tests must be performed by the central laboratory using the Nijmegen-modified Bethesda assay. The incidence of inhibitor formation for all (≥0.6 BU/mL), "high (≥5.0 BU/mL)" and "low (≥0.6 BU/mL and <5.0 BU/mL)" titer inhibitors from the central laboratory will be summarized for each age cohort and overall; a 95% CI using Clopper-Pearson method will be calculated for each incidence.

For the incidence calculations, any participant who develops an inhibitor following the initial BIVV001 administration will be included in the numerator, regardless of the number of EDs to BIVV001; the denominator will include participants who have an inhibitor as well as participants with a valid inhibitor test following at least 50 EDs to BIVV001. The calculation will also be performed with a denominator that includes all participants with a valid inhibitor test following at least 25 EDs to BIVV001 and a denominator that includes all participants with a valid inhibitor test, regardless of how many days they were exposed to BIVV001.

9.4.3 Secondary endpoint(s)

Participants who receive at least 1 dose of BIVV001 will be included in the FAS. Efficacy analyses will be based on the FAS. The efficacy and surgical/rehabilitation periods will be defined in the SAP for the purpose of determining the study periods during which data will be used for selected efficacy analyses. Data on bleeding and BIVV001 consumption will be based on the efficacy period; surgical evaluations will be based on the surgical/rehabilitation period.

Analysis of efficacy endpoints that are visit-based will include data from all study visits, whether or not in the efficacy period, unless a visit is coincidental with a surgical/rehabilitation period for a major surgery, in which case it would be excluded.

Annualized Bleeding Rate (ABR)

The mean and 95% CI of ABR will be estimated using a Negative-Binomial model. The model will include number of treated bleeding episodes during the efficacy period as response variable, log-transformed duration of efficacy period as offset variable to account for variable duration. Individual ABR will also be calculated for each patient. All analyses of bleeding endpoints will be based on treated bleeding episodes, except for the summary of ABR for all bleeding episodes which will include both treated and untreated bleeding episodes. Bleeding episodes that occur during surgical/rehabilitation period will be excluded and summarized separately.

In addition, ABR will be summarized descriptively by type of bleed (spontaneous or traumatic) and location of bleed (joint, muscle, internal, or skin/mucosa).

Hemophilia Joint Health Score

Changes in total HJHS score and specific domains such as swelling and strength will be summarized descriptively.

Secondary Safety Endpoints

All safety analyses will be performed on the Safety Analysis Set. Safety will be assessed through descriptive summaries of AEs, SAEs, laboratory results, physical examination, and vital signs.

The incidence of AEs will be summarized by system organ class and preferred term for each age cohort and overall. Clinical laboratory values will be summarized for change from baseline, shifts, and potentially clinically significant abnormalities.

The occurrence of embolic and thrombotic events will be described. The analysis will consist of a search of TEAE data using the Embolic and Thrombotic Events Standard MedDRA Query. Medical adjudication of the search results will also be performed according to the below definition.

Embolic and thrombotic events are defined as arterial or venous thrombosis, confirmed by imaging.

Coronary artery thrombosis/occlusion must be confirmed by coronary angiography to be included as part of medical adjudication.

Thrombosis involving the cerebral vasculature must be confirmed by imaging such as magnetic resonance imaging venogram, computed tomography venogram, magnetic resonance angiography, or computed tomography angiography to be included as part of medical adjudication.

An indwelling central venous access device is a well-established risk factor for thrombosis (47) and thrombotic events associated with such devices will not be included as part of medical adjudication. Occlusion or malfunction of a central venous access device also will not be included as part of medical adjudication.

Infusion thrombophlebitis is a recognized complication of peripheral vein infusion (48) and will not be included as part of medical adjudication.

Pharmacokinetics

Any participant with adequate BIVV001 PK data will be included in the PK Analysis Set. A noncompartmental analysis will be performed for each participant's BIVV001 baseline PK profile. At least 24 participants will be enrolled in the PK group. Instructions for wash-out and PK sampling are provided in Appendix 7, Section 10.7.4.

Pharmacokinetic parameters of BIVV001 activity including but not limited to C_{max}, CL, CL_{ss}, V_{ss}, AUC, DNAUC, MRT, IR, C_{trough} and time above 1% FVIII activity measured by aPTT clotting assay and chromogenic assay will be determined for BIVV001. Pharmacokinetic parameters will be summarized for each age cohort for BIVV001 with geometric means and their corresponding 95% CIs.

Other Secondary endpoints

All other secondary endpoints will be summarized descriptively.

The number and percentage of participants achieving trough FVIII activity levels above 1%, 3%, 5%, 10%, 15%, and 20% will be summarized. In these summaries, FVIII activity level will be based on the average trough samples (ie, nominal 168 hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52) using the one-stage aPTT assay and chromogenic assay. Participants with trough samples that are outside 168 ±5 hours from the previous dose will be excluded from this analysis.

The percentage of participants with resolution of at least 1 target joint and the percentage of total target joints that are resolved at 52 weeks will be summarized. A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) into which ≥3 spontaneous bleeding episodes occurred in a consecutive 6-month period and resolution is achieved when ≤2 bleeding episodes occur into that joint during 12 months of continuous exposure.

The consumption of BIVV001 will be annualized and summarized.

The number of injections and total dose of BIVV001 to treat a bleeding episode will be summarized on both a per-bleeding-episode and a per participant basis, where the per-participant basis will be determined as the average over all bleeding episodes for a given participant.

The participant's response to treatment of individual bleeding episodes will be summarized as the number and percentage of bleeding episodes with each response (excellent, good, moderate, or none).

The physician's global assessment of the participant's overall response to BIVV001 treatment will be summarized for each study visit and across all visits as the number and percentage classified as excellent, effective, partially effective, and ineffective.

For Haem-A-QoL, total score and physical health domain score will be summarized descriptively over time.

Surgical endpoints will be summarized descriptively for the surgical subgroup. Continuous endpoints will be summarized using the number of non-missing values (n), mean, SD, median, minimum, and maximum. Categorical endpoints will be summarized by counts and percentages.

9.4.4 Tertiary/exploratory endpoint(s)

Table 11 shows the concepts of measurement and their related COAs (caregiver- and/or patient-reported) questionnaires to be used in the study. All endpoints for COAs and health outcomes related to hemophilia (except for Haemo-QoL) are exploratory in nature. All endpoints for COAs and health outcomes related to hemophilia will be analyzed in a separate report by summarizing actual values and change from baseline as appropriate. If the final sample size is sufficient, then these summaries will also be presented stratified by previous episodic and previous prophylaxis treatment. For PROMIS endpoints, norm-based T-scores will be calculated for each domain such that a score of 50 (SD=10) represents the mean of the general population. T-scores will be summarized descriptively over time.

9.4.5 Other analyse(s)

Other analyses if any can be conducted for exploratory purposes and the details of the analyses will be defined in the SAP.

9.5 INTERIM ANALYSES

Interim analyses may be conducted for regulatory purposes, as needed. The SAP will describe the planned interim analyses in detail.

9.6 DATA MONITORING COMMITTEE (DMC)

An independent external Data Monitoring Committee (DMC) will be responsible for evaluating and monitoring the safety and tolerability of the study drug on an ongoing basis during the study. The specifics regarding the DMC organization and procedures will be outlined in the DMC Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant and his parents (and/or his designated healthcare professional, if so designated by the participant his parents is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
    - The participant in a clinical study and his parents has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant or his parents have opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant or his parents have decided to opt out, the Investigator must record in the site medical files that he or his parents do not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant and his legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants (if applicable) and their legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant or participant's legally authorized representative (eg, parent or legal guardian) must be provided with informed consent/assent document(s) prior to the screening visit to allow adequate time for review and opportunity to discuss the study with the investigator/designee. After reviewing, parents/legal guardians and participants (if applicable) will come to the clinic to sign the informed consent/assent. Participants (where applicable) and/or parents legal guardians must provide consent/assent before any screening assessments are performed.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-assented, and their legally authorized representative re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened and their legally authorized representative are required to sign a new ICF, when applicable.

The ICF will contain a separate section that addresses the use of remaining mandatory samples or new extra samples for optional exploratory research. The Investigator or authorized designee will explain to each participant's caregiver the objectives of the exploratory research. Participants and their caregivers will be told that they are free to refuse participation and may withdraw their consent at any time and for any reason during the storage period. A separate consent will be required to document a participant's caregiver/participant (where applicable) agreement to allow any remaining specimens to be used for exploratory research. The participant/caregiver who decline participation in this optional research will not provide this separate consent.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The race and ethnicity of participants will be collected in this study. These data may be used in the analysis of the safety and/or PK profile of the study treatment. In previous cross-sectional analyses of different ethnic groups, differences in the occurrence of FVIII inhibitors have been observed (49, 50). Additionally, differential responses to FVIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups (51).
- The participant and his legally authorized representative must be informed that participant personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/participant's caregiver as described in the informed consent.
- The participant and his legally authorized representative must be informed that participant medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publically accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) and ePD unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the caregiver/participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 13 will be performed by the central laboratory.
- Blood samples will be obtained as blood volume permits and should not exceed the blood volume collection limit of 3% of total blood volume over a 4 weeks period. The specific requirements for blood sampling and minimum interval between visits are described in the laboratory manual. Sampling should be prioritized for safety labs and PK.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF. Unless stated in the protocol, local laboratory results are not permitted for the assessment of inhibitor development as part of this study.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 13 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose (nonfasting)
	Potassium
	Sodium
	Chloride
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Alkaline phosphatase (ALP)
	Gamma glutamyl transferase (GGT)
	Total and direct bilirubin
	Total protein
Von Willebrand (VWF) comprehensive panel	
	VWF ristocetin cofactor activity
	VWF antigen
Immunogenicity	
	Nijmegen modified Bethesda inhibitor assay
	Anti-drug Antibodies (ADA)
	ADA subtype (FVIII, Fc, D'D3, or XTEN)
Coagulation parameters	
	Activated partial thromboplastin time (aPTT)
Other screening tests	
	HIV (HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen), HBV (HBV surface antigen, anti-HBV surface antibody and anti-HBV core antibody) and HCV (anti-HCV antibodies) for patients who have been historically negative
	CD4 count and viral load (for patients known to be HIV positive)

Abbreviations: ADA = Anti-drug Antibodies; ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; GGT= Gamma glutamyl transferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RBC = Red blood cell; SAE = serious adverse event; VWF = Von Willebrand; WBC = White blood cell

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (eg, hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiography [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, and are considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor (or representative) in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor (or representative). In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor (or representative).
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Not related: An adverse event will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (eg, the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.

Related: An adverse event will be considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor (or representative). However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor (or representative).**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor (or representative) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor (or representative) with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor (or representative) within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor (or representative) via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor (or representative) will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor (or representative) by facsimile transmission or email.
- Contacts for SAE reporting can be found in the Study Manual.

SAE reporting to Sponsor (or representative) via paper CRF

- Facsimile transmission or email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor (or representative*)* if the electronic data collection tools are not available.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

Not applicable.

10.5 APPENDIX 5: OVERDOSE

An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant according to the protocol.

All overdoses (symptomatic and asymptomatic) must be recorded on the overdose form of the CRF within 24 hours of the site becoming aware of the overdose. All study drug-related dosing information must be recorded on the dosing CRF.

The signs and symptoms associated with a symptomatic overdose (serious and/or non-serious) with IMP/NIMP must also be recorded as an AESI on the CRF (Section 8.3.1).

Asymptomatic overdoses are not considered AEs and should not be recorded as an AE on the CRF.

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.7 APPENDIX 7: ADDITIONAL APPENDICES

10.7.1 Definitions of minor and major surgery

Minor surgery is defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated and does not meet the criteria for major surgery (eg, dental extraction of <3 nonmolar teeth). Minor surgical procedures may be performed at a local health care provider institution.

Major surgery is defined as any invasive operative procedure that requires any of the following:

- Opening into a major body cavity (eg, abdomen, thorax, skull)
- Operation on a joint
- Removal of an organ
- Dental extraction of any molar teeth or ≥3 nonmolar teeth
- Operative alteration of normal anatomy
- Crossing of a mesenchymal barrier (eg, pleura, peritoneum, dura)

It is recommended that any elective non-dental major surgery be performed at a study site, when possible.

10.7.2 Definitions of minor, moderate, and major bleeding episodes

Minor

- Mild Epistaxis
- Early signs of joint bleeding
- Mild soft tissue bleed

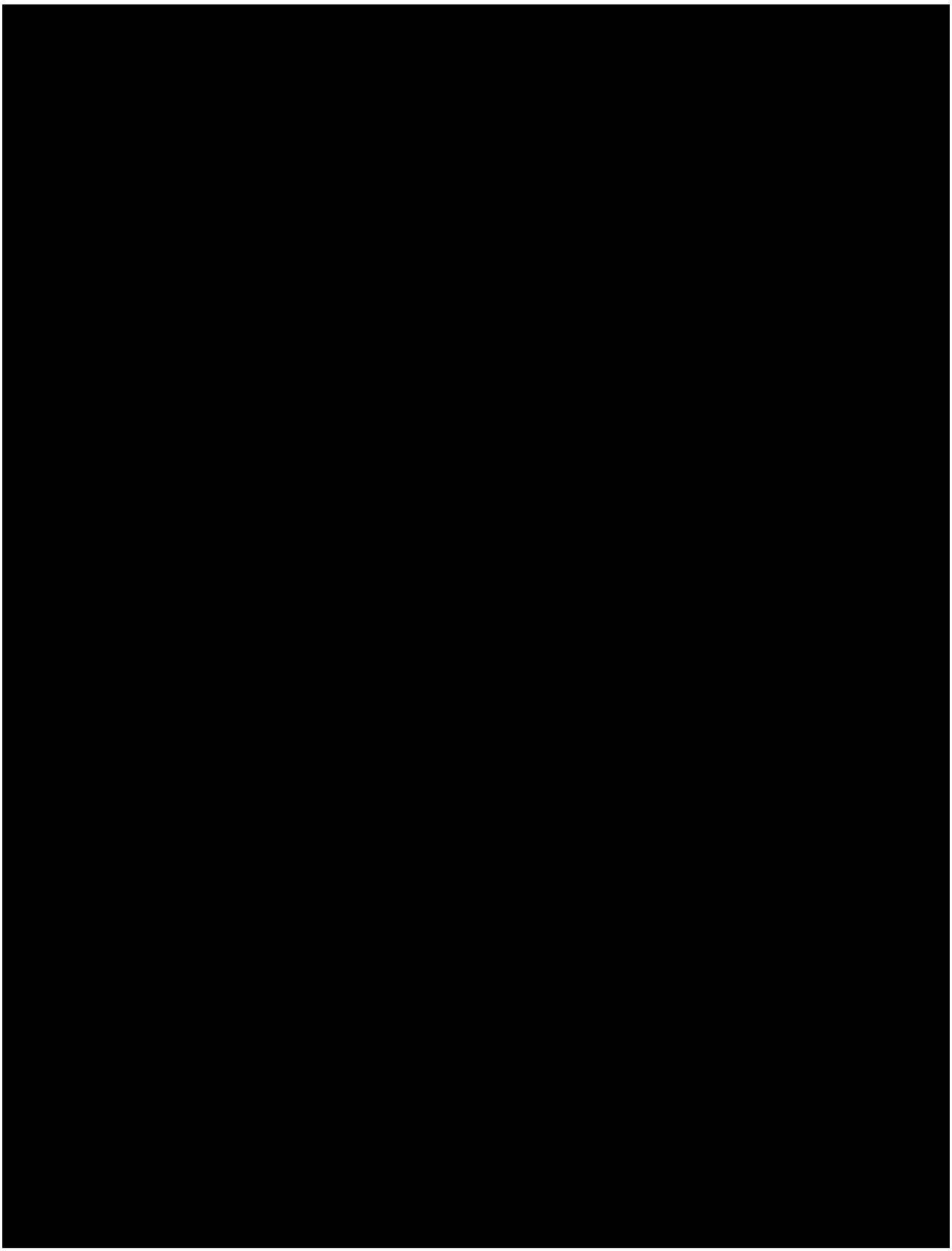
Moderate

- Epistaxis with heavy blood flow
- Muscle bleeding
- Gastrointestinal/oral mucosal bleeds
- Gum bleeding after dental extraction
- Hematuria
- Hemarthrosis

Major to life-threatening

- Epistaxis with very heavy blood flow
- Retropharyngeal and pharyngeal bleeding
- Abdominal and retroperitoneal bleeding
- Post-surgical bleeding
- CNS bleeding

10.7.3 Hemophilia joint health score (HJHS)



10.7.4 Washout and blood sampling summary

The following tables summarize the requirements for washout and blood sampling necessary to successfully complete both the washout and PK sampling. If a participant experiences a bleeding episode after receiving the dose of BIVV001 but prior to completing the PK sampling, PK sampling will be stopped at the time of the bleed.

