AMENDED CLINICAL TRIAL PROTOCOL 05

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 Patients ≥12 Years of Age With Severe Hemophilia A
Protocol number:	**EFC16293**
Amendment number:	**5**
Compound number (INN/Trademark):	**BIVV001 (efanesoctocog alfa)**
Study phase:	**Phase 3**
Short title:	**XTEND-1**
Sponsor name:	**Bioverativ Therapeutics Inc. (a Sanofi Company)**
Legal registered address:	**225 Second Avenue Waltham, MA 02451 United States**
Monitoring Team's Representative Name and Contact Information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 05	All	20 Aug 2021, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 04	All	13 May 2020, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 03	Italy only	06 April 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	France only	06 Feb 2020, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	28 August 2019, version 1 (electronic 1.0)
Original Protocol	All	17 June 2019, version 1 (electronic 1.0)

Amended protocol 05 (20 August 2021)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is amended with the following main changes:

- Addition of statistical testing for some secondary efficacy endpoints
- Addition of an exit interview for participants from selected countries

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page and Section 2 Introduction	The international nonproprietary name (INN), efanesoctocog alfa, was added.	To introduce the INN
Section 1.1 Synopsis, Section 3 Objectives and endpoints, Section 9 Statistical Considerations	The secondary efficacy endpoint analysis was revised to allow formal statistical testing and update the multiplicity adjustment for the Haem-A-QoL (≥17 years old) Physical Health score, PROMIS Pain Intensity 3a and Hemophilia Joint Health Score (HJHS) total score measures.	To include analysis of Patient Reported Outcomes within the overall statistical testing

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 9.1 Statistical Hypotheses and 9.2 Sample Size Determination	The selection of participants to be included in the analysis for the key secondary efficacy endpoint (ie, an intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR) was updated to clarify that participants in Arm A must have at least 6 months of study duration in both this study and in observational study 242HA201/OBS16221.	Update to align with the statistical analytical plan (SAP)
Section 1.3 Schedule of Activities (SoA), Section 3 Objectives and endpoints, Section 8.1.2 Patient reported outcomes, Appendix 10.14.11 Treatment Satisfaction Questionnaire for Medication	It was clarified that the 9-item version of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) is being used, and the appendix was updated to include a copy of the full questionnaire	For clarification
Section 1.3 Schedule of Activities (SoA), Section 3 Objectives and endpoints, Section 8.1.3 Exit interviews, Appendix 10.14.16	An exit interview and footnote "kk" related to the exit interview were added in Section 1.3 Table 1. A related endpoint was added to the exploratory objective for patient reported outcome measures in Table 5. A description of the assessment is provided in Section 8.1.3 (new section) and a copy of the instrument to be administered to participants was added to the appendix.	To evaluate participants' expectations of treatment and perception of treatment impact
Section 1.3 Schedule of Activities (SoA) and Section 8.3.8 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	In Table 1, footnote "*ll"* was added to clarify that only training on the electronic patient diary (ePD) is performed at the Screening visit. ePD devices are given to the patients at the baseline visit. In Section 8.3.8, the following text was added: (if a bleed occurs during the Screening period, before the baseline visit, it will be recorded in the eCRF).	To provide clarification that bleeds occurring during the Screening period should be recorded in the eCRF and not in the ePD.
Section 1.3 Schedule of Activities (SoA)	In Table 4, the following text was added to footnote "*h"*: In the case of minor dental surgery, blood samples can be drawn within 3 days prior to the day of surgery. In addition, footnote "*h"* was added to the blood draw for FVIII activity (1-stage clotting aPTT and 2-stage chromogenic assays) to be performed on the day of surgery.	To give greater flexibility to participants who undergo minor dental surgery outside of the hospital

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1.4 Surgical dosing and Section 8.1.1.6 Surgery	In Table 8, the text was updated as follows: Major surgery, ~~only~~ allowed after 6 EDs. In Section 8.1.1.6, the following text: "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" was revised to "Participants should have at least 6 EDs to BIVV001 to be eligible for major surgery. In addition, a negative inhibitor test within 4 weeks prior to surgery is required".	For clarification
Section 6.5 Concomitant Therapy	The list of Prohibited concomitant therapy was updated to allow the one-off use of another FVIII product in exceptional circumstances (described in Section 7.1.1) and to specify that the Investigator must discuss the use of anticoagulant agents with the Medical Monitor.	For clarification and to allow the one-off use of another FVIII product in exceptional circumstances
Section 7.1.1 Definitive discontinuation	The following was added as an event requiring permanent treatment discontinuation : Use of FVIII products other than BIVV001, unless it occurs in 1 life-threatening emergency or as a result of 1 accidental use and the Sponsor agrees to retain the participant in the study. Use must be recorded in the eCRF and the Investigator should contact the Medical Monitor.	For clarification
Section 8.1.2 Patient reported outcomes	The text was revised to state that the PROMIS-SF Physical Function - SF 6b instrument does not use a 7-day recall period	For clarification
Section 9 Statistical considerations	In addition to changes described above related to formal statistical testing of secondary efficacy endpoints, changes were made throughout this section to reflect updates to the SAP. The following sections were added: 9.4.1.5 Multiplicity issue 9.4.4 Immunogenicity analysis	To be consistent with the SAP
Appendix 10.14.13 Patient Global Impression of Severity (PGIS)	A copy of the instrument for assessing "Patient Global Impression of Severity – Physical activity" was added	For completeness
Throughout the document	Editorial corrections were made	For consistency and clarity

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1 PROTOCOL SUMMARY

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 Patients ≥12 Years of Age With Severe Hemophilia A

Short title: XTEND-1

Rationale: BIVV001 is designed to be a next-generation extended half-life (EHL) blood clotting factor VIII. Preclinical and clinical experience indicate that BIVV001 has an extended half-life, which can potentially achieve and maintain higher 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 every week (QW) prophylaxis or on-demand treatment.

Objectives and endpoints

Objectives	Endpoint
Primary Efficacy Objective • To evaluate the efficacy of BIVV001 as a prophylaxis treatment	**Primary Efficacy Endpoint** • Annualized bleeding rate (ABR) in Arm A
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A who participated in Study 242HA201/OBS16221, an observational study (**key secondary endpoint)** • ABR by type and location for prophylaxis treatment per study arm • ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm • Intra-patient comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B • Percentage of participants who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen • Percentage of bleeding episodes treated with a single injection of BIVV001 per study arm and treatment regimen • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale per study arm and treatment regimen

	• Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale per study arm and treatment regimen
• To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant per study arm and treatment regimen
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS) in Arm A • Annualized Joint Bleeding Rate (AJBR) per study arm and treatment regimen • Target joint resolution at Week 52, based on ISTH criteria in Arm A
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• Changes in Haem-A-QoL (≥17 years old) total score and physical health score measures from Baseline to Week 52 in Arm A • Changes in PROMIS Pain Intensity 3a from Baseline to Week 52 in Arm A • Changes in PROMIS SF Physical Function (≥18 years old) measures from Baseline to Week 52 in Arm A
• 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
Safety Objective • To evaluate the safety and tolerability of BIVV001 treatment	Safety Endpoints • 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 • Development of inhibitors (neutralizing antibodies directed against factor VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay • The occurrence of embolic and thrombotic events
Pharmacokinetic Objective • To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	Pharmacokinetic Endpoint • 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 (CLss), accumulation index (AI), area under the activity time curve (AUC), volume of distribution at steady state (Vss), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels

Overall design:

This is a multinational, multicenter, open-label Phase 3 study of the safety, efficacy, and PK of 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 2 Arms: Arm A and Arm B. Participants currently on a prophylaxis treatment regimen with FVIII will enter Arm A and receive BIVV001 at a dose of 50 IU/kg IV QW. Participants currently on an on-demand treatment regimen will enter Arm B for 26 weeks of on-demand treatment of bleeding episodes with BIVV001 at a dose of 50 IU/kg IV on demand, then switch to receive BIVV001 at a dose of 50 IU/kg IV QW on a prophylaxis treatment regimen for 26 weeks.

Following a washout period (at least 4 to 5 days, depending on current therapy), all participants (except those in the sequential PK subgroup of Arm A) will undergo abbreviated PK sampling after the first dose of BIVV001 (Baseline). The washout period before the Baseline Visit for subjects in abbreviated PK sampling may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor. Sixteen participants at selected sites will participate in the sequential PK subgroup of Arm A and will undergo more extensive PK sampling at Baseline and again at Week 26.

Participants from any arm who undergo major surgery during the study will be included in the surgery subset. A minimum of 10 major surgeries in at least 5 patients will be targeted to assess control and prevention of bleeding in the surgical setting. The definition of major surgery is included in Section 10.7.

Disclosure Statement: This is a Parallel Treatment study with 2 arms that is open label for PTPs 12 years of age or older with severe hemophilia A.

Number of participants:

Approximately 150 participants will be enrolled to collect sufficient data to assess the safety, efficacy, and PK of IV BIVV001 in this population. Approximately 124 participants will be in Arm A, of which at least 75 participants will have had at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline. Sixteen participants from Part A will be included in the sequential PK subgroup. Approximately 26 participants will be in Arm B. For the surgery subset, a minimum of 10 major surgeries in at least 5 participants will be targeted to assess control and prevention of bleeding in the surgical setting.