Washout and pk sampling requirements

Screening: all participants	**Washout** • First attempt: Washout of at least 48 hours before Screening inhibitor test to obtain interpretable test results[a]. Repeat this washout if participant treats a bleed prior to 48 hours (follow second attempt). • Second attempt: Conduct same washout as first attempt. • If the second attempt at washout fails, additional attempts may be considered after consultation with the medical monitor[a].
Baseline PK sampling: PK subgroup	
Day 1 Baseline PK sampling: 12 subjects <6 years of age	**Washout** • First attempt: Washout of at least 72 hours (3 days); repeat this washout if participant treats a bleed prior to 72 hours (follow second attempt)[a]. • Additional attempt(s): Conduct same washout as first attempt[a]. • If the second attempt at washout fails, additional attempts may be considered after consultation with the medical monitor. **PK Sampling** • First attempt: PK sampling period with collection of PK samples (Table 2) to 168 hours (Day 8) is required. If a participant treats a bleeding episode after receiving the dose of BIVV001 for PK evaluation but prior to completing the PK sampling period, PK sampling will be stopped at the time of the bleed and a second attempt (repeat) PK sampling period should be conducted. • Second attempt: Participants are required to undergo a 240 hour (10 Day) washout from the prior BIVV001 dose, which is then followed by the PK sampling period with collection of PK samples (Table 2) to 168 hours (Day 8). • If the second attempt at PK sampling period fails due to the participant treating a bleed prior to collection of the 168-hour (Day 8) sample, the participant will remain in the study but will no longer be included in the PK subgroup. The participant will be replaced in the PK subgroup and will continue with prophylactic BIVV001 dosing regimen.
Day 1 Baseline PK sampling: 12 subjects 6 to <12 years of age	**Washout** • First attempt: Washout of at least 96 hours (4 days); repeat this washout if participant treats a bleed prior to 96 hours (follow second attempt)[a]. • Additional attempt(s): Conduct same washout as first attempt. If the second attempt at washout fails, additional attempts may be considered after consultation with the medical monitor[a]. **PK Sampling** • First attempt: PK sampling period with collection of PK samples (Table 2) to 168 hours (Day 8) is required. If a participant treats a bleeding episode after receiving the dose of BIVV001 for PK evaluation but prior to completing the PK sampling period, PK sampling will be stopped at the time of the bleed and a second attempt PK sampling period should be conducted.

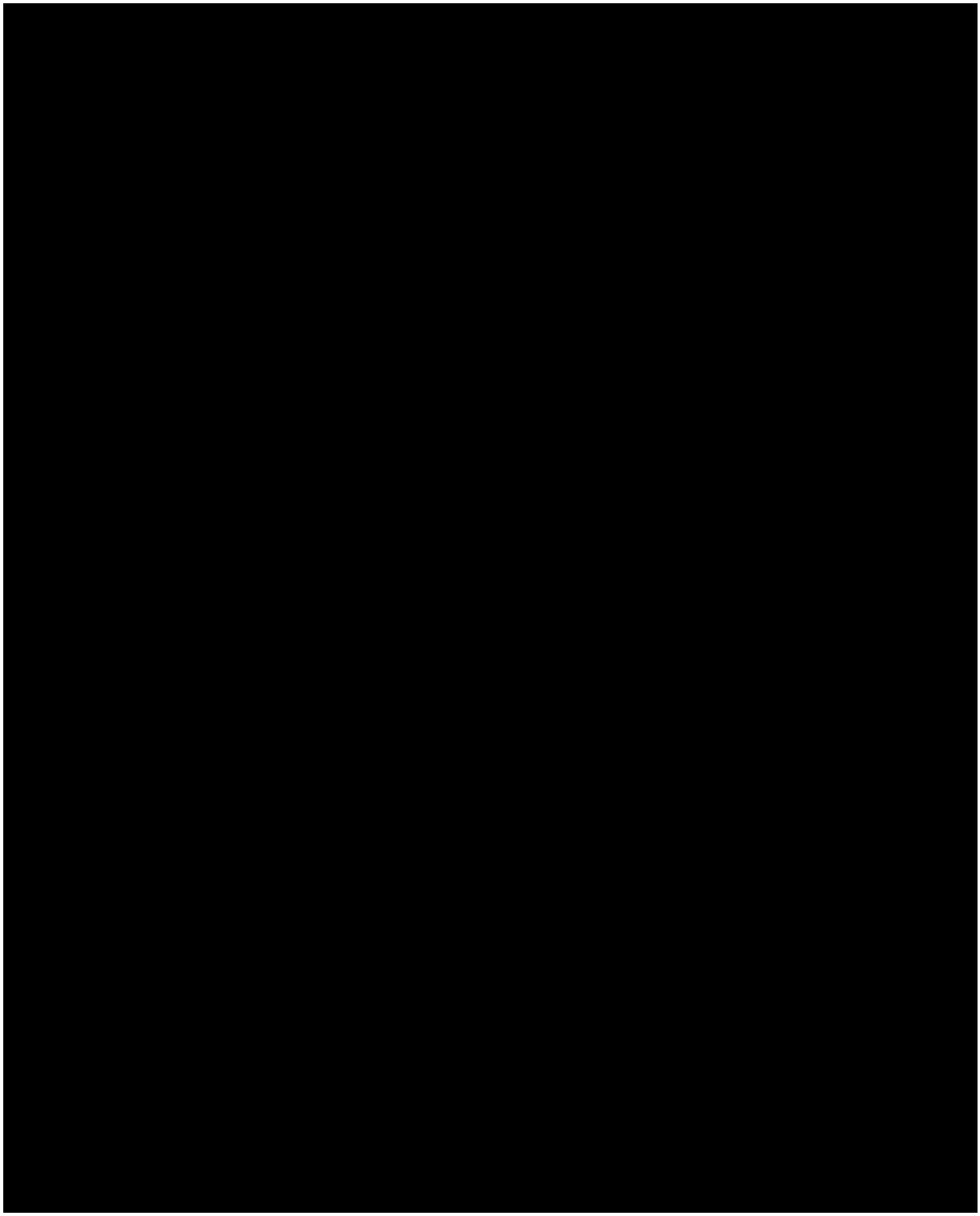
	• Second attempt: Participants are required to undergo a 240 hour washout[a] after previous dose, which is then followed by the PK sampling period with collection of PK samples (Table 2) to 168 hours (Day 8). • If the second attempt at PK sampling period fails due to the participant treating a bleed prior to collection of the168-hour (Day 8) sample, the participant will remain in the study but will no longer be included in the PK subgroup. The participant will be replaced in the PK subgroup and will continue with prophylactic BIVV001 dosing regimen.
Peak and trough sampling: All Participants except PK subgroup at Day 1	**Washout** • First attempt: Washout of at least 72 hours (3 days) or 96 hours (4 days) for < 6 yr and 6 to <12 yr participants, respectively; repeat this washout if participant treats a bleed prior to 72 hours and 96 hours for <6 yr and 6 to <12 yr participants respectively (follow second attempt)[a]. • Additional attempts: Conduct same washout as first attempt. • If the second attempt at washout fails, additional attempt may be considered after consultation with the medical monitor. **PK Sampling** • Collection of sample at trough (immediately pre-injection) and peak at 15 ±3 mins from start of injection. If the participant is being treated for an acute bleeding prior to collection of the peak and trough sample collection, no repeat sampling is needed and the patient will remain in the study and collect peak and trough at the next scheduled visit.
Peak and trough sampling: All Participants after Day 1	**Washout** • No washout required. Participants should visit clinic 7 ±1 day after previous dose. • If the participant has treated a bleeding episode since his last dose, the scheduled visit should be postponed for 7 ±1 day after previous dose. **PK Sampling** • Collection of sample at trough (immediately pre-injection) and peak at 15 ±3 mins from start of injection. If the participant treats a bleed prior to collection of the peak and trough sample collection, no repeat sampling is needed and the participant will remain in the study and collect peak and trough at the next scheduled visit.

a The washout period may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor

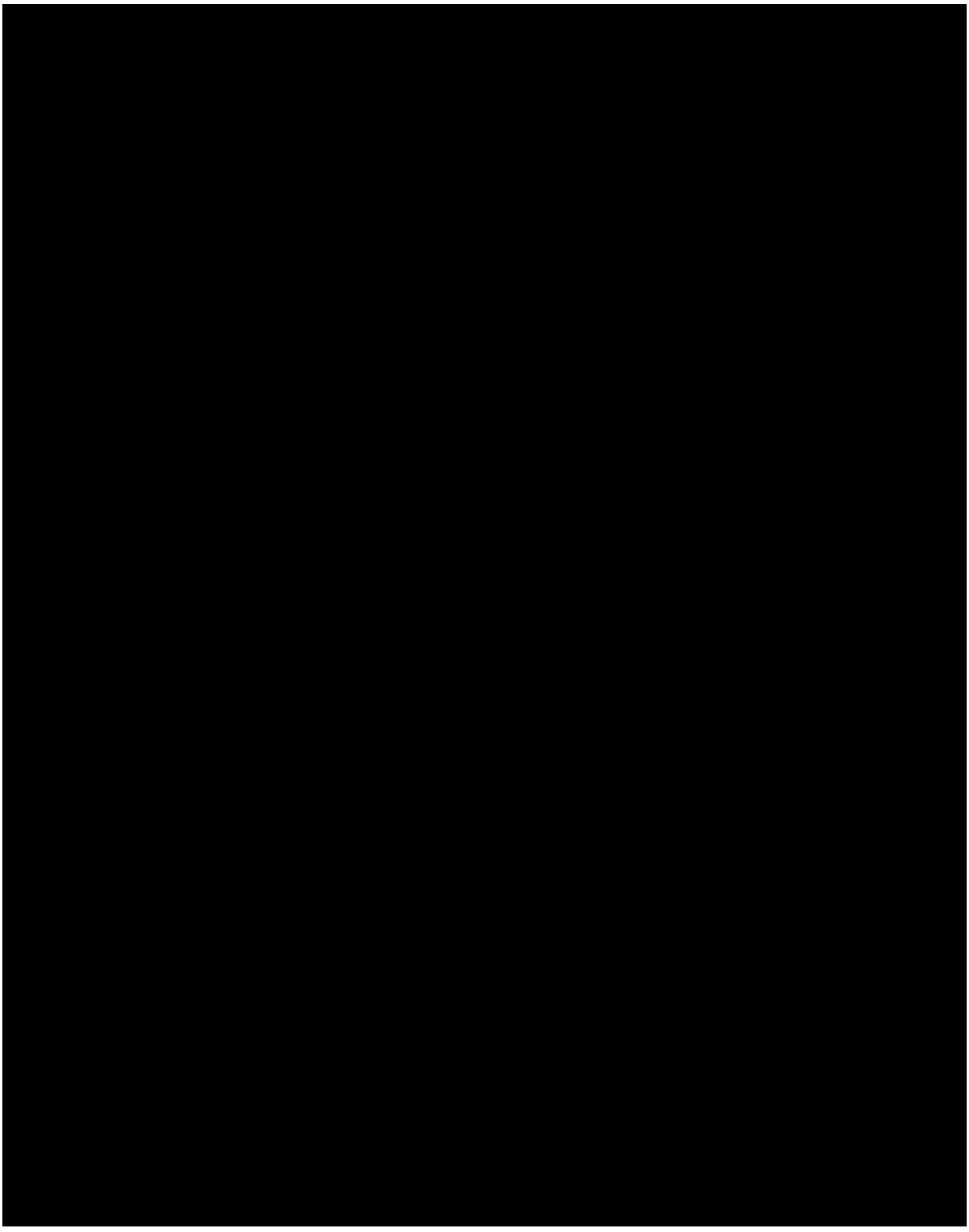
10.7.5 Caregiver - and/or patient-reported clinical outcome assessments

10.7.5.1 PROMIS instruments

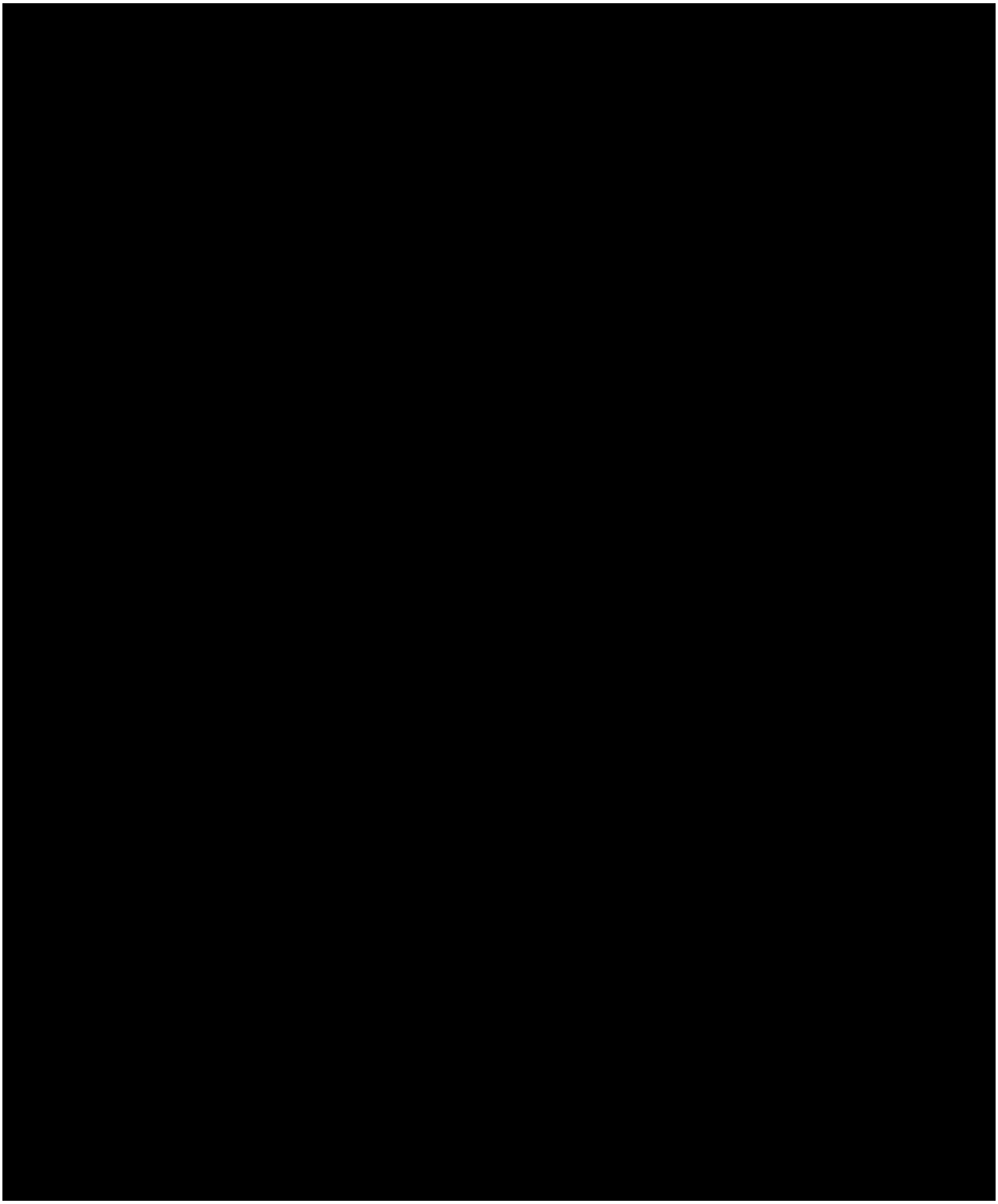
10.7.5.1.1 PROMIS pediatric numeric rating scale pain intensity v1.0



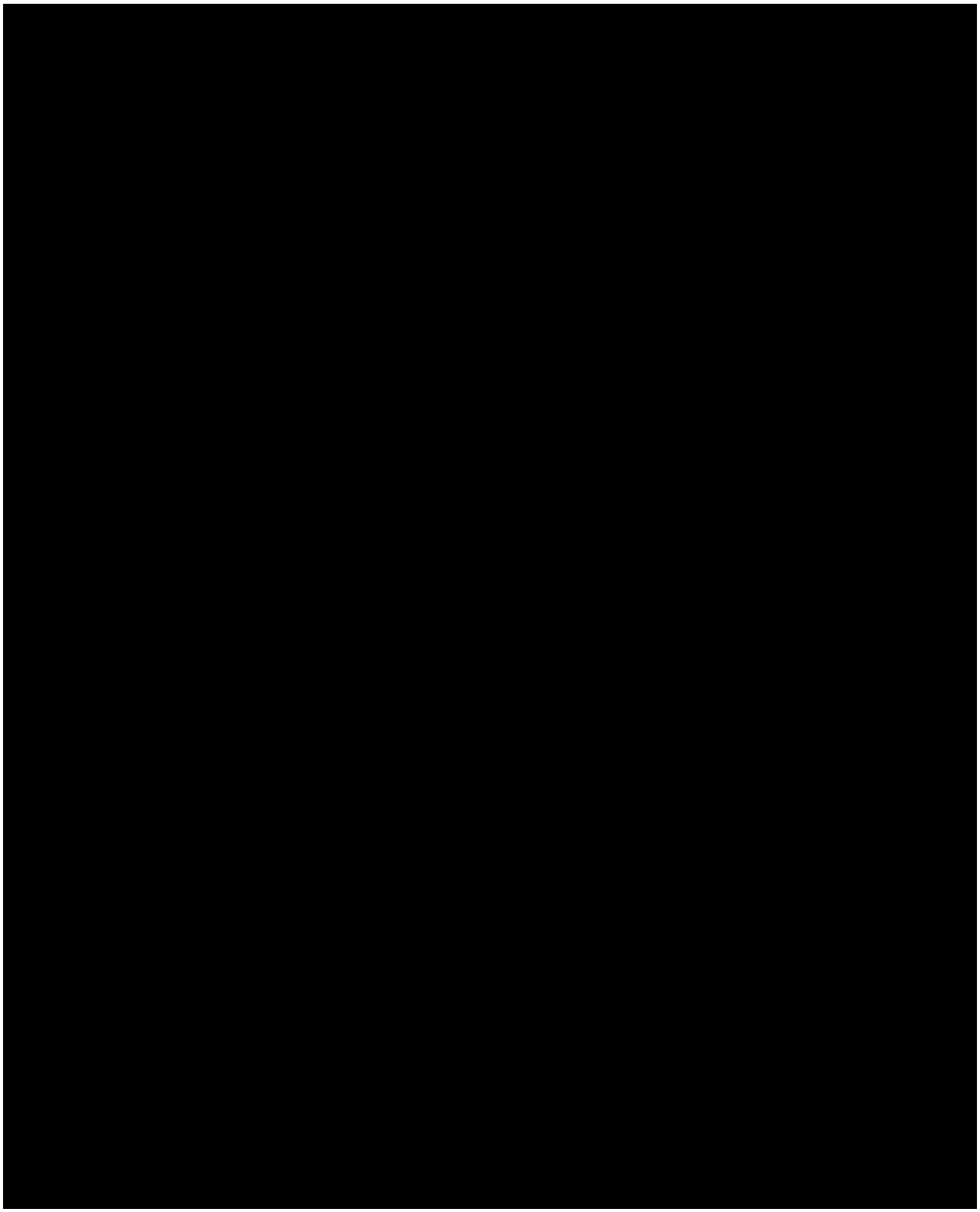
10.7.5.1.2 PROMIS Pediatric-SF v2.0 - pain interference 8a



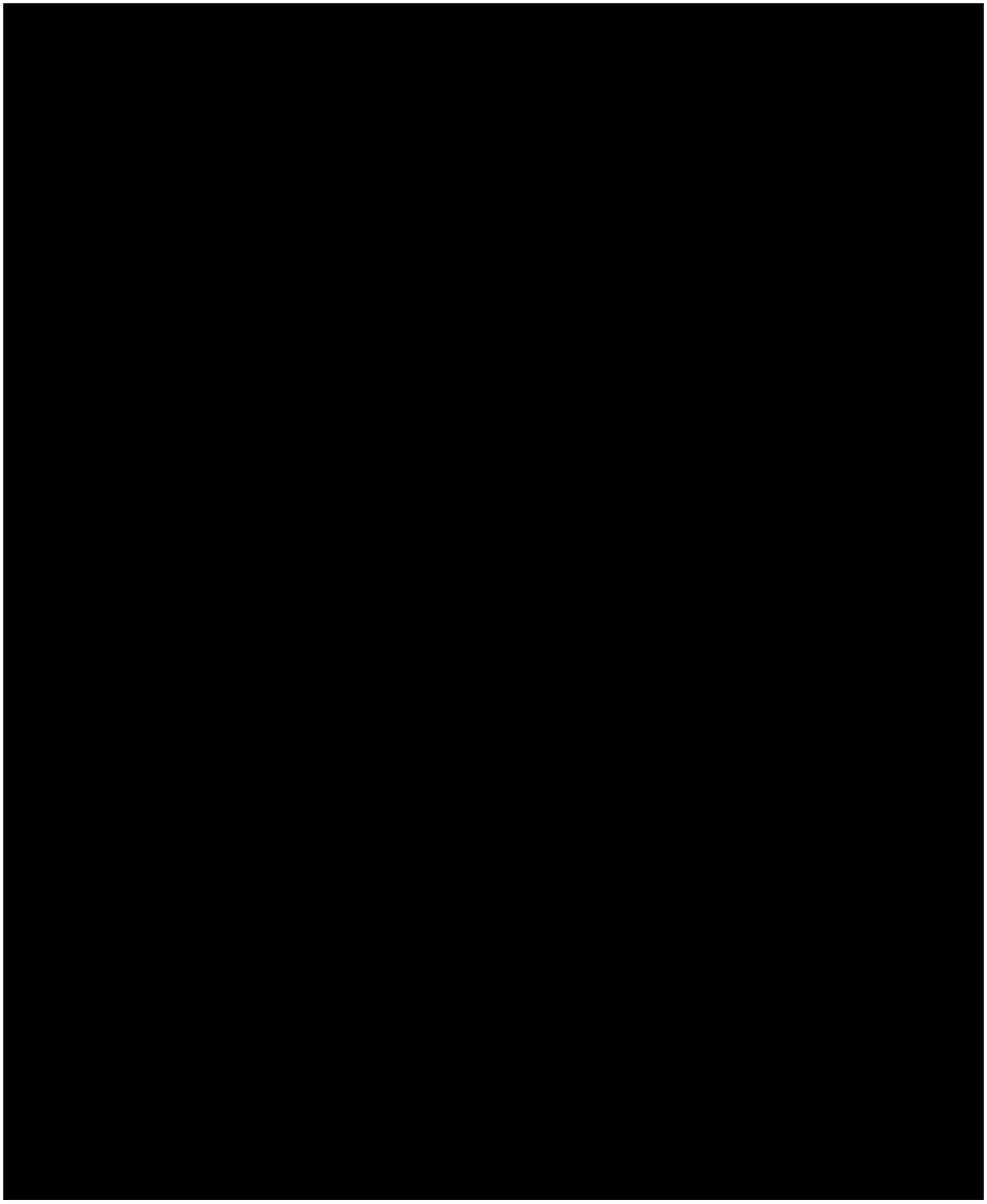
10.7.5.1.3 PROMIS Pediatric-SF v1.0 - physical activity 8a



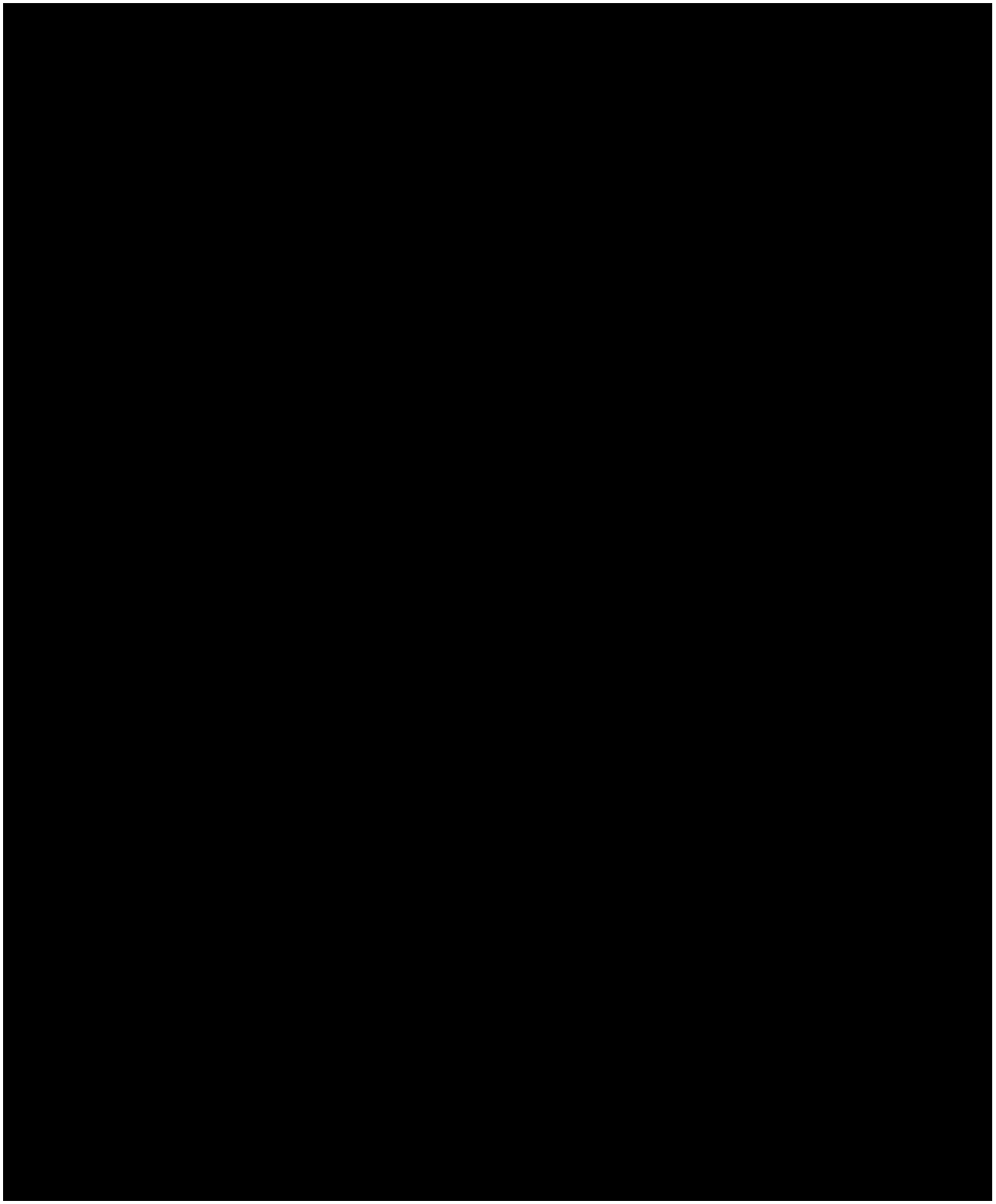
10.7.5.1.4 PROMIS parent proxy numeric rating scale pain intensity v1.0