Intervention groups and duration:

Participants in Arm A will receive a QW prophylactic dose of BIVV001 for 52 weeks. Participants in Arm B will receive BIVV001 on demand for 26 weeks followed by a switch to QW prophylaxis for another 26 weeks.

Study intervention(s)

Investigational medicinal product(s)

- Formulation: Recombinant coagulation factor VIII Fc-von Willebrand Factor XTEN Fusion Protein.
- Route(s) of administration: Intravenous
- Dose regimen: The dose regimen of Arm A consists of a prophylactic dose regimen of 50 IU/kg IV QW for 52 weeks. The dose regimen of Arm B is comprised of 2 parts: an on-demand dose regimen of 50 IU/kg IV for 26 weeks, and a prophylactic regimen of 50 IU/kg IV QW for 26 weeks.

Statistical considerations:

Sample size calculations: The sample size was estimated to rule out a greater-than-acceptable risk of immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 participants in the prophylaxis arm is expected to provide 104 evaluable participants with at least 50 exposure days (ED). If ≤2 participants out of 104 evaluable participants develop an inhibitor, then the upper bound of an exact 95% confidence interval would exclude 6.8%, a threshold determined at the FDA Factor VIII FDA Inhibitor Workshop that was held in 2003.

The primary efficacy objective of this study is to evaluate the efficacy of BIVV001 weekly prophylaxis as estimated by the mean ABR and one-sided 97.5% CI in Arm A. Based on currently marketed FVIII products, mean ABR during clinical trials typically ranges from 2 to 5 bleeds per year but can be as high as 6 bleeding episodes per year (1, 2, 3, 4, 5, 6, 7). This indicates that while the ABR is typically low with adequate treatment, there is variability in clinical bleeding phenotype with some severe hemophilia A participants having higher bleeding rates than others. In order to show adequate control of bleeding consistent with currently marketed FVIII products, and to account for this variability, a clinically meaningful treatment effect may be claimed if the upper bound of the confidence interval of the estimated ABR is less than or equal to 6. In a Phase 3 study of rFVIIIFc, the mean ABR for an individualized prophylaxis arm was 2.9 (6) and the dispersion factor was estimated at 2.3 (REF: data on file). Based on 2000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 participants will provide at least 90% power for the upper bound of the one-sided 97.5% confidence interval to exclude an ABR greater than 6, assuming a 15% drop out rate.

For the key secondary efficacy endpoint, an intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR will be performed using non-inferiority testing for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221. The non-inferiority margin was estimated based on the known treatment effect between on-demand and prophylaxis treatment. A meta-analysis of Phase 3 registrational studies for recombinant FVIII products that include both on-demand and prophylaxis treatment arms estimated an average reduction of 31 bleeds per year between on-demand and prophylaxis treatment regimens (5, 6, 7, 8, 9, 10, 11). The lower bound of this treatment effect was 27 bleeds per year. Using a fixed margin approach to maintain a substantial amount (85%) of the treatment effect results in a non-inferiority margin of 4. Further details of the

meta-analysis and derivation of the non-inferiority margin will be specified in the Statistical Analysis Plan. For a non-inferiority test of the null hypothesis (median difference in ABR exceeds or is equal to non-inferiority margin) versus the alternative hypothesis (median difference in ABR is less than non-inferiority margin), a sample size of 63 achieves 90% power to detect non-inferiority using a one-sided paired Wilcoxon Signed Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is 4. Without prior knowledge of the standard deviation of the paired differences, a conservative estimate of 10 was assumed. In order to account for drop-out and the use of the Per Protocol Set, at least 75 participants who have completed at least 6 months of participation in observational Study 242HA201/OBS16221 will be enrolled in Arm A.

Primary efficacy analysis: The primary analysis of the primary endpoint will estimate the mean ABR and one-sided 97.5% confidence interval using a Negative-Binomial regression model for weekly prophylaxis treatment arm (Arm A). If the upper limit of the confidence interval is less than or equal to 6, the weekly prophylaxis treatment regimen will be considered to provide adequate bleeding control.

Key secondary efficacy analysis: The analysis of the key secondary efficacy endpoint will estimate that the paired differences in ABR between BIVV001 weekly prophylaxis treatment and historical prophylaxis for participants in Arm A who have at least 6 months of participation in the study and at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221 is less than the non-inferiority margin of 4 bleeds per year using the Negative-Binomial regression model. If non-inferiority is achieved, superiority will be evaluated sequentially using the Full Analysis Set.

Secondary efficacy analyses for Haem-A-QoL (≥17 years old) Physical Health score, PROMIS Pain Intensity 3a and HJHS total score: The mixed-effects model repeated measures (MMRM) analysis will be conducted on the 3 endpoints in Arm A. The adjusted mean change in each of the 3 endpoints from baseline to Week 52, along with its 95% CI, will be estimated by the MMRM model.

Analysis of other secondary efficacy endpoints: All secondary efficacy endpoints will be summarized descriptively by treatment arm, as applicable. 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.

The multiplicity will be adjusted through a hierarchical testing framework.

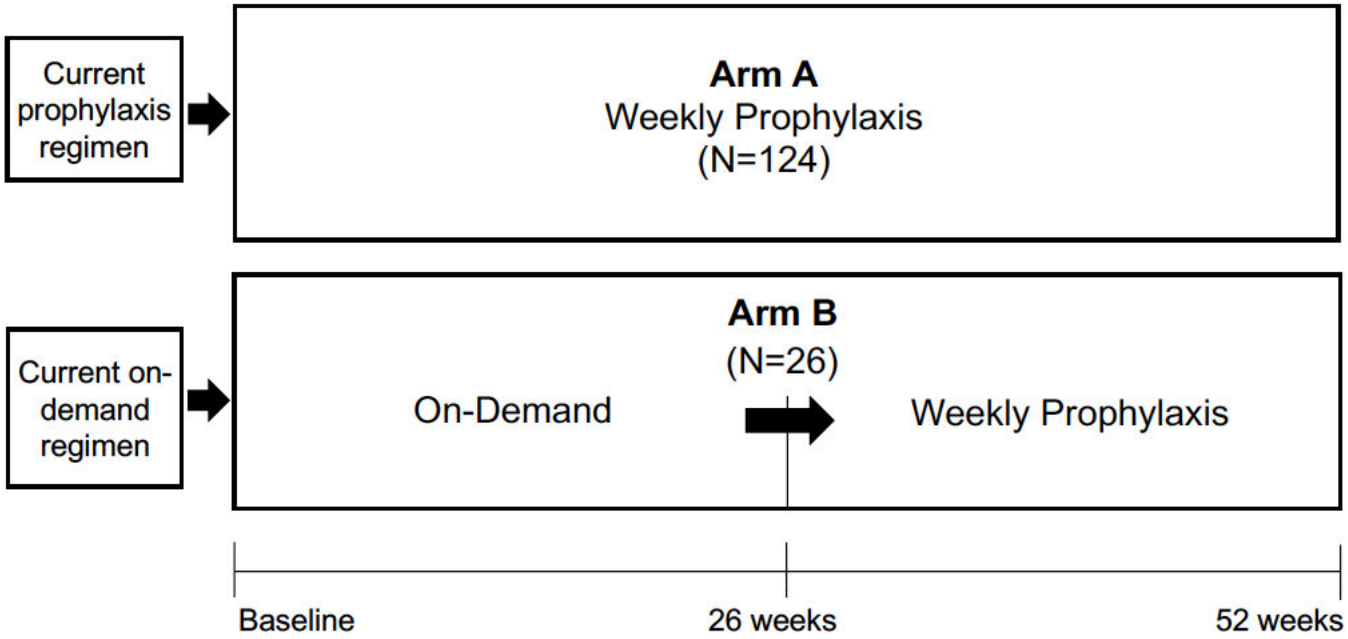
Analysis of safety endpoints: The incidence and severity of AEs will be assessed by study arm, treatment regimen, and overall. Clinically significant changes from baseline in laboratory parameters, vital signs, and physical examination findings will be summarized using descriptive statistics. In addition, incidence of inhibitor development will be assessed using an exact 95% confidence interval based on the binomial distribution. The occurrence of embolic and thrombotic events will be described.

Analysis of PK endpoints: PK parameters will be summarized descriptively for both the one-stage aPTT clotting assay and two-stage chromogenic assay.

Data Monitoring Committee: No

1.2 SCHEMA

Figure 1 - Graphical study design



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

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

Tests and assessments	Screening[a] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c,d] ±7 days	Week 39[c] ±7 days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
Participant's completion of ePD including at-home dosing, bleeding episodes, and assessment of response to treatment of bleeding episodes[aa]		<<ongoing >>							
Pharmacokinetics									
Abbreviated pharmacokinetic Sampling[bb]		X							
Sequential pharmacokinetic sampling[cc]		X			X				
FVIII peak and trough sampling[dd]			X Arm A only	X Arm A only	X	X	X		
Participant-Reported Outcomes									
PROMIS Assessments[ee]		X			X		X		
Haem-A-QoL (≥17 years old) or Haemo QoL (<17 years old)		X			X		X		
HAL (≥18 years old) or pedHAL (<18 years old)		X			X		X		
TSQM-9		X			X		X		
Patient Global Impression of Severity (activity and joint)[ff]		X			X		X		
Patient Global Impression of Change					X		X		
EQ-5D-5L		X			X		X		
Treatment Preference Survey[gg]							X		
Physical Activity Monitor (ActiGraph Activity Monitor)[hh]	X	X	X	X	X	X	X		
Exit interview[kk]							X		
Healthcare Resource Utilization		X			X		X		

BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HJHS=Hemophilia Joint Health Score HAL=Hemophilia Activities List, pedHAL=Pediatric Hemophilia Activities List, TSQM=Treatment Satisfaction Questionnaire for Medications, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity

a 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. Washout prior to the Screening inhibitor test is at least 48 hours to obtain interpretable test results.

b Washout prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. The washout period before the Baseline Visit for subjects in abbreviated PK sampling may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor.