10.7.5.1.5 PROMIS parent proxy-sf v2.0 - pain interference 8a

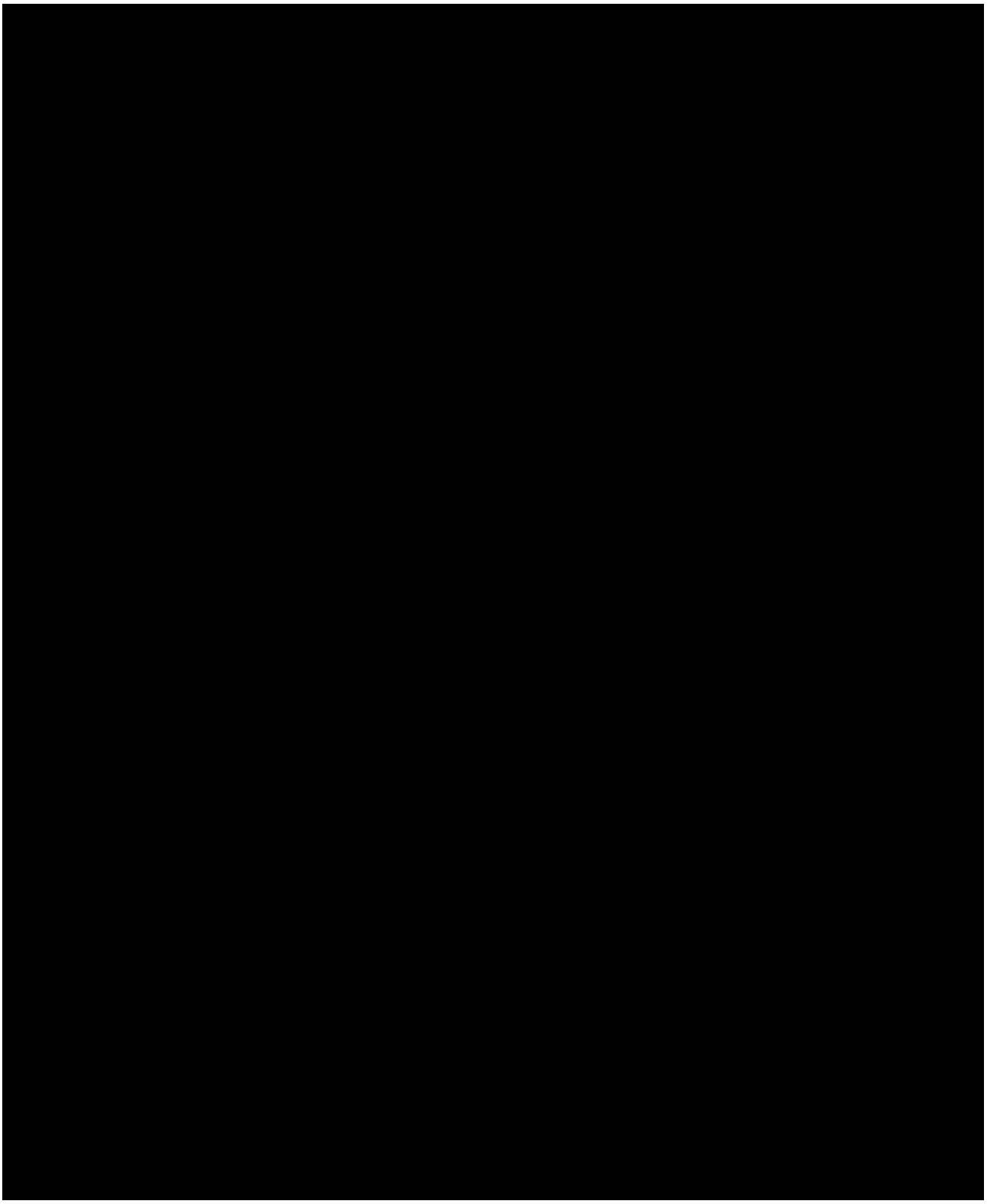


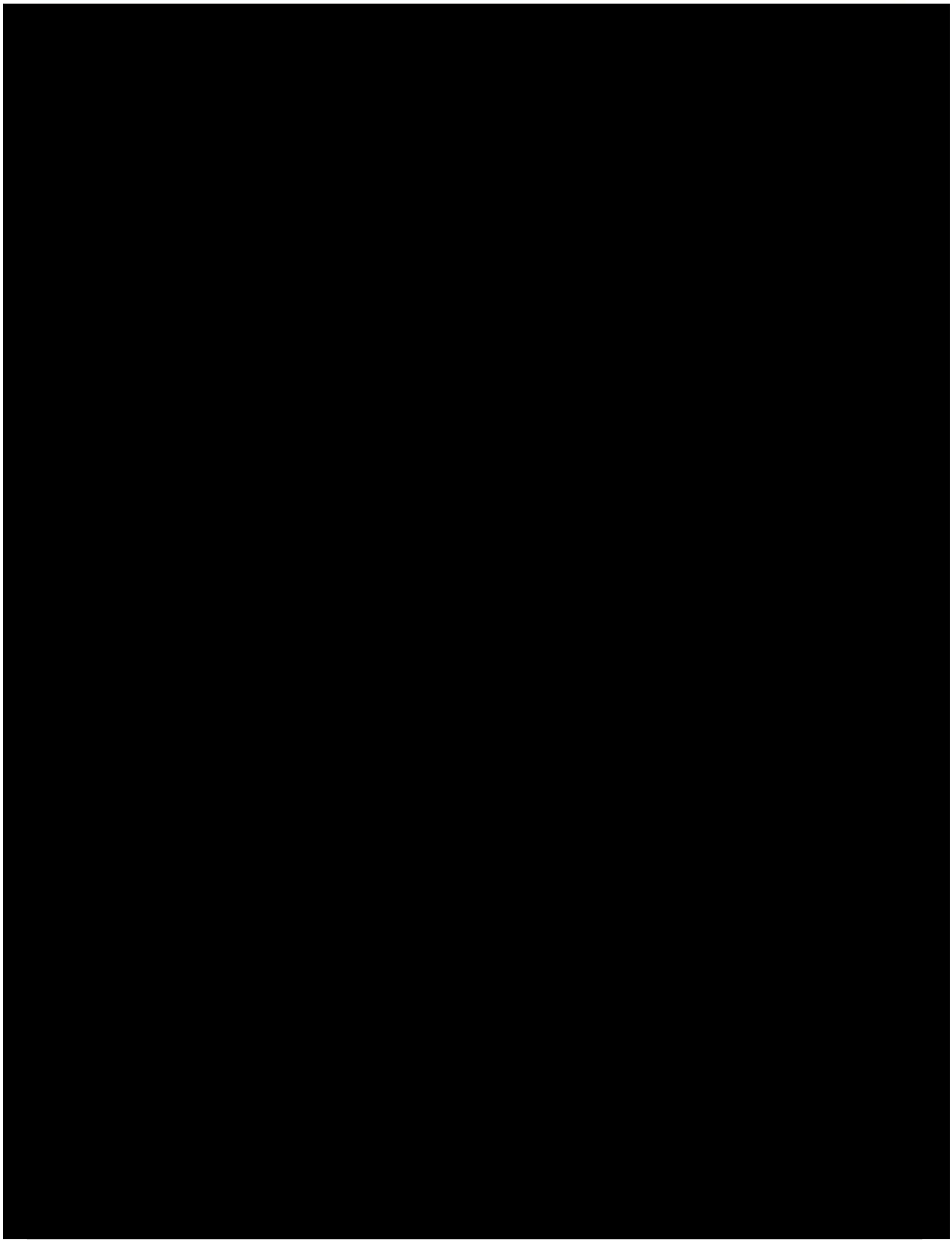
10.7.5.1.6 PROMIS parent proxy-sf v1.0 - physical activity 8a



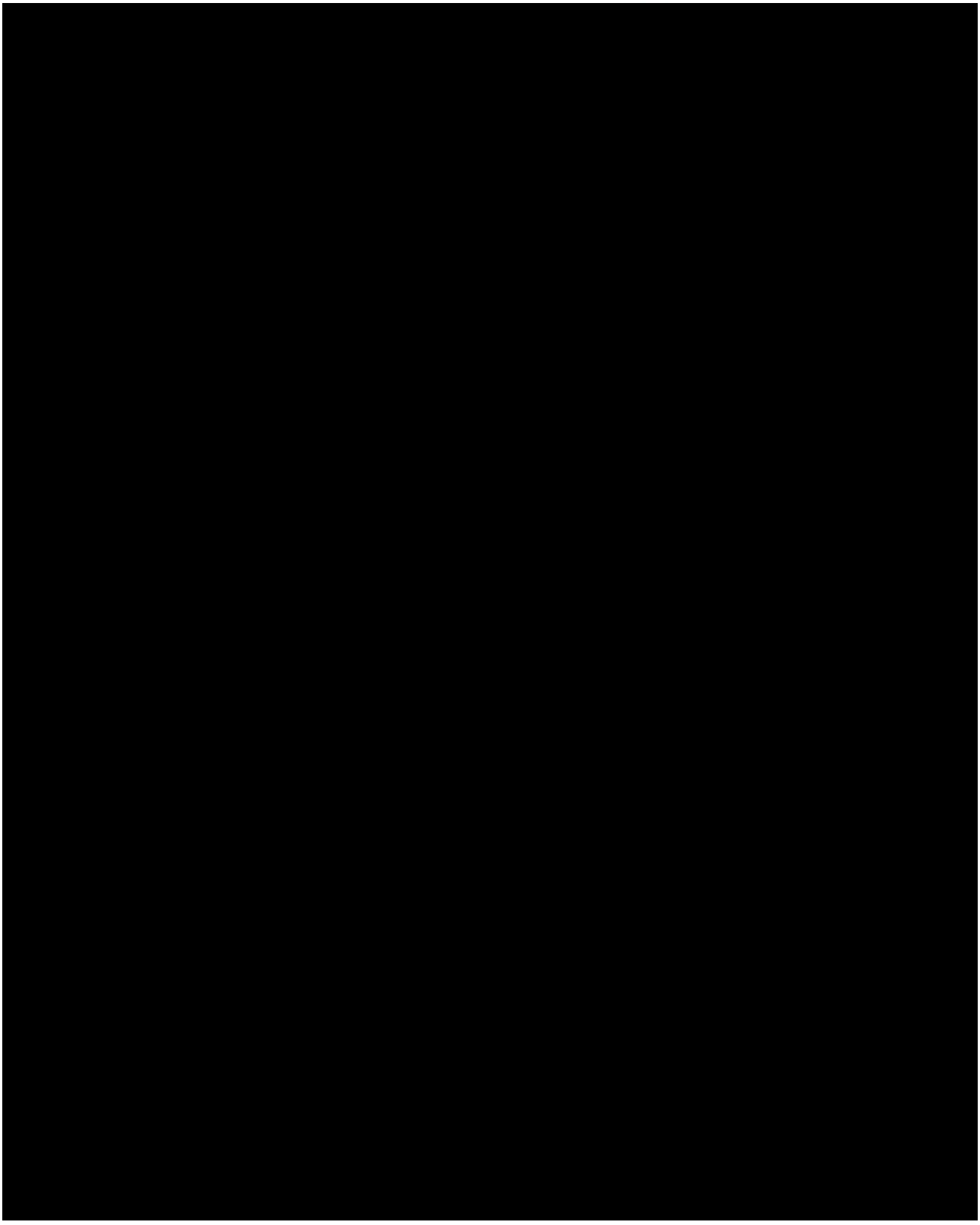
10.7.5.2 Haemo-QoL

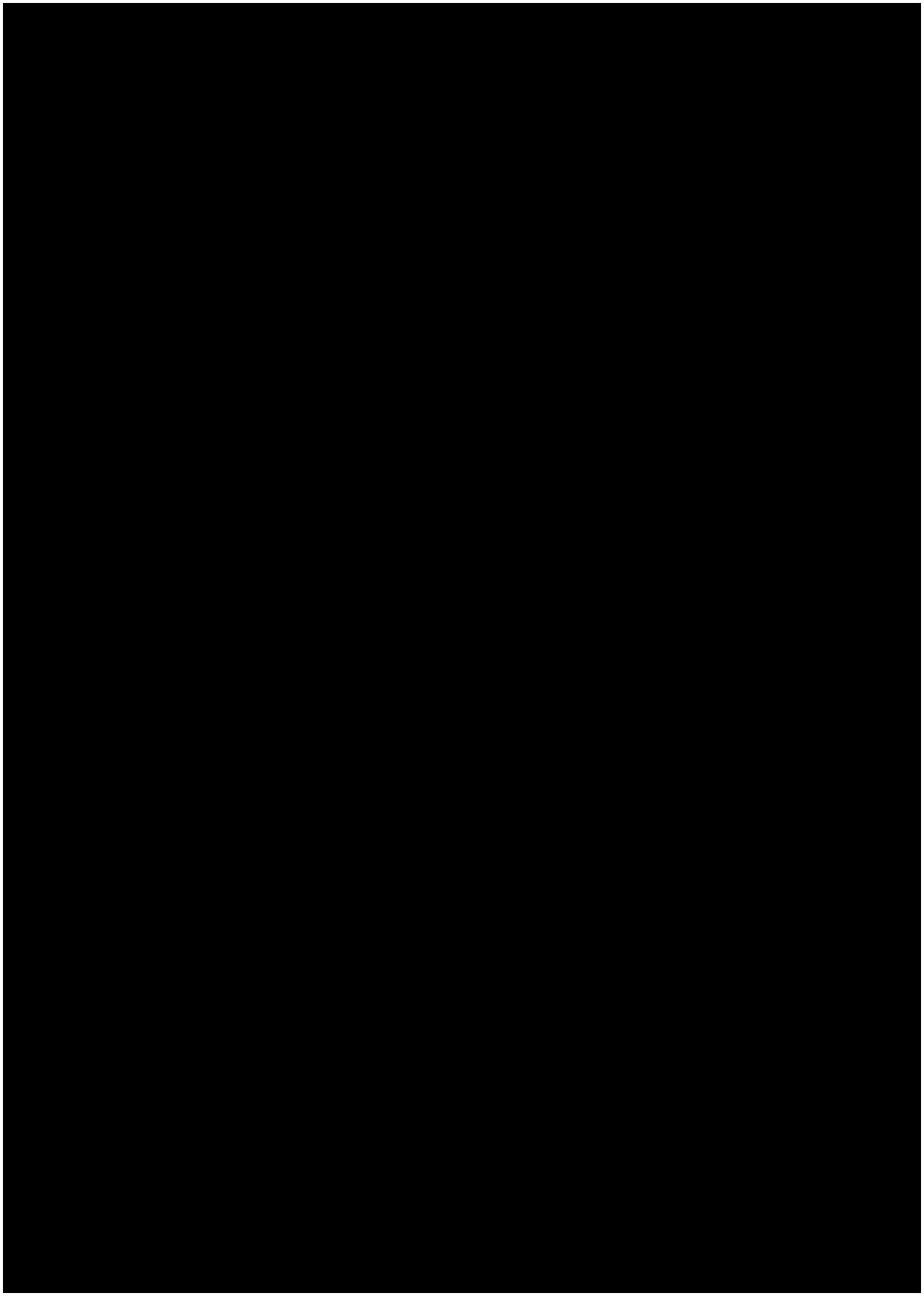
10.7.5.2.1 Haemo-QoL short children version (4-7 years)