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

d At this visit, participants in Arm B (on-demand treatment) switch to prophylaxis. Participants in the Sequential PK arm should schedule their Week 26 study visit to be 7 (+2) days after the previous prophylactic dose of BIVV001.

e 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.

f This call or visit will occur 14 (+7) days after the last dose of BIVV001, unless the participant enrolls in the open-label extension study. For France specific pregnancy testing at the safety follow-up visit refer to Section 10.11.1.

g Informed consent from the participant or 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, or the country's local regulations. Participant assent must also be obtained where applicable (according to the study site's geographic region).

h 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.

i 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.

j Collection of samples for genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate informed consent. HLA genotype will not be needed if previously documented.

k Washout prior to the Screening inhibitor test is at least 48 hours to obtain interpretable test results. Washout prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. The washout period prior to BIVV001 Day 1 dose administration for subjects in abbreviated PK sampling may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor. Washout prior to all other scheduled inhibitor tests must be at least 7±1 days. Inhibitor and ADA samples will be collected prior to BIVV001 dosing. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (ADA) 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). 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 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks of the original sample. 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.

l Participants in Arm A will have BIVV001 doses given at each applicable scheduled visit. Participants in Arm B will have BIVV001 doses at visits Day 1, Weeks 26, 39, and 52. During the Scheduled study visits, BIVV001 will be delivered via a slow push IV injection of 8 ±2 minutes, at a rate of administration determined by the participant's comfort level. For all BIVV001 injections performed at home BIVV001 will be delivered via a slow push IV injection at a rate of administration determined by the participant's comfort level according to the vial and injection rate recommendations (Table 7). Injection start and stop time will be recorded in the eCRF. Other doses may be self/caregiver administered at home (or in clinic) (Table 3)

m Vital signs include blood pressure, pulse rate, respiratory rate, and 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. Vital signs should also be taken at any unscheduled visit.

n Applicable to female participants only. A serum pregnancy test should be performed at screening. For all other time points, the choice of the pregnancy test (urine or serum) is at the discretion of the Investigator. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from further participation if the serum pregnancy result is positive.

o 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.

p 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.

q 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.

r 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. Blood samples for clinical chemistry analysis will be collected prior to BIVV001 dosing.

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

t Adverse events (AEs) and serious adverse events (SAEs) occurring after signing of the informed consent form (ICF) through the Safety Follow-Up Call or Visit will be recorded on the case report form (CRF).

u Prior and concomitant 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 CRF. Pain medication related to Hemophilia and administered within 2 weeks prior to the visit will be recorded on the CRF.

v In addition to scheduled clinic visits, telephone calls are planned approximately once a month 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.

w 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 ISTH criteria.

x For bleeding episodes treated at the study sites, the Investigator will contact the participant approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode and record the participant'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, participants will record response to bleeding episodes in the ePD.

y Anatomical structural joint-health assessment via ultrasound imaging per Joint Tissue Activity and Damage Examination (JADE) protocol and/or Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) in a subpopulation of participants from Arm A at selected sites. The Ultrasound can be performed at the Baseline visit or up to 2 weeks after the Baseline Visit.

z 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 will sign an additional consent for this research.

aa Participants will record all bleeding episodes in the ePD beginning at Baseline. Assessment of response to bleeding episodes using a 4-point bleeding response scale. The participant 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 participant's response to treatment via the eCRF.

bb All participants (except those in the sequential PK subgroup of Arm A) will undergo abbreviated PK sampling after the first dose of BIVV001 (Baseline). See abbreviated PK sampling details in Table 2.

cc Participants in the sequential PK subgroup (n=16) will undergo more extensive PK sampling at Baseline and again at Week 26. See sequential PK sampling details as described in Table 3.

dd Peak and trough sample only (collected within 30 min prior to rFVIIIFc-VWF-XTEN dosing and 15 min ± 3 min post injection. This trough sample should be collected at the same time point as the trough inhibitor and anti-drug antibody (ADA) samples taken predose (Table 2).

ee PROMIS Assessments to include Pain Intensity, Pain Interference (PROMIS-SF Pain Interference ≥18 years old or PROMIS Pediatric-SF Pain Interference <18 years old), and Physical Function (PROMIS-SF Physical Function ≥18 years old or PROMIS Pediatric-SF Physical Activity <18 years old). See Section 8.1.2.

ff Patient Global Impression of Severity (PGIS) assessment will include a single question on patient perception of activity and a single question on patient perception of joint health. See Section 8.1.2.

gg Treatment preference survey will consist of 2 questions on patient preference and a single question on Patient Global Impression of Change (PGIC). See Section 8.1.2.

hh Where available, assessments of physical activity (PA) will be done by using a triaxial medical grade accelerometer (ActiGraph Activity Monitor) worn on the nondominant wrist. Device will be worn daily for 8 consecutive days after the scheduled visits at Screening, Baseline, Weeks 4, 13, 26, 39, and for 8 consecutive days before the Week 52 visit. Refer to Section 8.1.4

ii Coagulation parameters include activated partial thromboplastin time (aPTT)

jj Please refer to Section 10.11.2 for Italy specific requirement

kk Interviews will be conducted with a subset of participants and may be done up to 6 months after the Week 52/EOS Visit, but before the EOS is declared.

ll ePD training only. ePD devices are given to the patients at the baseline visit

Table 2 - Abbreviated PK sampling schedule of activities

Assessments[a]	Pre-Dose[b]	Post-Dose[c]				
	Day 1 Week 1	Day 1 Week 1		Day 2	Day 4	Day 8[d] (study drug can be taken after assessments on Day 8)
		15 m (±3 m)	3 h (±15 m)	24 h (±2 h)	72 h (±5 h)	168 h (±5 h)
FVIII activity (measured by one-stage clotting aPTT and two-stage chromogenic assays)[e]	X	X	X	X	X	X

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

a All participants (except those in the sequential PK subgroup in Arm A) regardless of treatment arm.
b Washout of at least 96 hours (for participants who were on conventional FVIII product) and at least 120 hours (for participants who were on EHL product) prior to sample collection is required. 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
e Details regarding sample handling and volume are provided in the Central Laboratory Manual

Table 3 - PK sampling schedule of activities first dose (Week 1) and Week 26 for sequential PK subgroup

Assessment[a]	Pre-Dose[b]	Post-Dose[c]						
	Day 1/ Week 1 and Week 26[d]	Day 1		Day 2	Day 4	Day 8	Day 11	Day 15[e]
		15 m (±3 m)	3 h (±15 m)	24 h (±2 h)	72 h (±5 h)	168 h (±5 h)	240 h (±5 h)	336 h (±5 h)
FVIII activity (measured by 1-stage clotting and 2-stage chromogenic assays)[f]	X	X	X	X	X	X	X	X

Note: Participants in the sequential PK subgroup will not receive BIVV001 at Week 2 and Week 27 (or 1 week after the repeat PK).

a For a subset of participants who are in the sequential PK subgroup (n=16 from Arm A).
b For Day 1, a washout of at least 96 hours (for participants who were on conventional FVIII product) and at least 120 hours (for participants who were on EHL product) prior to sample collection is required. For Week 26, a washout of 7 (+ 2) days is required.
c All sampling times are relative to the start of injection

d At Week 26, repeat the Day 1 sampling from Pre-Dose through Day 15 hour 336. If repeat PK assessments cannot be done at Week 26, an additional visit should be done as soon as possible and prior to Week 39. In this instance, peak and trough measurements will need to be done at Week 26 and an additional visit scheduled to conduct the repeat PK profile. These assessments must be done before Week 39. Home nursing may be used.

e Study drug will be withheld on Week 2 and Week 27 to allow for continued PK sampling on Day 8 Day 11, and Day 15. Study drug should then be taken after blood draw on Day 15.

f Details regarding sample handling and volume are provided in the Central Laboratory Manual

Table 4 - 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	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[h,i]	X	
Nijmegen-modified Bethesda Assay (inhibitor assay)	X[d]	X[h]		
Anti-rFVIIIFc-VWF-XTEN Antibody (ADA)	X[d]	X[h]		
BIVV001 surgical administration		X[i]	X[j]	
BIVV001 between-clinic visit administration(s)	<continued>			
ePD training review	X[d]			

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
Participant's assessment of response to treatment of bleeding episode in the ePD[k]	<<ongoing as applicable>>			
Surgeon's/Investigator's assessment of response to surgery[l]			X	
Investigator's assessment of response to a bleeding episode treated at the study site[m]	<<ongoing as applicable>>			
Adverse events/ serious adverse event recording	<<continuous>>			
Concomitant medications, therapies, and procedures	<<continuous>>			

BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII.

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

c Day 1/Week 1 PK profile with BIVV001 must be available to determine the doses and intervals to provide hemostasis during the surgical treatment period. 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/on-demand treatment. 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.