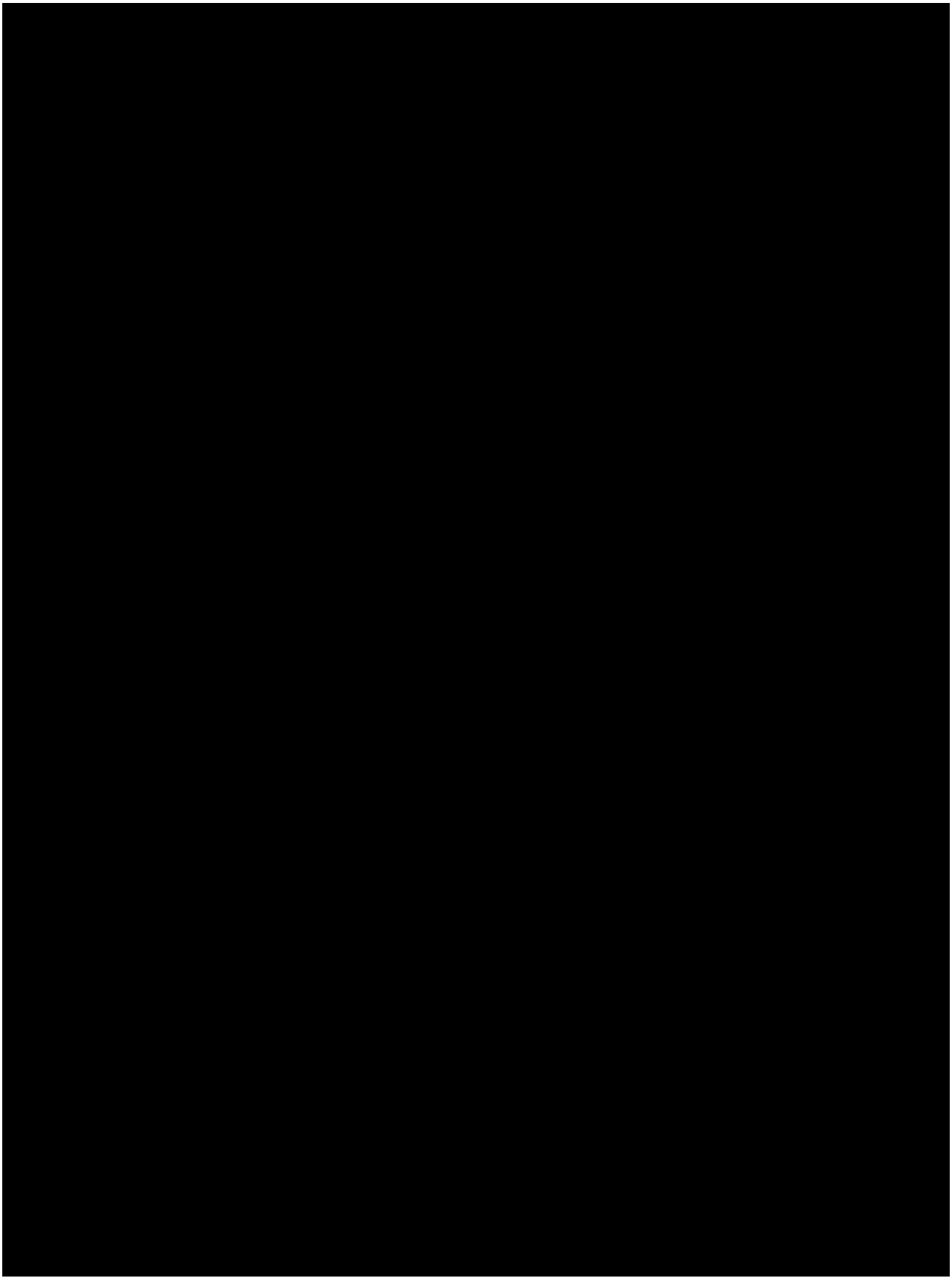




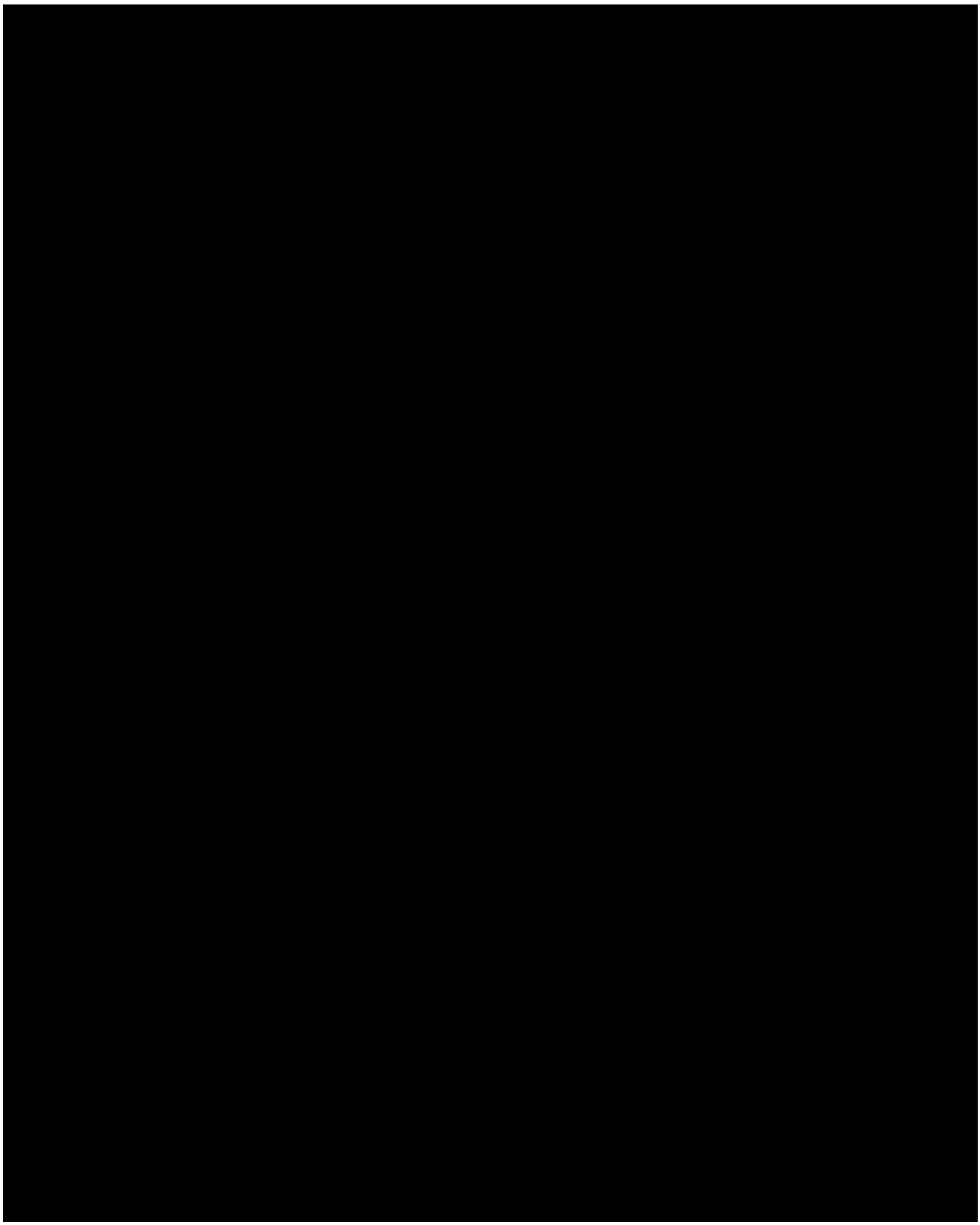
10.7.5.2.2 Haemo-QoL short children version (8 to <12 years)

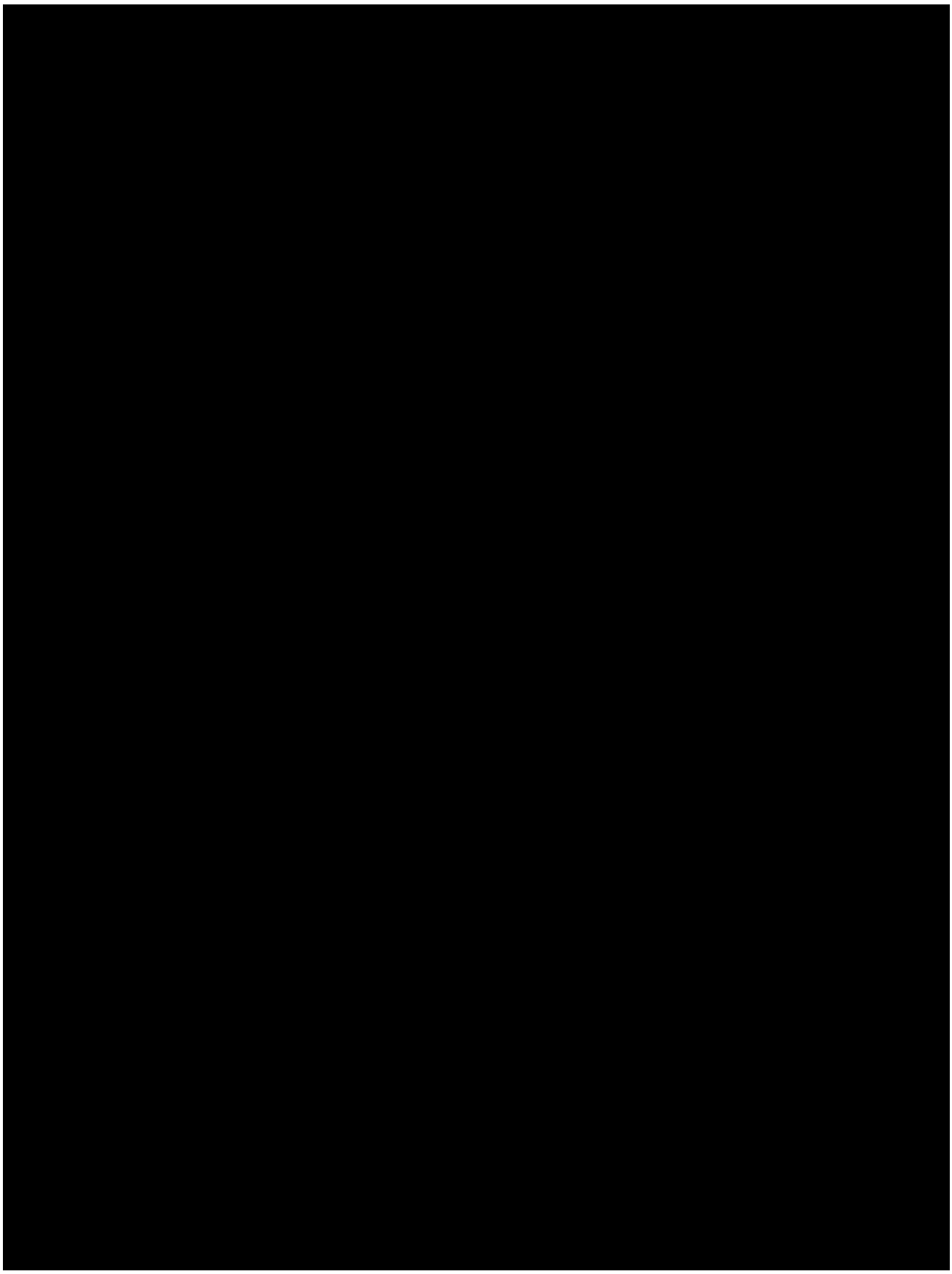




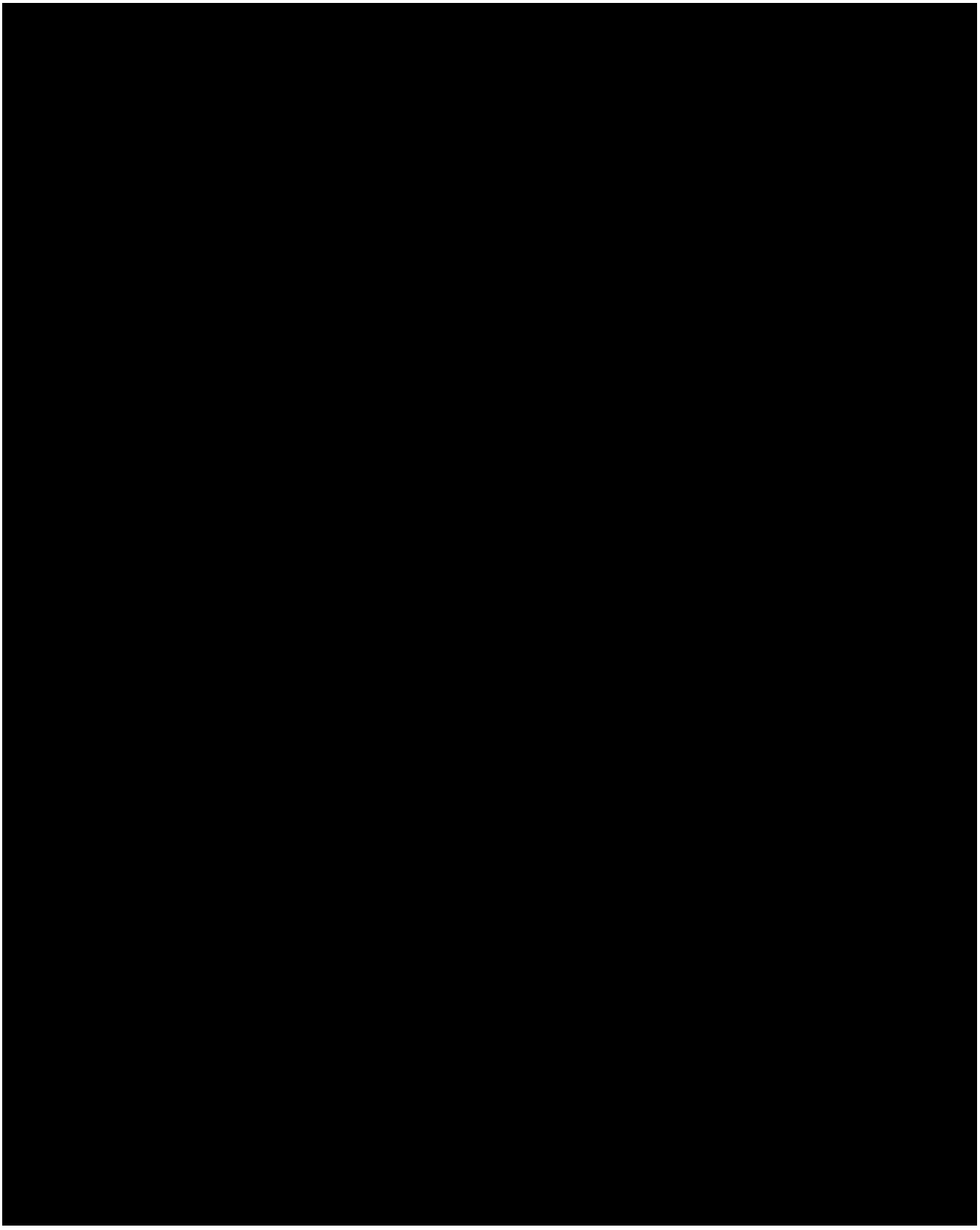


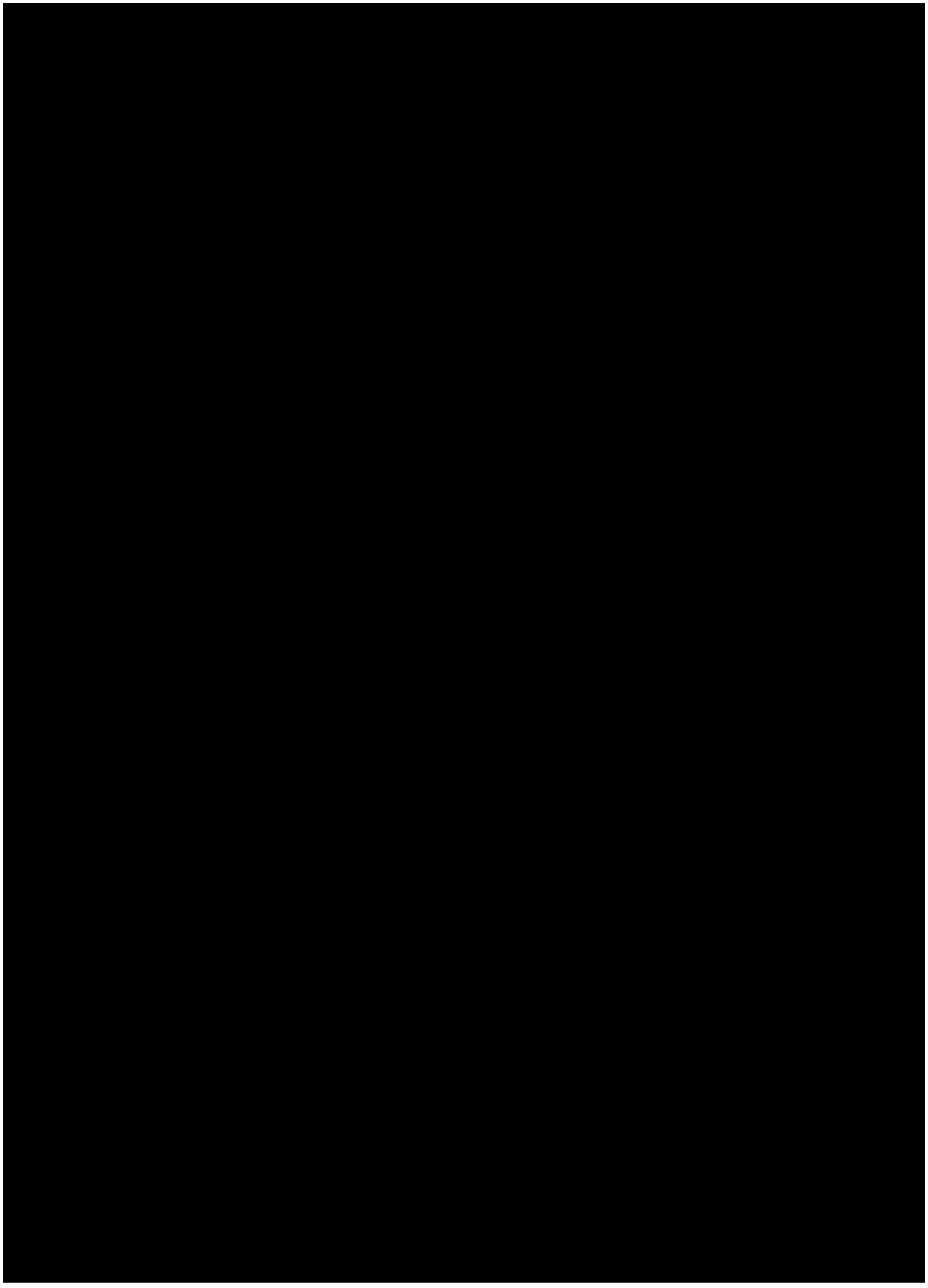
10.7.5.2.3 Haemo-QoL parent proxy short version (children 4-7 years)