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 comprehensive panel (includes assessments of von Willebrand Factor [VWF] 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. In the case of minor dental surgery, blood samples can be drawn within 3 days prior to the day of 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 8.1.1.6. 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 should record assessment of response to treatment of bleeding episode in the ePD, approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode.

l Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment on the ISTH 4 point response for surgical procedures scale when the participant has completed the surgical period, which includes the 24-hour postoperative period.

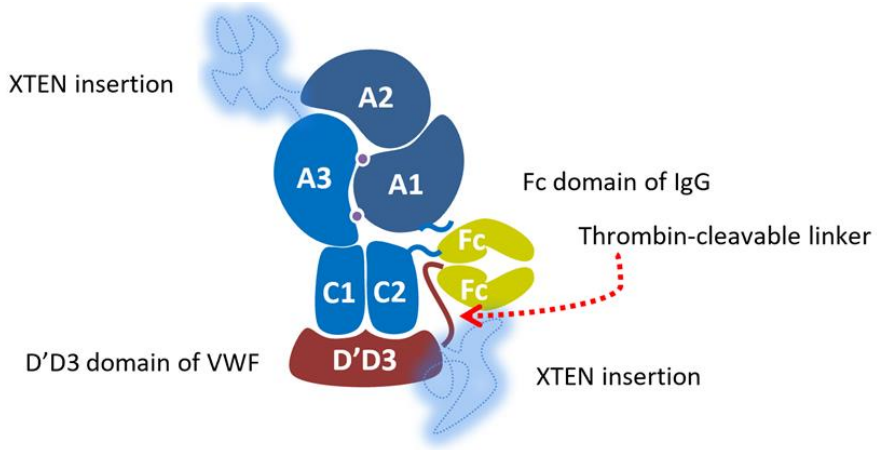
m For bleeding episodes treated in-clinic/hospital, the investigator will contact the participant approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode and record the participant's assessment of response to BIVV001 treatment on the eCRF using a 4-point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

2 INTRODUCTION

Recombinant coagulation factor VIII Fc – von Willebrand factor – XTEN fusion protein (rFVIIIFc-VWF-XTEN, efanesoctocog alfa) (BIVV001; BIIB073) is designed to be a next-generation extended half-life (EHL) blood clotting factor VIII (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), the FVIII-binding D'D3 domain of human von Willebrand factor (VWF), and 2 XTEN polypeptide linkers. The Fc, VWF, and XTEN linker portions of the molecule are each designed to extend the half-life of the FVIII molecule in plasma.

Figure 2 - Overall design and components of BIVV001



2.1 STUDY RATIONALE

BIVV001 is designed to be a next-generation extended half-life (EHL) blood clotting factor VIII. Preclinical and clinical experience indicate that BIVV001 has an extended half-life, which can potentially achieve and maintain substantially higher 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 intravenously (IV) every week (QW) as prophylaxis or on-demand treatment.

Hemophilia A is an X chromosome-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 (12, 13). The worldwide prevalence of

hemophilia A is estimated to be 1 in 10,000 and worldwide incidence is approximately 1 in 5000 male births (14). Hemophilia A appears to be equally distributed across the world (15, 16). 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 (17, 18, 19).

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 (20). 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 (21). Significant effects on physical and psychosocial well-being and quality of life and substantial financial burden have been reported in patients with severe hemophilia (22).

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 (23, 24). In the 1970s and 1980s, techniques were developed to eliminate infectious agents, including treatment with heat and detergent, as well as immunoaffinity chromatography (25).

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 (26). 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 (27) and randomized clinical trials (28, 29, 30) 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) (31, 32). With prophylactic treatment, annual median bleeding rates of less than 10 to as low as 1 bleeding episode per year have been reported (31). As a result, prophylaxis treatment regimens are being adopted as the standard of care in many countries, with episodic treatment an alternative option.

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 (33). This also includes newer generation extended half-life FVIII therapies that still require 2 to 3 injections per week to maintain activity levels ≥1% (34). 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 (IV) 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 (35).

Next-generation 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 the quality of life for hemophilia patients. Products with a longer t½ 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 (36). Indeed, it is well established that the accepted minimum targets of FVIII activity trough level (1 to 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 (37, 38, 39). The ability to increase patient protection by achieving higher sustained levels of factor activity remains a critical need for patients (40) and follows recommendations from World Federation of Hemophilia (15).

2.2 BACKGROUND

2.2.1 BIVV001

BIVV001 is a recombinant fusion protein consisting of single-chain FVIII, the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D′D3 domain of von Willebrand factor (VWF), and 2 XTEN linkers. It is believed that the plasma t½ of FVIII is prolonged by its interaction with VWF. All current EHL rFVIII products interact with VWF and have comparable circulating half-lives, consistent with upper limits on the half-life of rFVIII variants, owing to the approximate 15-hour t½ of endogenous VWF (41). BIVV001 is the first rFVIII engineered to be independent of VWF, theoretically extending its t½. Nonclinical studies of BIVV001 have demonstrated that its t½ is significantly prolonged compared with current FVIII products.

BIVV001 was engineered to include an rFVIIIFc containing a B-domain deleted human FVIII covalently linked to the Fc domain of human IgG1 that is currently approved for individuals with hemophilia A (42). 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 t½ than endogenous FVIII. The fusion of Fc to human FVIII utilized a proven approach for increasing the t½ of therapeutic proteins, including several approved drugs (43, 44). 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 t½ imposed by VWF (45, 46). 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 half-life of the fusion protein by altering the hydrodynamic radius of the molecule, which in turn reduces its clearance (47).

Brief summary of clinical data of BIVV001

The BIVV001 clinical development program includes a completed Phase 1/2a study (242HA101) and a clinically completed 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. In Study 242HA102, 24 participants had received at least 1 dose of BIVV001.

Study 242HA101

Study 242HA101 was a FIH, 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 previously treated patients (PTPs) with severe hemophilia A and completed on 12 November 2018 (last patient last visit). Participants received a single IV dose of 25 IU/kg or 65 IU/kg rFVIII comparator (Advate) in the low and high dose cohorts, respectively, 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 both 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 serious 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 (25 IU/kg) 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 of half-life was 37.6 hours for BIVV001 compared with 9.1 hours for Advate based on FVIII activity measured by the one-stage aPTT clotting assay [GMR=4.1 (95% CI: 2.9, 5.8); $p<0.001$] in the low-dose (25 IU/kg) 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 in the high-dose (65 IU/kg) cohort, 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 of half-life 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 [geometric means ration (GMR)=3.2 (95% CI: 2.8, 3.8); p<0.001] in the high-dose (65 IU/kg) cohort.

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 that was clinically completed on 12 April 2019 (last patient last visit). Participants enrolled into either Cohort 1 or Cohort 2 to receive a total of 4 once-weekly doses (Days 1, 8, 15, and 22) of BIVV001 at 50 IU/kg and 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 (168h) sample taken prior to dosing on Days 8, 15, and 22. A total of 10 participants enrolled in the 50 IU/kg dosing cohort and 14 participants enrolled in the 65 IU/kg dosing cohort. All 10 participants in the 50 IU/kg dosing cohort received 4 doses of BIVV001 and all 14 participants enrolled in the 65 IU/kg dosing cohort received 4 doses of BIVV001.

Safety results

All 24 participants enrolled received at least 1 dose of BIVV001 and were included in the safety analysis. Overall, 25 TEAEs were reported in 12 participants. There were no serious or related TEAEs reported and no participant discontinued the study due to a TEAE. The most common TEAEs were rhinitis (4 participants), arthralgia, upper respiratory tract infection, headache (2 participants, each). No inhibitor development to FVIII was detected and there were no reports of serious hypersensitivity or anaphylaxis.

Pharmacokinetic results

The PK analysis set (PKAS) included 9 participants from the 50 IU/kg dosing cohort and 14 participants from the 50 IU/kg dosing cohort who had adequate blood sample collections following BIVV001 administration.

Following BIVV001 dosing of 50 IU/kg on Day 1, mean FVIII activities based on one-stage and chromogenic assays were 45.53% and 29.37% at 72 hours, 21.56% and 13.49% at 120 hours, and 7.91% and 5.97% at 168 hours, respectively. On Day 22 with QW dosing, mean FVIII activities based on one-stage and chromogenic assays were 46.28% and 30.46% at 72 hours, 22.30% and 14.48% at 120 hours, and 9.83% and 6.74% at 168 hours, respectively.

Following BIVV001 50 IU/kg QW dosing, the geometric mean elimination half-life ($t_{1/2}$) of FVIII activities with one-stage and chromogenic assays were 41.25 and 43.87 hours, respectively. Following Day 1 dosing at 50 IU/kg, the geometric mean maximum FVIII activities (C_{max}) with one-stage and chromogenic assays were 113 and 108 IU/dL, respectively, and those following Day 22 dosing were 131 and 115 IU/dL, respectively.

Following Day 1 dosing at 50 IU/kg, the geometric mean cumulative FVIII activities ($AUC_{0\text{-}tau}$) with one-stage and chromogenic assays were 7650 and 5630 hr*IU/dL, respectively, and those

following Day 22 dosing were 8290 and 5860 hr*IU/dL, respectively, indicating minimal accumulation after the weekly dosing regimen.