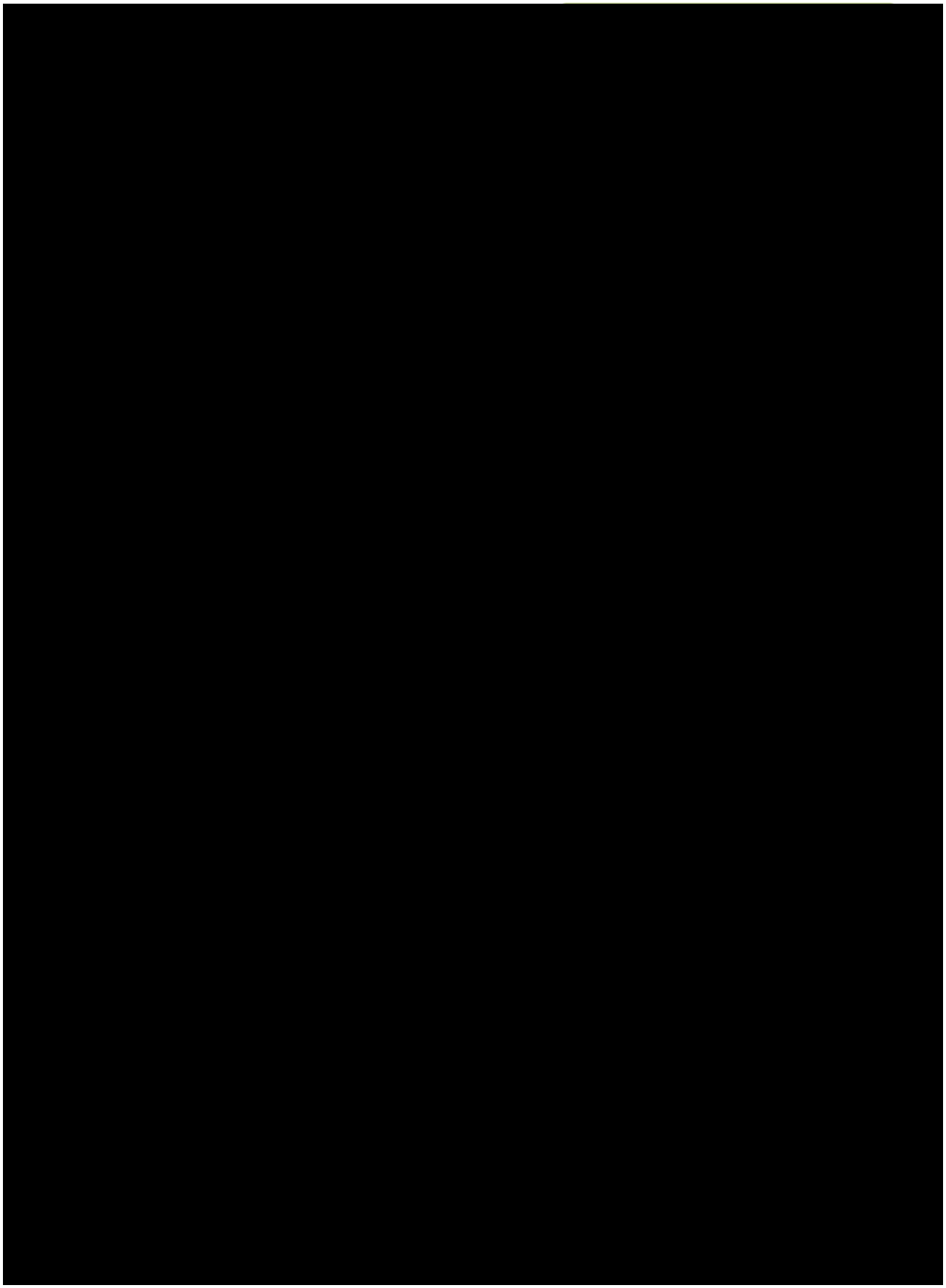




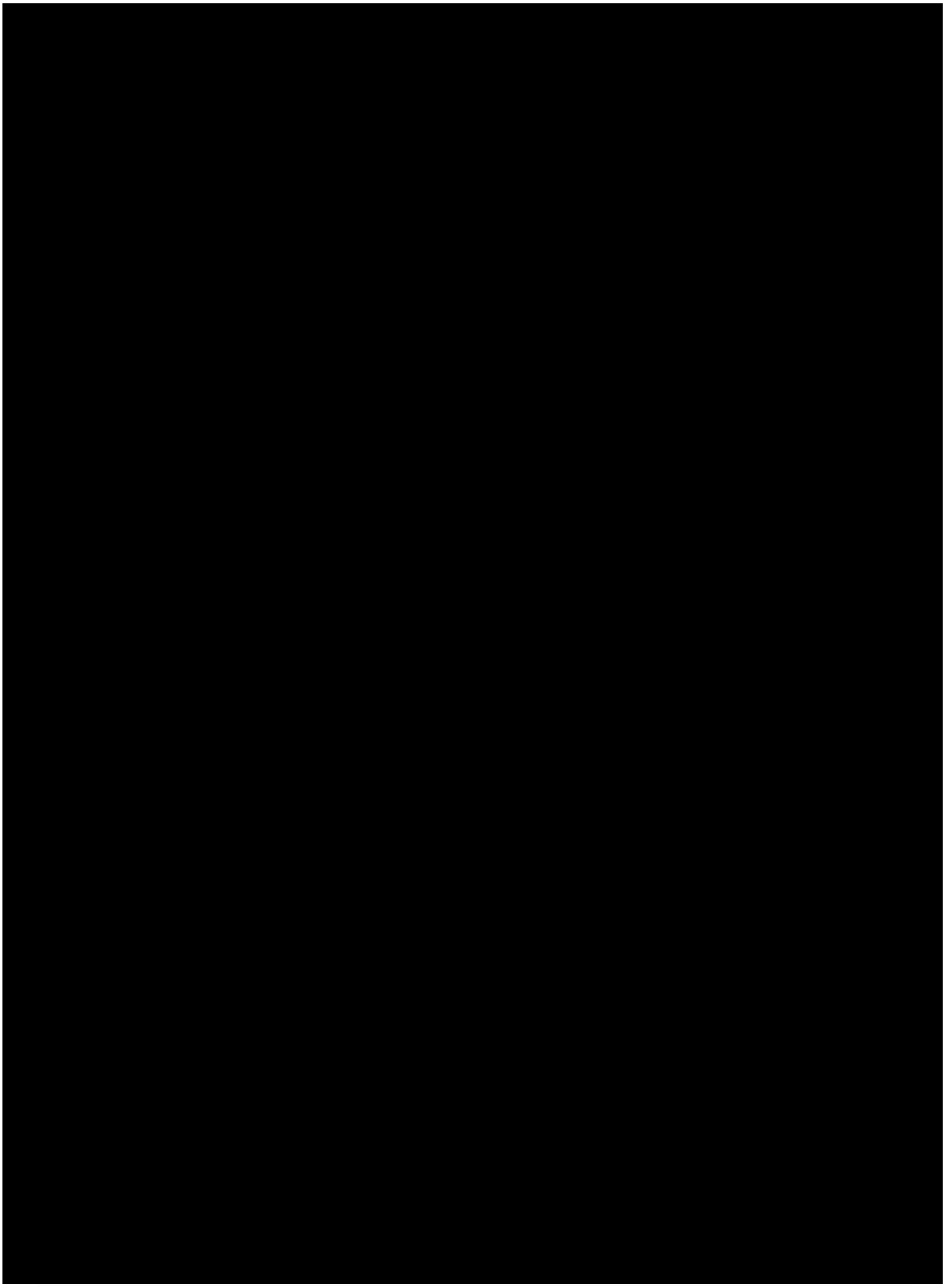
10.7.5.2.4 Haemo-QoL parent proxy short version (children 8 to <12 years)