Following BIVV001 dosing of 65 IU/kg on Day 1, mean FVIII activities based on one-stage and chromogenic assays were 65.65% and 35.09% at 72 hours, 26.88% and 14.32% at 120 hours, and 10.54% and 6.49% at 168 hours, respectively. On Day 22 with QW dosing, mean FVIII activities based on one-stage and chromogenic assays were 69.31% and 37.63% at 72 hours, 27.21% and 16.51% at 120 hours, and 11.81% and 7.64% at 168 hours, respectively.

Following BIVV001 65 IU/kg QW dosing, the geometric mean $t_{1/2}$ of FVIII activities with one-stage and chromogenic assays were 37.31 and 42.51 hours, respectively. Following Day 1 dosing at 65 IU/kg, the geometric mean C_{max} with one-stage and chromogenic assays were 158 and 155 IU/dL, respectively, and those following Day 22 dosing were 171 and 172 IU/dL, respectively. Following Day 1 dosing at 65 IU/kg, the geometric mean $AUC_{0\text{-}tau}$ with one-stage and chromogenic assays were 10500 and 7100 hr*IU/dL, respectively, and those following Day 22 dosing were 11200 and 7870 hr*IU/dL, respectively, indicating minimal accumulation after the weekly dosing regimen.

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

2.3 BENEFIT/RISK ASSESSMENT

Benefits

BIVV001 is designed to be a new class of blood clotting FVIII engineered to be independent of VWF. A new class of FVIII products that prevents and controls bleeding episodes for longer periods of time potentially reduces the burden of frequent IV administration and in turn, may improve adherence and outcomes, including quality of life for individuals with hemophilia A. In addition to the patient burden that results from frequent administration (33) it is well established that the currently accepted FVIII activity trough level (1 to 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 (39, 37, 38). The ability to increase patient protection by achieving higher sustained levels of factor activity remains a critical need for patients (40) and follows recommendations from the World Federation of Hemophilia (15). BIVV001 has the potential to achieve and maintain higher factor activity levels than currently available therapies, with less frequent administration, which would represent a major advance in hemophilia management.

Risks

There is a long history of therapeutic use of rFVIII products in the treatment of hemophilia A, with a well characterized safety profile. Patients treated with other rFVIII products have reported adverse reactions that include hypersensitivity, anaphylaxis, and development of inhibitors to FVIII. Based on the currently available non-clinical 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). Based on final data from these completed studies, single and repeat doses of BIVV001 were well tolerated and no safety concerns were identified.

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 half-life that offers increased protection in the treatment of individuals with hemophilia A.

More detailed information may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 5 - Objectives and endpoints

Objectives	Endpoint
Primary Efficacy Objective	**Primary Efficacy Endpoint**
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) in Arm A
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A who participated in Study 242HA201/OBS16221, an observational study (**key secondary endpoint)** • ABR by type and location for prophylaxis treatment per study arm • ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm • Intra-patient comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B • Percentage of participants who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen • Percentage of bleeding episodes treated with a single injection of BIVV001 per study arm and treatment regimen • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale per study arm and treatment regimen • Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale per study arm and treatment regimen
• To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant per study arm and treatment regimen
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS) in Arm A • Annualized Joint Bleeding Rate (AJBR) per study arm and treatment regimen • Target joint resolution at Week 52, based on ISTH criteria in Arm A

Objectives	Endpoint
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• Changes in Haem-A-QoL (≥ 17 years old) total score and physical health score measures from Baseline to Week 52 in Arm A • Changes in PROMIS Pain Intensity 3a from Baseline to Week 52 in Arm A • Changes in PROMIS SF Physical Function (≥18 years old) measures from Baseline to Week 52 in Arm A
• 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
Safety Objective • To evaluate the safety and tolerability of BIVV001 treatment	Safety Endpoints • 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 • Development of inhibitors (neutralizing antibodies directed against factor VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay • The occurrence of embolic and thrombotic events
Pharmacokinetic Objective • To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	Pharmacokinetic Endpoint • 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 (CLss), accumulation index (AI), area under the activity time curve (AUC), volume of distribution at steady state (Vss), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate joint-health structural outcomes via ultrasound using the Joint Activity and Damage Exam (JADE) protocol and/or Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)	• Changes in anatomical structural joint health outcomes via the JADE and/or HEAD-US protocol for ultrasound imaging from Baseline to Week 52 in a subpopulation at selected sites in Arm A
• To assess the impact of BIVV001 treatment on patient reported outcome (PRO) measurements and physical activity (measures per study arm and treatment regimen)	• Changes in PRO measures and physical activity per study arm and treatment regimen - PROMIS-SF Physical Function (≥18 years old) or PROMIS Pediatric-SF Physical Activity (<18 years old)

Objectives	Endpoint
	- Haem-A-QoL (≥17 years old) or Haemo-QoL (<17 years old) total score and subscale scores - PROMIS-SF Pain Interference (≥18 years old) or PROMIS Pediatric-SF Pain Interference (<18 years old) - EQ-5D-5L - Treatment Satisfaction Questionnaire for Medications (TSQM-9) - Patient Global Impression of Severity (PGIS) (activity component) - PGIS (joint component) - Change in physical activity measures (ActiGraph Activity Monitor) - Hemophilia Activities List (HAL) (≥18 years old) or pedHAL (<18 years old) • Change in HJHS total score and domain score (eg, swelling and strength) in Arm B by treatment regimen • Patient Global Impression of Change (PGIC) at Week 26 and Week 52 per study arm and treatment regimen • Patient Preference at Week 52 per study arm and treatment regimen • Exit interview at Week 52 (or at subsequent follow-up visit)

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 any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 3, open-label, multinational, multicenter study of the safety, efficacy and PK of IV BIVV001 in approximately 150 previously treated patients PTPs ≥12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). Approximately 124 participants currently on a prophylaxis treatment regimen with FVIII will enter Arm A and receive BIVV001 at a dose of 50 IU/kg IV once-weekly (QW) on a prophylaxis treatment regimen for 52 weeks. At least 75 participants of Arm A will have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline. Approximately 26 participants currently on an on-demand treatment regimen will enter Arm B and receive BIVV001 at a dose of 50 IU/kg IV on an on-demand basis for 26 weeks, then receive BIVV001 at a dose of 50 IU/kg IV QW on a prophylaxis treatment regimen for 26 weeks.

All participants (except those in the sequential PK subgroup of Arm A) will undergo abbreviated PK sampling after the first dose of BIVV001 (Baseline). Participants in the Sequential PK Subgroup of Arm A will undergo more extensive PK sampling at Baseline and again at Week 26.

In addition, participants from any arm 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 Section 10.5.

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/her 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 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) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. The washout period prior to the Baseline Visit for subjects in abbreviated PK sampling 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 124 participants will be enrolled into Arm A: Prophylaxis Treatment regimen and 26 participants will be enrolled in Arm B: On-Demand Switch to Prophylaxis Treatment regimen; 16 participants will be enrolled in the sequential PK subgroup of Arm A.

Participants who enter Arm A will receive BIVV001 as weekly prophylaxis for 52 weeks. Additional doses will be given as necessary to treat breakthrough bleeding episodes according to Section 6.1.1.2. Doses will be given in clinic according to the Schedule of Activities (Table 1). Other doses will be administered by the participant or caregiver at home, or in clinic.

Participants who enter Arm B will receive BIVV001 to treat bleeds during the 26-week on-demand period. See Section 6.1.1.3 on doses for treatment of bleeds. At Week 26, participants in Arm B will switch to prophylaxis dosing, and dose BIVV001 at 50 IU/kg once weekly, until Week 52. Additional doses will be given as necessary to treat breakthrough bleeding episodes during the 26-week prophylaxis period, according to Section 6.1.1.2. Doses will be given in clinic according to the Schedule of Activities (Table 1). Other doses will be administered by participant or caregiver at home, or in clinic.

Participants 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. Participants will be prompted to enter bleeding location, type (spontaneous or traumatic), and reasons for dosing (prophylaxis or treatment of a bleeding episode). An ePD training will be completed at the study site at the Baseline visit. Training of participants and/or caregivers should be documented in the appropriate source record. The ePD refresher training should also be provided at any point during the study.

Participants with pre-planned surgery participating in the sequential PK subgroup should not enter the surgery subgroup until repeat PK sampling has been completed 26 weeks following the BIVV001 Day 1 PK profiling.

Participants from any arm who undergo major surgery during the study will be included in the surgery subgroup. A minimum of 10 major surgeries in at least 5 participants will be targeted to assess control and prevention of bleeding in the surgical setting.

All participants will have an initial dose of BIVV001 on Day 1 and have subsequent PK assessments.

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 participants in Arm A: 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.

A subgroup of participants in Arm A (Sequential PK subgroup) will undergo Baseline BIVV001 PK sampling and repeat BIVV001 PK sampling at the Week 26 Visit (to occur 7 (+2) days after preceding prophylaxis dose).

For participants in Arm B: each scheduled study visit subsequent to Week 26 is to be arranged when a scheduled dose is due 7 days (±1 day) after the preceding prophylaxis dose. The participant should withhold the weekly prophylaxis dose, so that it can be administered at the study visit.

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 weeks (±7 days) post-Baseline, or earlier if EOS has been declared.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This multicenter, open-label, Phase 3 clinical study is being conducted to determine the safety, efficacy, and PK of BIVV001, administered as QW prophylaxis or on-demand at a dose of 50 IU/kg IV. The study will enroll previously treated patients (PTPs) with severe hemophilia A aged 12 years or older. The study design takes into consideration the published guidelines for the clinical investigation of recombinant and human plasma-derived factor VIII products per the EMA guidelines (48). Based on current treatment patterns for hemophilia A, the current study design allows for inclusion of hemophilia patients treated with either prophylactic therapy (Arm A) or on-demand therapy (Arm B).

Arm A will enroll participants currently treated with prophylactic therapy to receive prophylactic BIVV001 at QW dosing interval for 52 weeks. Arm B will enroll participants currently treated with on-demand therapy. Participants in Arm B will enter to receive BIVV001 at a dose of 50 IU/kg IV on an on-demand basis for 26 weeks, then switch to receive BIVV001 at a dose of 50 IU/kg IV QW on a prophylaxis treatment regimen for 26 weeks.

The primary efficacy endpoint will be ABR for prophylaxis treatment. 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. Efficacy assessments in clinical studies of novel hemophilia therapies have

typically compared prophylaxis to on-demand treatment regimens. However, it is now well recognized that prophylaxis is considered standard-of-care therapy for hemophilia A and reflected in current hemophilia treatment guidelines (49). Therefore, to more appropriately reflect the current practice patterns and treatment guidelines of hemophilia, the primary efficacy will be assessed for prophylaxis treatment in Arm A. Given the robust information available from previously marketed FVIII products and the well-characterized efficacy of prophylaxis treatment, an estimation approach will be used for the primary efficacy analysis. The mean annualized bleeding rate and one-sided 97.5% confidence interval will be estimated for prophylaxis treatment in Arm A using a Negative-Binomial regression model with a pre-defined success threshold based on published historical data from other marketed FVIII products. Notably, recently approved hemophilia therapies have also utilized the estimation approach for key efficacy endpoint analysis (50, 51).

In addition, a key secondary efficacy endpoint will compare ABR between BIVV001 weekly prophylaxis treatment and historical prophylaxis treatment using an intra-patient comparison for participants in Arm A who participated in observational Study 242HA201/OBS16221. A non-inferiority test using a margin that preserves a substantial amount of the treatment effect will provide meaningful data in the context of current standard of care therapy. The observational study allows prospective data collection on bleeding episodes and treatment administration for participants on marketed FVIII products. Utilization of an ePD for data collection in a similar manner to the data collection in this Phase 3 study facilitates a robust comparison to support the primary endpoint results.

While prophylactic therapy continues to evolve as the standard of care, it is well recognized that there are still many hemophilia patients around the world who continue with on-demand treatment regimens for a multitude of reasons, including high treatment burden of current prophylactic FVIII replacement therapies (33). This also includes newer generation extended half-life FVIII therapies that still require 2 to 3 injections per week to maintain activity levels ≥1% (34). On-demand treatment regimens continue to persist throughout the world, where it is estimated that one-third to one-half of patients are not on routine prophylactic therapy (52, 53). Thus, many hemophilia patients continue with on-demand treatment as overall prophylactic treatment as standard-of-care continues to become more prevalent (35). Including an on-demand arm for BIVV001 Phase 3 study is also consistent with clinical studies of recently approved hemophilia A therapies (11, 54, 51). Given that the superiority of prophylaxis treatment compared to on-demand treatment has already been established, and prophylaxis treatment is continuing to evolve as standard-of-care therapy, the traditional comparison of ABR between on-demand and prophylaxis treatment regimens will be performed as a secondary efficacy analysis. The switch design of Arm B enables an intra-subject comparison of on-demand treatment vs prophylactic treatment. Finally, Arm B will also support evaluation of efficacy of BIVV001 for on-demand treatment of bleeding episodes and surgical management.

4.3 JUSTIFICATION FOR DOSE

The dose of 50 IU/kg IV QW was selected as the prophylactic and on-demand dose in adults and adolescents ≥12 years. The once-weekly dosing schedule was chosen to optimize participant protection and to reduce the treatment burden on participants and their families. The dose was

selected and confirmed 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, and simulations were performed to understand steady state kinetics of BIVV001.

At a dose of 50 IU/kg IV QW, the model predicted a population mean time for which there is normal or near normal FVIII activity levels of greater than 40% for 3.3 days with the one-stage aPTT assay and 2.3 days with the chromogenic assay, providing a sustained level of protection. The model predicted for this dose, a population mean C_{max} of less than or approximately 150 IU/dL (120 and 159 IU/dL for the chromogenic and 1 stage aPTT assay respectively) which is the upper limit of the physiological range of FVIII activity. At the dose of 50 IU/kg, the population mean C_{trough} was 10 and 7 IU/dL, and C_{avg} was 51 and 37 IU/dL based on one-stage aPTT and chromogenic assays, respectively. Recent literature suggests that maintenance of C_{avg} >20% may significantly reduce joint bleeds in the hemophilia population (38, 55).

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 (34). BIVV001 is the first FVIII replacement therapy to overcome the half-life limitations of VWF (41) and could thus allow for higher sustained levels of protection. In addition, 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.

Development of an extended half-life FVIII replacement therapy whose half-life 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 patients with hemophilia A targeted FVIII activity levels of ≥1% (29). 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 (39, 56). Manco-Johnson and colleagues recently evaluated prophylaxis use in the United States in relation to bleeding rates and joint health outcomes (37). 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 MRI at an early age (28) 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 (57). Further evidence in severe hemophilia A patients demonstrates improved bleeding rates in patients targeting high troughs (8%-12%) vs the low troughs (1%-3%), with a similar safety profile (58). Thus, the continued development of joint damage despite prophylactic treatment suggests that current treatment regimens targeting FVIII activity trough levels of ≥1% are inadequate (40). Recommendations from World Federation of Hemophilia have supported the maintenance of higher FVIII activity levels (15).

It is recognized that chronic elevations in FVIII above the physiological upper range of 150 IU/dL in patients without hemophilia or deficits in coagulation increases thrombotic risk in a dose-dependent manner (59). Data from the 65 IU/kg cohort in Study 242HA101 demonstrate that mean C_{max} levels were maintained in the physiological upper range of FVIII activity and similar to the mean C_{max} levels for a recently approved EHL FVIII replacement therapy with a dose of 60 IU/kg (60). Additionally, following 4 weekly doses of BIVV001 with 50 IU/kg dose, the mean FVIII activity level did not reach 150 IU/dL. A population PK model using data from Studies 242HA101 and 242HA102 with a BIVV001 dose of 50 IU/kg at steady state predicted a median time above 150% activity level of 0.77 hours and 0 hours for the one-stage aPTT and two-stage chromogenic assays, respectively. Therefore, the Sponsor believes the proposed dose of 50 IU/kg will yield potential benefit by sustaining FVIII activity levels without an unacceptable thrombotic risk to participants in the Phase 3 studies.

The dose of BIVV001 recommended for treating bleeding episodes and surgical management follows published treatment guidelines to achieve minimum FVIII activity levels (16). 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 surgery as defined by WFH guidelines (16).

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 2 to 3 days postdose. Using the same dose for treatment of bleeding episodes as for the prophylactic treatment regimen is recommended to avoid complexity and dosing mistakes. Most bleeding episodes will require treatment with 1 dose of BIVV001. On clinical indication, 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 Section 10.10 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 is recommended.

4.4 END OF STUDY DEFINITION

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

- 104 participants have reached 50 exposure days (EDs) and have completed a valid inhibitor test after the 50th ED.
- At least 63 participants in Arm A have at least 6 months of participation in this study and have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline.

- Thirteen participants in the PK subgroup have completed the BIVV001 Day 1 PK profile, and a repeat 14-day BIVV001 PK profile 26 weeks later with adequate estimate of terminal half-life.

If there are participants still ongoing in the study when EOS is declared, they will return to the study for an EOS visit to complete their participation.

For France specific clarification on end of study requirements refer to Section 10.11.1.

4.5 STUDY STOPPING RULES

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

For France specific clarification on end of study requirements refer to Section 10.11.1

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 3 or more participants following administration of BIVV001 (See Section 8.3.1.1 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, are 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 equal to or greater than 12 years of age inclusive, 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 activity 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.

I 04. Current regimen includes one of the following:

- Prophylactic treatment regimen with a FVIII product or prophylactic emicizumab therapy for at least 6 months during the previous 12 months. Appropriate washout time needs to be taken into account.
- On-demand regimen with a FVIII product with a history of at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment.
    - On-demand participant is accepting to move to a prophylaxis treatment regimen after 26-week on-demand period.

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 participant or surrogate (a caregiver or a family member ≥18 years of age) to complete training in the use of the study electronic Patient Diary (ePD) and to use the ePD throughout the study.

Sex

I 08. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants
   - No contraceptive measures required for this study.

b) Female participants
   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
   - Is not a woman of childbearing potential (WOCBP), as defined in Section 10.4

or

- Is a WOCBP and using an acceptable contraceptive method as described Section 10.4 during the intervention period (at a minimum until Safety Follow-up Call or Visit). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

and

- A WOCBP must have a negative highly sensitive pregnancy test before the first dose of study intervention as described in Section 10.2. A serum pregnancy test should be performed at screening. For all other time points, the choice of the pregnancy test (urine or serum) is at the discretion of the Investigator.