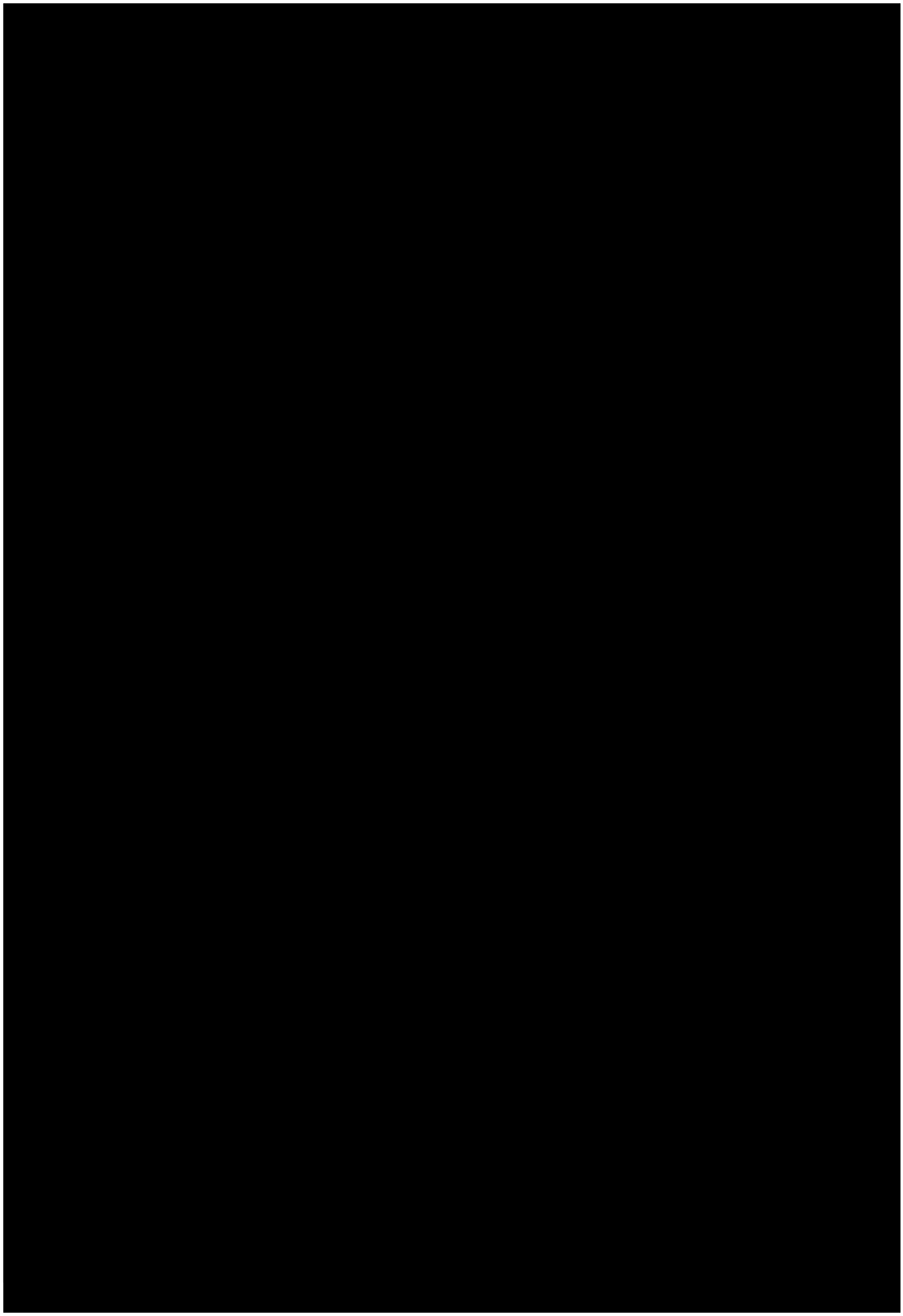


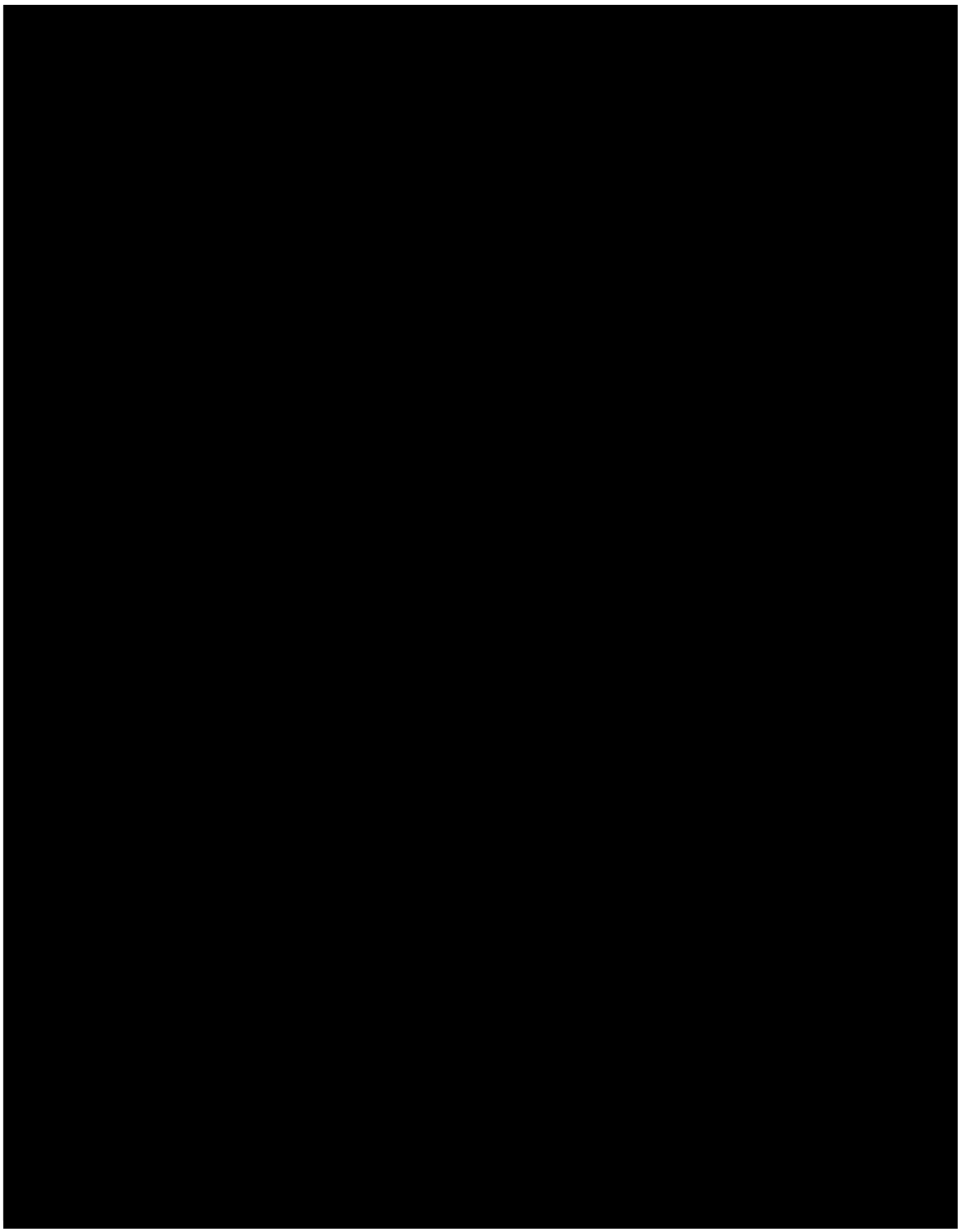




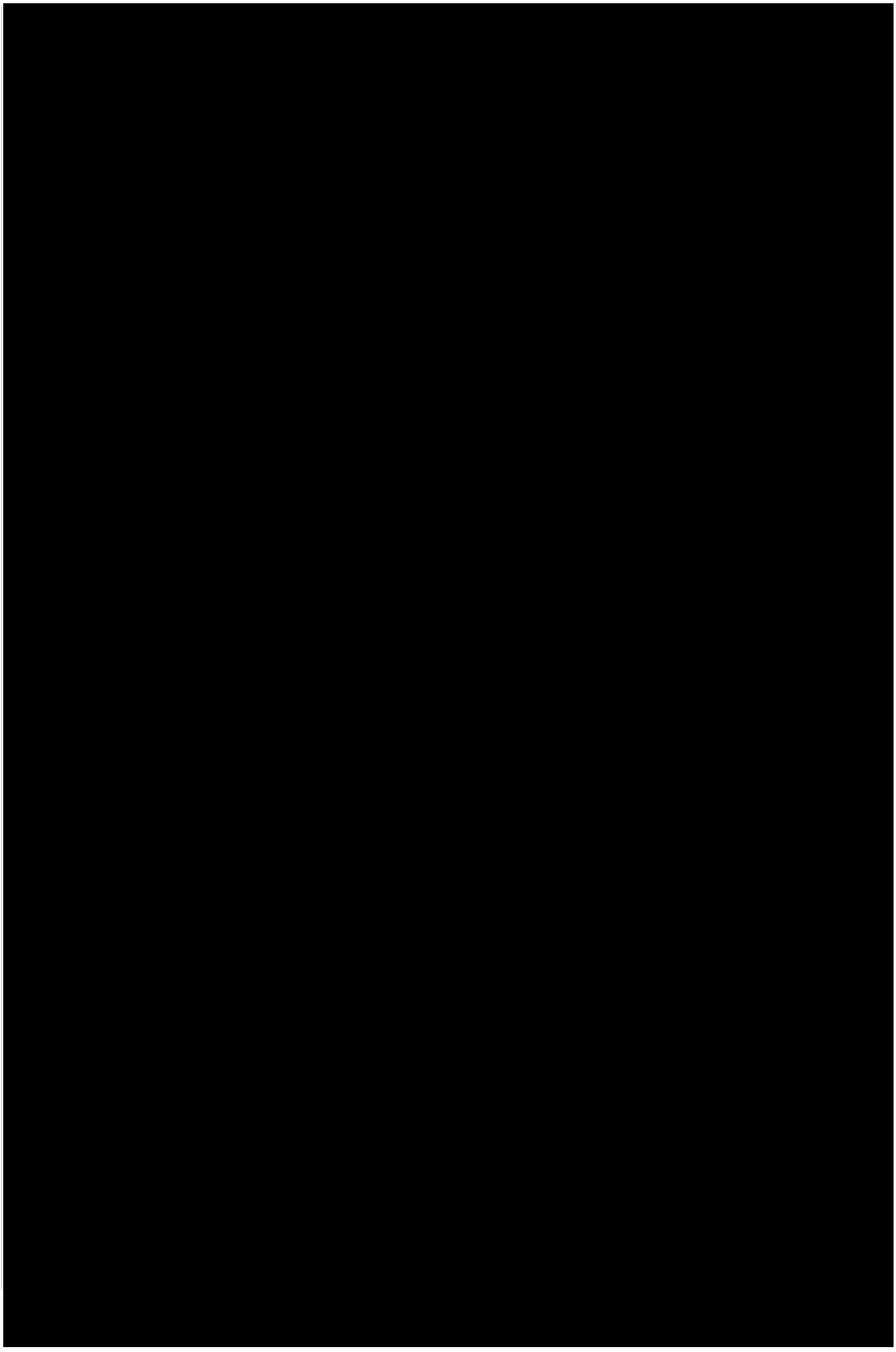
10.7.5.3 EuroQoL 5-dimension 5-level youth (EQ-5D-Y)

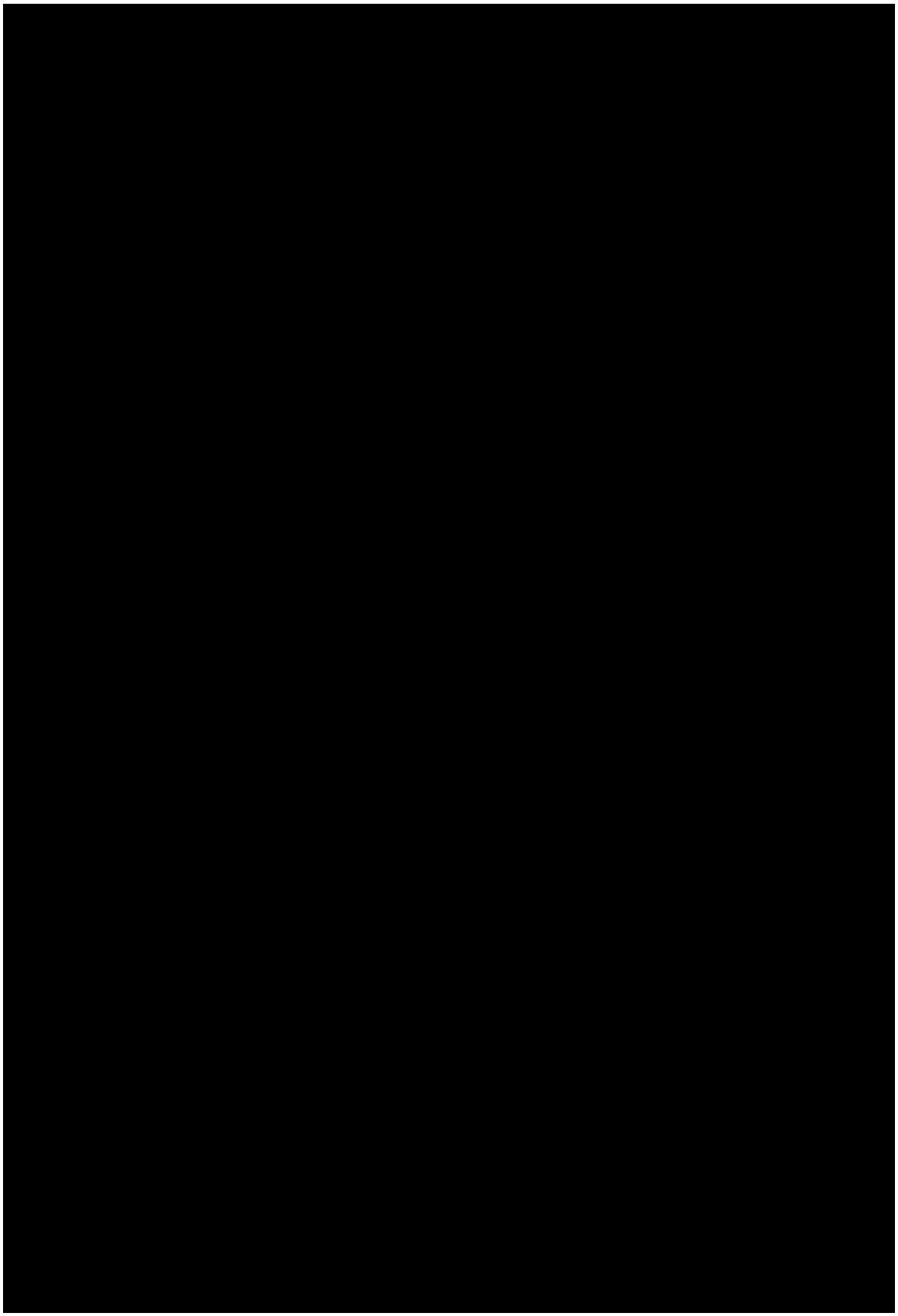


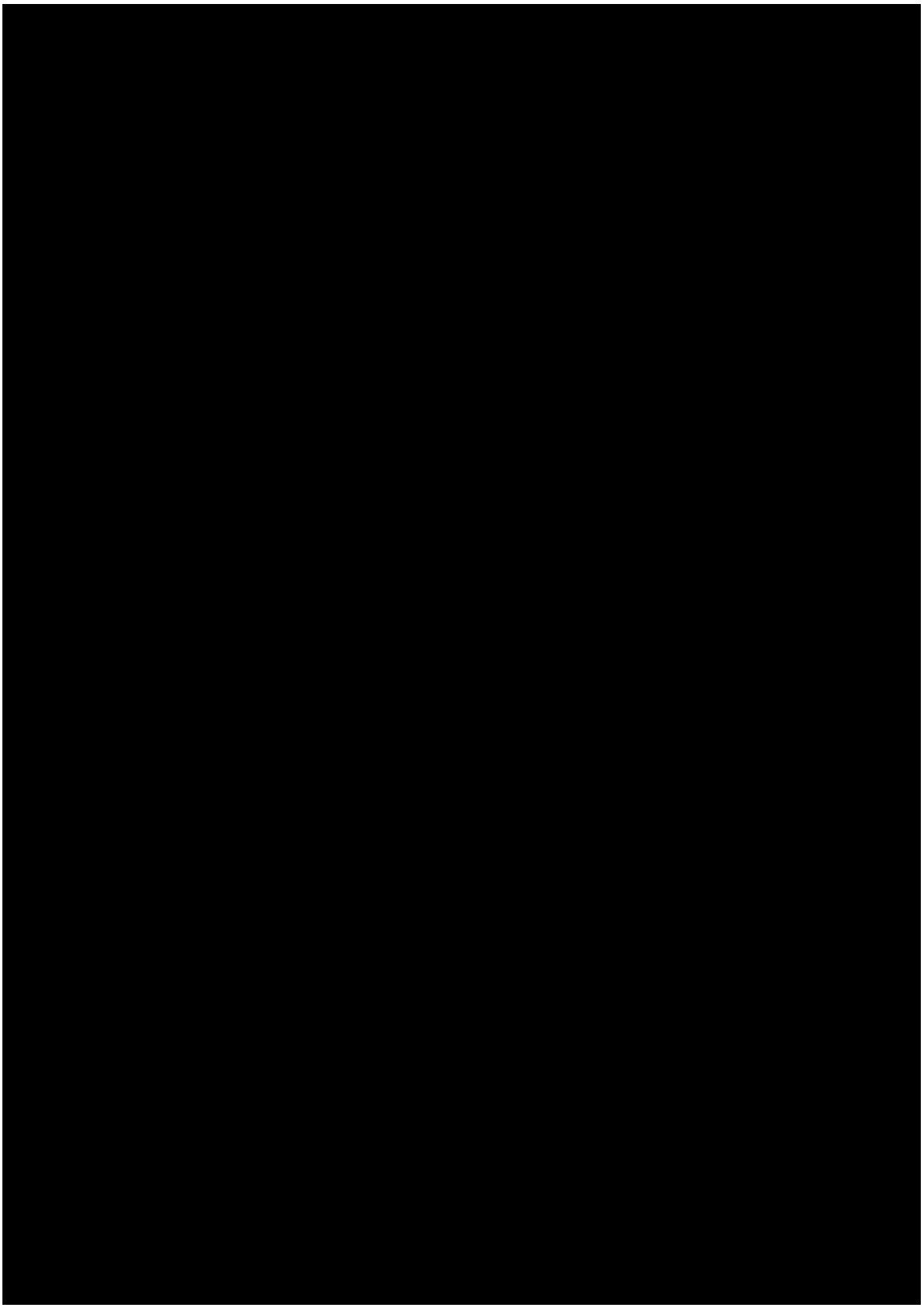




10.7.5.3.2 EQ-5D-Y parent proxy version (for children 4-7 years)







10.7.5.4 Caregivers interviews guide

Assessing Experiences With BIVV001 for Hemophilia A: Caregiver Interview Guide for ETC16295 Study

I.	Introduction	5 min

*[Introduce interviewers; confirm caregiver's first name **before** starting the interview; confirm with the caregiver that now is still a convenient time for the interview—if the caregiver expresses any concerns or hesitancy (or based on the interviewer's judgment), reschedule the interview.*

Remind caregiver about key elements in consent form, including the following:]

The purpose of today's interview is to learn more about your experiences, specifically:

- Your experiences caring for someone with hemophilia A and its treatments
- Your expectations about the study medication before starting the study
- Your observations related to the medication your [care recipient] received during the study and any improvements you may have noticed

The information you provide today will be used to help the study sponsor better understand people's experiences with hemophilia and with BIVV001. Please feel to speak openly and share your opinions freely. There are no wrong answers.

Our discussion today is scheduled to take about 60 minutes. We are audio recording and transcribing all interviews to make sure we do not miss any important information. The transcripts from the interviews will be given to the study sponsor at the end of this study, with only your [care recipient's] study ID number attached. Please remember that today's interview is completely voluntary; you can take a break or end the discussion at any time.

If you report a potential side effect during today's call, I will have to notify the study sponsor, who may follow-up with you for more information.

Do you have any questions before we begin? *[Answer any questions]*

START RECORDING; STATE [CARE RECIPIENT'S] CLINICAL STUDY ID AND INTERVIEW DATE FOR AUDIO RECORDING

We have started the audio recording. Do we have your permission to continue with the interview?

☐ Yes → **CONTINUE**

☐ No → **STOP INTERVIEW**

II. Background Information and Pre-Study Experiences 20 Min

First, I would like to learn a little more about you and about your experiences as a caregiver for someone with hemophilia A.

1. **How old are you?** *[Confirm from recruitment log]*
2. **What is your relationship to the [care recipient]?** *[Confirm from recruitment log; Use patient's name throughout the rest of the guide where 'care recipient' is stated]*
3. **How old is your [care recipient]?**
4. **Before participating in the study, did your [care recipient] bleed frequently in any joint(s)?** *[May select more than one answer].*
   - ☐ Left Knee
   - ☐ Right Knee
   - ☐ Left Ankle
   - ☐ Eight Ankle
   - ☐ Left Elbow
   - ☐ Right Elbow
   - ☐ Left Hip
   - ☐ Right Hip
   - ☐ Left Shoulder
   - ☐ Right Shoulder
   - ☐ Left Wrist
   - ☐ Right Wrist
   - ☐ Other (specify, _____)
5. **Before starting the clinical study, how often did your [care recipient] have bleeds?**
6. **How did the different types of bleeds impact your life?** *[probe if bleeds were considered minor or life-threatening]*
   a) Joint bleeds?
   b) Muscle bleeds?
   c) Other bleeding?