Additional requirements for pregnancy testing during and after study intervention are located in Section 10.2.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

I 09. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. [In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative].

I 10. Ability of the participant or his or her 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. Any concurrent clinically significant liver disease that, in the opinion of the Investigator, would make the participant unsuitable for enrollment. This may include, but is not limited to cirrhosis, portal hypertension, and acute hepatitis.

E 02. Serious active bacterial or viral infection (other than chronic hepatitis or HIV) present within 30 days of Screening.

E 03. Other known coagulation disorder(s) in addition to hemophilia A.

E 04. History of hypersensitivity or anaphylaxis associated with any FVIII product

E 05. History of a positive inhibitor 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 06. Positive inhibitor result, defined as ≥0.6 BU/mL at Screening.

E 07. Abnormal renal function, defined as serum creatinine >2.0 mg/dL taken at Screening. For Italy-specific E07 requirements refer to Section 10.11.2.

E 08. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN) taken at Screening.

E 09. Serum total bilirubin >3 x ULN, taken at Screening.

Prior/concomitant therapy

E 10. Vaccination within 30 days of Screening.

E 11. Treatment with acetylsalicylic acid (ASA) or non-NSAID anti-platelet therapies within 2 weeks prior to screening.

E 12. 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 13. 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.

Prior/concurrent clinical study experience

E 14. Emicizumab use within the 20 weeks prior to Screening.

E 15. Previous enrolment in this study; participants who fail Screening may re-screen.

E 16. 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 17. 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 18. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 19. Any country-related specific regulation that would prevent the participant from entering the study – see Appendix 10 (Section 10.11) (country specific requirements).

E 20. 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 21. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 22. 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 23. 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. For additional France-specific exclusion criteria refer to Section 10.11.1.

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 dosing BIVV001 in Arms A and B (prophylaxis period) 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 screen failure reasons, and any serious adverse event (SAE).

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/her source documents and on the Screening log. Reasons for screen failure will be captured in the IXRS.

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 6 - Overview of study interventions administered

ARM name	Prophylaxis	On-demand
Intervention name	rFVIIIFc-VWF-XTEN (BIVV001)	rFVIIIFc-VWF-XTEN (BIVV001)
Type	Drug	Drug
Dose formulation	Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent)	Lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent)
Unit dose strength(s)	250, 500, 1000, 2000, 3000 and 4000 IU per vial	250, 500, 1000, 2000, 3000 and 4000 IU per vial
Dosage level(s)	50 IU/Kg every week	50 IU/Kg
Route of administration	Intravenous	Intravenous
IMP and NIMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement	Study Intervention will be provided in vials. Each vial will be labeled as required per country requirement.
[Current/Former name(s) or alias(es)]	---	---

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 includes either of 250, 500, 1000, 2000, 3000 or 4000 IU of BIVV001 in the formulation buffer (10 mM L-histidine, 250 mM Arginine-HCl, 5mM CaCl2, 5% (w/v) sucrose, 0.05% (w/v) polysorbate 80, pH 7.0). Please refer to the BIVV001 Directions for Handling and Administration (DHA), which is part of the 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 participants or to caretakers and legal guardians of participants enrolled in this study. Once BIVV001 is prepared for a participant, it can be administered only 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.

6.1.1.1 Study treatment schedule and administration

Instructions for the preparation and administration of BIVV001 are provided in the Directions for Handling and Administration (DHA) and the Information for Patients.

The prophylactic treatment regimen is once weekly (every 7 days) dosing with 50 IU/kg BIVV001. The dose was determined based on a population PK simulation with PK parameters derived from Study 242HA101. The aim of the 50 IU/kg IV QW treatment regimen is to provide sustained FVIII activity levels in the normal to mild hemophilia range (maintaining FVIII trough level between about 10% and 20% at Day 7) and to decrease treatment burden with once weekly dosing. (For full details see Section 4.3)

During Scheduled study visit BIVV001 will be delivered via a slow push IV injection of 8 ±2 minutes, at a rate of administration determined by the participant's comfort level. For all BIVV001 injections performed at home BIVV001 will be delivered via a slow push IV injection at a rate of administration determined by the participant's comfort level according to the vial injection rate recommendations (Table 7).

Table 7 - Home Injection: BIVV001 weight-based vial injection rate recommendations

Participant Weight	Minimum Injection Duration Per Vial
<=55 kg	2 minutes per vial
>55 kg	1 minute per vial

Any missed 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.

During the clinic visits and monthly telephone calls, the study site staff will verify whether or not a bleeding episode has occurred, and it was "spontaneous" or "traumatic". During the monthly telephone call, the participant or participant's parent/caregiver will also be reminded about the requirement that ePD data be entered as soon as possible, (within a maximum of 7 days) following an injection, as well as verify treatment regimen compliance.

6.1.1.2 Treatment of bleeding episodes during Prophylactic Treatment Regimen

The patient will be instructed by the clinic on how to treat a bleeding episode at home and record this in the ePD (Section 8.1.1.1).

Bleeding episodes requiring treatment during prophylaxis with BIVV001 will be treated with a single dose of 50 IU/kg, as described in Table 8.

Major bleeding episodes will be treated in the hospital/clinic or at home, as applicable. The participant will be instructed to consult the investigational site prior to dosing a follow-up injection. Administration of a second dose of BIVV001 as follow-up treatment will be determined by the Investigator and participant 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/she 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 was treated with an initial dose of 30 IU/kg or 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.

6.1.1.3 Treatment of bleeding episodes during the On-Demand Treatment Regimen

Bleeding episodes during the on-demand treatment regimen with BIVV001 (first 26 weeks of Arm B) will be treated with a single dose of 50 IU/kg BIVV001. Bleeding episodes will be treated in the hospital/clinic or at home, as applicable. The participant will be instructed to consult the investigational site prior to dosing a follow-up injection. Administration of a second dose of BIVV001 as follow-up treatment will be determined by the Investigator based on the participant's clinical condition. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. 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.

6.1.1.4 Surgical dosing

Minor surgeries can be performed while participating in this trial by administering a dose of 50 IU/kg BIVV001 (Table 8).

Participants from any arm who undergo major surgery during the study will be included in the surgery subset. Definitions for major and minor surgery are listed in Section 10.7.

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 8. 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 infusion will not be allowed in 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. All patients will receive a pre-operative loading dose prior to the surgical procedure. 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 WFH Guidelines.

Post-operatively, FVIII activity levels should be monitored by daily measurements of FVIII activity locally as long as the patient is hospitalized; a portion of the samples should also be sent to the central laboratory for analysis. FVIII levels should be maintained at recommended levels and duration according to WFH Guideline. 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 half-life of BIVV001, the frequency of dosing in the post-surgical period may be extended after the first week post-surgery.

Table 8 - 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 occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose may also be used.
Minor surgery	50 IU/kg	Single dose prior to surgery
Major surgery, 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 Section 10.10 for definitions of minor, moderate, and major bleeding episodes.

6.1.1.5 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 Table 8.

Section 10.9 provides detailed guidelines for washout and sampling details.

6.1.2 BIVV001 dosing calculations

6.1.2.1 Definitions of Nominal Strength versus Actual Potency

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.

Definitions

The *nominal strength* is the target potency of the vial (that is, 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU, or 4000 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.)

Calculation and Recording of Actual versus Nominal Dosing

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

Baseline PK, Sequential PK (Baseline and Week 26), and all Peak and Trough: 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 DHA 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:

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 DHA 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 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. BIVV001 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 Directions for Handling and Administration (DHA).

Any quality issue noticed with the receipt or use of an IMP/NIMP/device (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 (see Section 8.3.8).

A potential defect in the quality of IMP/NIMP/device 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/device and eliminate potential hazards.

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

6.2.3 Study drug preparation

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

6.2.4 Study drug administration

The study site staff should follow the BIVV001 DHA 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 DHA 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 DHA for specific instructions on its disposal.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label study and will not utilize randomization or blinding. The primary efficacy analysis will be based on the Full Analysis Set. The key secondary efficacy analysis will include participants in Arm A who have at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221. Because poor quality or adherence to the protocol can introduce bias towards the alternative hypothesis in a non-inferiority analysis, the key secondary efficacy analysis will be based on the Per Protocol Set. In order to minimize potential selection bias for the key secondary efficacy analysis, sites who participate in observational Study 242HA201/OBS16221 are expected to enroll qualified participants into this Phase 3 study with prior participation in the observational study. In addition, at least 75 participants with at least 6 months of participation from the observational study will be targeted to enroll in Arm A before additional participants from the observational study are enrolled in Arm A. Additional sites that are not participating in the observational study may enroll participants directly into this Phase 3 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 Team. 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 at the time of enrollment or receives during the study must be recorded along with:

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the Follow-up Visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

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 at Screening and 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. Acetylsalicylic acid (ASA) or non-NSAID anti-platelet therapies.
2. NSAIDs at doses above the maximum dose specified in local prescribing information.
3. Systemic treatment with chemotherapy and/or other immunosuppressive drugs (except for the treatment of hepatitis C virus [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 a 14 day duration. Local, topical, and/or inhaled steroid use is permitted.
4. Any other FVIII product (with exceptions listed in Section 7.1.1).
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. The Investigator must discuss the use of anticoagulant agents with the medical monitor.