7. **Before starting the clinical study, what about hemophilia A do you think bothered <u>your [care recipient]</u> the most? What bothered <u>you</u> the most about hemophilia A?**

8. *[If treated for hemophilia A]* **Before starting the clinical study, what about hemophilia A treatment do you think bothered your [care recipient] the most? What bothered you the most about hemophilia A treatment?**

9. *[If treated for hemophilia A]* **In general, what did you like about the previous hemophilia A treatments your [care recipient] has used before this study?**

10. *[If treated for hemophilia A]* **<u>Before your [care recipient] started the clinical study</u>, how satisfied were you overall with their hemophilia treatment**
[Read the response scale as often as needed]

- ☐ -2 = Very dissatisfied
- ☐ -1 = Dissatisfied
- ☐ 0 = Neither satisfied or dissatisfied (neutral)
- ☐ 1 = Satisfied
- ☐ 2 = Very satisfied

11. *[If treated for hemophilia A]* **In general, what did you dislike about the previous hemophilia A treatments your [care recipient] has used before this study?** *[Listen for reports on issues related to efficacy, dosing frequency, convenience, mode of administration, side effects, etc.]*

IMPACT

Now I'd like you to think back to **BEFORE** your [care recipient] started the study...

12. **Thinking back to the year <u>before starting the clinical study</u>, how did hemophilia or its treatment affect <u>your [care recipient's]</u> daily life and functioning?** *[If not already mentioned, ask each of the following questions]*

[Probe separately about (1) impact of hemophilia and (2) its treatment; Probe about the most significant impact]

a) **Daily Activities** (e.g., household chores)

b) **Physical health/physical functioning** (e.g., mobility, restriction of motion, stiffness, fear of hurting, pain, joint health, vein health, time to get ready)

c) **Mood/emotions** (e.g., depressed mood, anxiety, fear or worry about condition or bleeding, isolation, distress with breakthrough bleeding, sense of purpose, self worth)?

d) **School** (e.g., missing school, productivity at school, relationship with friends, special accommodations at school, changing schools, participation in after school activities like sports)

e) **Social life/activities** (e.g., less social, missing social events, participating in physical activities with friends/family)?

13. **Thinking back to the year <u>before starting the clinical study</u>, how did hemophilia or its treatment affect <u>your</u> daily life and functioning?** *[If not already mentioned, ask each of the following questions]*

[Probe separately about (1) impact of hemophilia and (2) its treatment; Probe about most significant impact]

a) **Daily Activities** (e.g., household chores/errands, childcare for siblings, ordering supplies/preparing medications, medical appointments, travel to hospital/clinic)

b) **Physical health/physical functioning** (e.g., exercise)

c) **Mood/emotions** (e.g., depressed mood, anxiety, stress, fear or worry about condition or infection or bleeding, distress with breakthrough bleeding)?

d) **Self-care** (e.g., time for self, give up certain things)

e) **Work/School** (e.g., missing work/school, productivity, career path)

f) **Finances** (e.g., hospitalizations, medication costs, changes in income due to employment)

g) **Managing hemophilia treatment** (e.g., time commitment for infusion, ordering medications/supplies, travel for treatment, planning administration)

h) **Impact on family** (e.g., impact on your family life and significant other, impact on siblings or care recipient)

III. Treatment Expectations 10 Min

Now I'd like you to think back to **BEFORE** your [care recipient] started the study...

14. **Before starting the clinical study, what specific symptoms/problems did you most want the study treatment to help? Why?**

15. **Before starting the clinical study, what changes (if any) did you think you might see through your [care recipient's] participation in this study?** *[Focus on domains identified by interviewee earlier; Probe on the following if not spontaneously reported]*

    a) **Daily Activities** (e.g., household chores)

    b) **Physical health/physical functioning** (e.g., mobility, restriction of motion, stiffness, fear of hurting, improvement in joint pain, joint health, vein health, time to get ready)

    c) **Mood/emotions** (e.g., depressed mood, anxiety, fear or worry about condition or bleeding, isolation, distress with breakthrough bleeding, sense of purpose, self worth)?

    d) **School** (e.g., missing school, productivity at school, relationship with friends, special accommodations at school, changing schools, participation in after school activities like sports)

    e) **Social life/activities** (e.g., less social, missing social events, participating in physical activities with friends/family)?

IV. During Study Experiences 15-20 Min

Now I'd like to talk to you about your experiences **DURING** the study.

16. **What improvements in symptoms and impacts, if any, have you noticed in your [care recipient] as a result of the clinical study participation (or the investigational treatment)?**

    a. *[Ask the participant to describe each improvement. Allow for spontaneous reports. If not already mentioned, probe to see if the symptoms experienced before the study improved. If so, have the participant describe the improvement and rate the importance of the improvement below]*

    b. **Please rate the importance of the improvement to you in** *[symptoms]* ***on the following scale from 1 to 5). I will read the scale to you:***

    - ☐ 1 = Not at all important
    - ☐ 2 = A little important
    - ☐ 3 = Somewhat important
    - ☐ 4 = Very important
    - ☐ 5 = Extremely important

i. Tell me what you were thinking about when you selected this response. *[Ask for each improvement]*

17. How, if at all, did these improvements affect your [care recipient's] daily life and functioning? *[Allow for spontaneous response; Ask probes below if not mentioned]*

a) **Daily Activities** (e.g., household chores)

b) **Physical health/physical functioning** (e.g., mobility, restriction of motion, stiffness, fear of hurting, improvement in joint pain, joint health, vein health, time to get ready)

c) **Mood/emotions** (e.g., depressed mood, anxiety, fear or worry about condition or bleeding, isolation, distress with breakthrough bleeding, sense of purpose, self worth)?

d) **School** (e.g., missing school, productivity at school, relationship with friends, special accommodations at school, changing schools, participation in after school activities like sports)

e) **Social life/activities** (e.g., less social, missing social events, participating in physical activities with friends/family)?

18. Were there any other improvements you noticed as a result of your [care recipient] participating in the clinical study?

19. How soon after starting the study, did you notice these improvements in your [care recipient]?

– What, specifically, did you notice first?

20. How, if at all, did these improvements affect your daily life and functioning? *[Focus on domains identified by interviewee earlier; Allow for spontaneous response. Ask probes below if not already mentioned]*

f) **Daily Activities** (e.g., household chores/errands, childcare for siblings, ordering supplies/preparing medications, medical appointments, travel to hospital/clinic)

g) **Physical health/physical functioning** (e.g., exercise)

6

h) **Mood/emotions** (e.g., depressed mood, anxiety, stress, fear or worry about condition or infection or bleeding, distress with breakthrough bleeding)?

i) **Self-care** (e.g., time for self, give up certain things)

j) **Work/School** (e.g., missing work/school, productivity, career path)

k) **Finances** (e.g., hospitalizations, medication costs, changes in income due to employment)

l) **Managing hemophilia treatment** (e.g., time commitment for infusion, ordering medications/supplies, travel for treatment, planning administration)

m) **Impact on family** (e.g., impact on your family life and significant other, impact on siblings or care recipient)

21. **Were there any disadvantages you noticed as a result of your [care recipient] participating in the clinical study?** *[Allow for spontaneous response; Probe if response not specific to study treatment]*

V. Importance of Changes 5-10 Min

Thinking in general about a treatment for hemophilia A...

22. **How important to you as a caregiver would it be for a hemophilia treatment to...** *[Use the 1-to-5 rating scale below for each item. Repeat scale as often as needed]*

- ☐ 1 = Not at all important
- ☐ 2 = A little important
- ☐ 3 = Moderately important
- ☐ 4 = Very important
- ☐ 5 = Extremely important

a) Decrease bleeds?

b) Decrease pain?

c) Prevent the development of inhibitors?

d) Be convenient (e.g., easy to carry, administer)?

e) Improve convenience of treatment?

f) Improve the ability of your [care recipient] to participate in sports and social activities?

g) Improve the ability for your [care recipient] to move around easily?

h) Improve the health of your [care recipient's] joints?

i) Feeling that your [care recipient] is well protected?

j) Allow your [care/recipient] to not worry about hemophilia?

k) Minimize your anxiety/stress related to managing your [care recipient] with hemophilia?

VI. Treatment Satisfaction 5 Min

For these final questions, please think about your [care recipient's] hemophilia A and related issues before your [care recipient] started the study medication compared to how your [care recipient] is feeling now (today).

23. Overall, how satisfied or dissatisfied are you with the study medication as a treatment for hemophilia A?

- ☐ -2 = Very dissatisfied
- ☐ -1 = Dissatisfied
- ☐ 0 = Neither satisfied or dissatisfied
- ☐ 1 = Satisfied
- ☐ 2 = Very satisfied

Tell me why you selected that response. *[Probe to better understand what specifically influenced participant's response to this question]*

24. If you had to choose, would you prefer your previous hemophilia treatment or the study treatment? Tell me why. *[Probe if they would be willing to continue the study medication after the clinical study]*

25. Overall, based on your [care recipient's] experience in the study, please select a response on the scale below[1]:

☐ -3	☐ -2	☐ -1	☐ 0	☐ 1	☐ 2	☐ 3

[1] Adapted from Patients' Qualitative Assessment of Treatment_Version 2 (PQATv2) © Sanofi, 2016-2017 (not to be reproduced without permission)

The disadvantages of the study treatment significantly outweigh the benefits			There were equal benefits and disadvantages of the study treatment			The benefits of the study treatment significantly outweigh the disadvantages

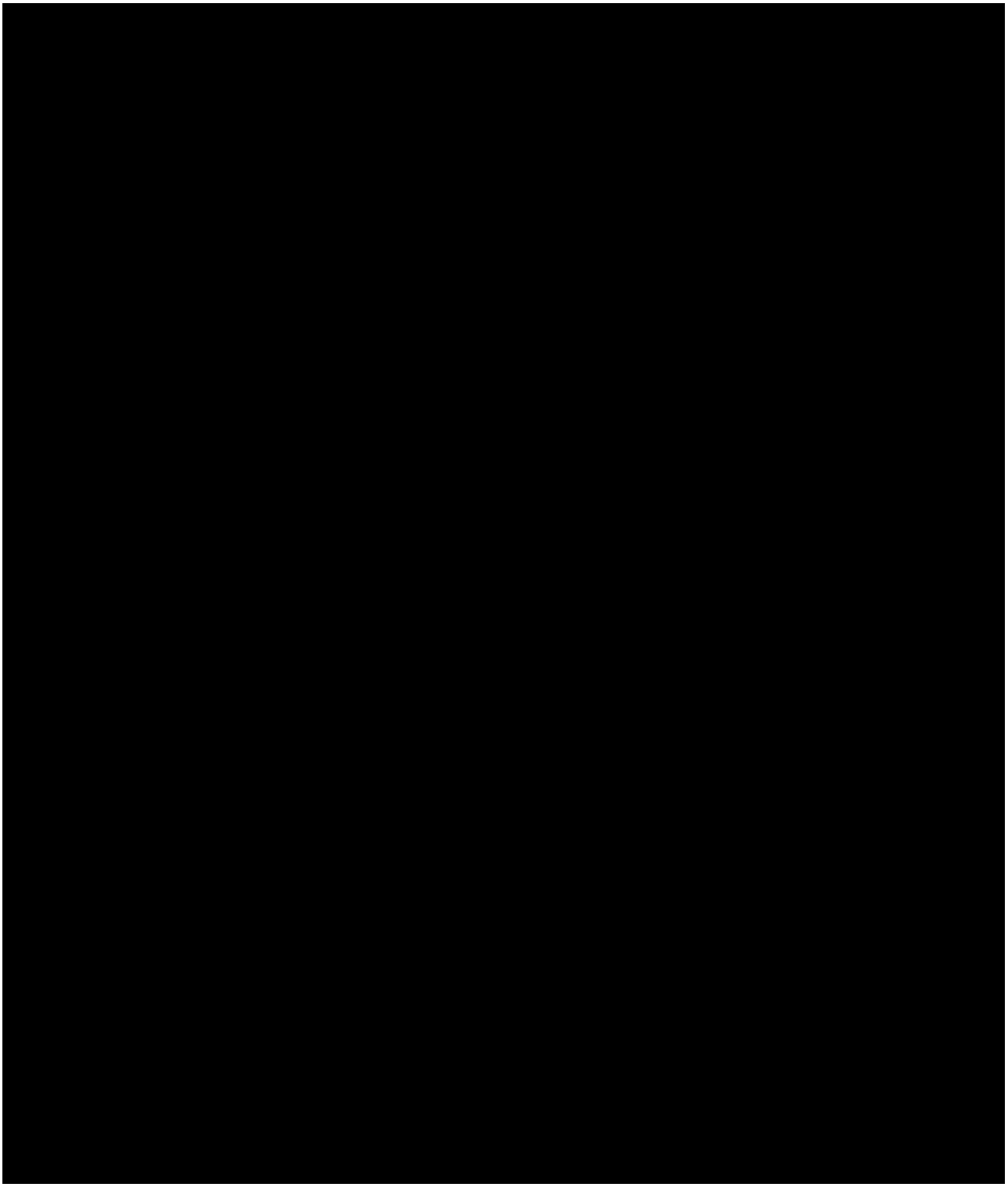
VII. Summing up 2 Min

Thank you for sharing your thoughts and experiences with us today. This information is very valuable and will help the study sponsors understand more about participants experiences with hemophilia A and the impact of the study medication.

Is there anything else you think we should know (i.e., anything we should have asked but didn't)?

[THANK PARTICIPANT – CONCLUDE INTERVIEW]

10.7.6 Healthcare resource utilization (HRU)



10.8 APPENDIX 8: ABBREVIATIONS

ABR:	annualized bleeding rate
AE:	adverse event
AESI:	adverse events of special interest
AJBR:	annualized joint bleeding rate
aPTT:	activated partial thromboplastin time
ASA:	acetylsalicyclic acid
AUC:	area under the activity-time curve
BDD:	B-domain deleted
BU:	Bethesda units
Cavg:	average activity after reaching steady state
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CL:	total clearance
CLss:	total clearance at steady state
C_{max}:	maximum activity
COA:	clinical outcome assessment
CONSORT:	consolidated standards of reporting trials
CRA:	clinical research associate
CRF:	case report form
CTCAE:	common terminology criteria for adverse events
C_{trough}:	trough activity
DMC:	Data and Safety Monitoring Committee
DNAUC:	dose-normalized area under the activity-time curve
DRE:	disease related event
ECG:	electrocardiography
eCRF:	electronic case report form
ED:	exposure day
EMA:	European Medicines Agency
EOS:	end of study
ePD:	electronic patient diary
EQ-5D-Y:	EuroQoL-Youth
ET:	early termination
FAS:	full analysis set
FVIII:	factor VIII
GCP:	Good Clinical Practice
GMP:	Good Manufacturing Practice
GMR:	geometric mean ratio
Haemo-QoL:	hemophilia quality of life questionnaire
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
HJHS:	hemophilia joint health score
HLA:	human leukocyte antigen
HRU:	healthcare resource utilization

IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Council for Harmonization
IEC:	Independent Ethics Committee
IgG1:	immunoglobulin G1
IMP:	investigational medicinal product
IR:	incremental recovery
IRB:	Institutional Review Board
IRT:	interactive response technology
ISTH:	International Society on Thrombosis and Haemostasis
IV:	intravenous
MRT:	mean residence time
NIH:	National Institute of Health
NSAID:	non-steroidal anti-inflammatory drug
PGA:	physician's global assessment
PK:	pharmacokinetics
PROMIS:	patient-reported outcomes measurement information system
PTP:	previously treated patient
QoL:	quality of life
QW:	once-weekly
rFVIII:	recombinant factor VIII
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SUSAR:	suspected unexpected serious adverse reaction
$t_{1/2}$:	half-life
V_{ss}:	volume of distribution at steady state
VWF:	von Willebrand factor
WFH:	World Federation of Hemophilia

10.9 APPENDIX 9: PROTOCOL AMENDMENT HISTORY

Not applicable.

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