As stated in Section 5.3, 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 in Arms A and B (prophylaxis period) 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 parent 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 assessments at EOS/ET visit. See the Schedule of Assessments (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 8.3.1.1 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.
- Use of FVIII products other than BIVV001, unless it occurs in 1 life-threatening emergency or as a result of 1 accidental use and the Sponsor agrees to retain the participant in the study. Use must be recorded in the eCRF and the Investigator should contact the Medical Monitor.
- A female becomes pregnant while participating in the study.
- The participant withdraws consent.

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

Participants (or their parent) may decide to discontinue IMP.

If a participant discontinues dosing due to an AE or SAE, the event should be followed as described in Section 8.3.4. 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 EOT/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

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- 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 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 withdraws 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/she 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 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 may withdraw his/her 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.

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 or she 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 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 (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 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 (Table 1).

8.1 EFFICACY ASSESSMENTS

8.1.1 Efficacy assessments

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

8.1.1.1 Bleeding episode data

In this study, a standardized definition of a bleeding episode based on International Society on Thrombosis and Haemostasis (ISTH) criteria will be used (61). 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 to 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, the Investigator will review the bleeding episode data in the ePD. If the Investigator judges that the classification by the participant/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/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 completion and Investigator review of the participant's ePD are captured by the participant using the ePD. The date and details of injection and bleeding episodes will be recorded by the participant in the ePD.
- Bleeding episodes in-clinic and doses to treat bleeds given at the clinic are captured by the Investigator in the eCRF.
- 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: 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.

8.1.1.2 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 (61, Table 9). The assessment should be performed approximately 72 hours after the initial treatment for the bleeding episode.

Table 9 - 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

8.1.1.3 Physician's Global Assessment (PGA)

The PGA is an assessment of the physician's assessment of the participant's response to treatment using a 4-point response scale (Table 10).

Table 10 - 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.

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.
Ineffective	• Routine failure to control hemostasis or hemostatic control required additional agents.

8.1.1.4 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 Hemophilia Joint Health Score (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. 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 assessed at Baseline, Weeks 26 and 52 (Section 10.13).

8.1.1.5 Target joint resolution

The Investigator will assess target joints at Baseline according to the International Society on Thrombosis and Haemostasis (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.

8.1.1.6 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 should have at least 6 EDs to BIVV001 to be eligible for major surgery. In addition, a negative inhibitor test within 4 weeks prior to surgery is required. 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 8. 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 6.1.1.4. 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/on-demand treatment. 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 remain in their assigned arms and be treated with BIVV001 during the minor intervention according to the guidelines on surgical dosing found in Section 6.1.1.4. 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 electronic case report form (eCRF). Any doses administered outside of the clinic 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 previous treated arm (Arm A or B). 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.

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 11 - 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

8.1.2 Patient reported outcomes

Table 12 shows the concepts of measurement and their related patient reported outcomes (PRO) questionnaires to be used in the trial. The Sponsor or designee will provide the translations for all PRO instruments, where translations are available. Where available, the PROs (excluding the HRU assessment) will be distributed to adult and pediatric patients as specified in the SoA (Table 1). All PROs, excluding the HRU, are collected via an electronic tablet and transmitted to a third party vendor data server over public networks using encrypted data.

Table 12 - Patient reported outcome concepts and questionnaires

Concept	PRO questionnaire	Assessment schedule
Pain and Physical Function (PROMIS Instruments)	1. PROMIS Pain Intensity 2. PROMIS-SF Pain Interference (≥18 years old) or PROMIS Pediatric-SF Pain Interference (<18 years old) 3. PROMIS-SF Physical Function (≥18 years old) or PROMIS Pediatric-SF Physical Activity (<18 years old)	Baseline, Weeks 26,52
Hemophilia specific	Haem-A-QoL (≥17 years old) or Haemo QoL (<17 years old)	Baseline, Weeks 26,52
Activities list	HAL (≥18 years old) or pedHAL (<18 years old)	Baseline, Weeks 26, 52
Treatment satisfaction	TSQM-9	Baseline, Weeks 26, 52

Concept	PRO questionnaire	Assessment schedule
Health status	EQ-5D-5L	Baseline, Weeks 26 ,52
Global impression of change	PGIC	Weeks 26, 52
Global impression of severity	1. PGIS - activity component 2. PGIS - joint component	Baseline, Weeks 26, 52
Patient preference survey	Preference questionnaire	Week 52
Healthcare resource utilization	HRU questionnaire	Baseline, Week 26, Week 52

PROMIS Instruments

PROMIS (Patient-Reported Outcomes Measurement Information System) is a system of reliable and precise measures of participant-reported heath status (62). 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 and, with the exception of the PROMIS-SF Physical Function - SF 6b instrument, have a recall period of the past 7 days. The PROMIS instruments will be administered at Baseline and Weeks 26 and 52.

PROMIS-SF v 1.0 Pain Intensity 3a

The PROMIS Pain Intensity instrument assesses pain intensity on a 5-point Likert scale (all participants). The estimated completion time is <1 minute (Section 10.14.1).

PROMIS-SF v1.0 – Pain Interference 6a

The PROMIS-SF v1.0 – Pain Interference 6a is a participant-assessed instrument and is used in adults to measure pain interference. The estimated time of completion is 1-2 minutes (Section 10.14.2).

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. The estimated time of completion is 1 minute (Section 10.14.3).

PROMIS-SF v2.0 Physical Function 6b

The PROMIS-SF v2.0 Physical Function 6b is used to access physical functioning in adults. The estimated completion time is 1 minute (Section 10.14.4).

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. The estimated completion time is 1-2 minutes (Section 10.14.5).

Haem-A-QoL

The Haem-A-Qol questionnaire for participants with hemophilia who are ≥17 years of age consists of 46 items pertaining to 10 dimensions including physical health (5 items), feeling (4 items), view of self (5 items), sports and leisure (5 items), work and school (4 items), dealing with hemophilia (3 items), treatment (8 items), future (5 items), family planning (4 items), and partnership and sexuality (3 items). Estimated completion time is approximately 14 minutes (63). The Haem-A-QOL instruments will be administered at Baseline and Weeks 26 and 52 (Section 10.14.6).

Haemo-QoL

The Haemo-QoL questionnaire for children with hemophilia is available for participants <17 years of age. Estimated completion time is approximately 14 minutes (64).The instrument (children's long version for age group II/III [8-16 years of age]) will be administered to adolescents at Baseline and Weeks 26 and 52 (Section 10.14.7).

HAL/pedHAL

The Hemophilia Activities List (HAL) and pediatric HAL (pedHAL) questionnaires will assess the participant's functional ability to perform activities of daily living (65). The HAL will be assessed in patients ≥18 years of age, and the pedHAL will be assessed in patients <18 years of age. The HAL/pedHAL will be administered at Baseline, Weeks 26 and 52 (Section 10.14.9 and Section 10.14.10).

TSQM-9

The 9-Item Treatment Satisfaction Questionnaire for Medication (TSQM-9) will assess patient satisfaction with treatment. The TSQM-9 is a validated psychometric tool that provides a general measure of patient satisfaction with medication (66). The TSQM-9 will be administered at Baseline, Weeks 26 and 52 (Section 10.14.11).

Patient global impression of severity

Patient global impression of severity (PGIS) is a single item scale in which patients indicate an overall assessment of their symptoms. Two components of the PGIS will be utilized for joint symptoms and physical activity. The PGIS will be administered at Baseline, Weeks 26 and 52 (Section 10.14.13).

Patient global impression of change

The Patient Global Impression of Change (PGIC) consists of one item adapted to the patient that evaluates all aspects of patients' health and assesses if there has been an improvement or decline

in clinical status since they started taking the study medication. The PGIC will be administered at Weeks 26 and 52 (Section 10.14.14).

Health status

The EuroQoL 5-dimension 5-level (EQ-5D-5L) is used widely in clinical trials to assess 5 dimensions of health outcome (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) from a wide variety of interventions on a common scale, for purposes of converting into a single summary score of health state. The EQ-5D-5L will be administered at Baseline, Weeks 26 and 52 (Section 10.14.12).

Patient preference survey

The patient preference survey is a 2-item questionnaire developed to evaluate the perceived impact of treatment at the end of the study. The questionnaire will be administered at the end of the study at Week 52 (Section 10.14.15).

8.1.3 Exit interviews

Qualitative semi-structured interviews will be conducted in a subset of adult participants from selected countries within 6 months of exiting the study but before the EOS is declared. Participants must be willing and able to participate in a 60-minute telephone interview. The interviews will evaluate participants' expectations from treatment, and perception of treatment impact. The interviews will be conducted by trained interviewers from RTI Health Solutions or their qualitative research partner following a semi-structured interview guide (Appendix 10.14.16).

8.1.4 Physical activity monitoring

Where available, assessments of physical activity (PA) will be done by using a triaxial medical grade accelerometer (ActiGraph Activity Monitor). Patients will be issued the wrist-worn device for continuous monitoring during pre-specified intervals as outlined in the SoA. The monitoring intervals will be 8 consecutive days after the scheduled visits at Screening, Baseline, Weeks 4, 13, 26, 39, and for 8 consecutive days before the Week 52 visit (in order to collect data for a full week 7 + 1 additional day). The device will be worn on the non-dominant wrist throughout the monitoring periods. Physical activity measures will include raw acceleration, activity counts, steps taken, physical activity intensity, activity bouts, sedentary bouts and body position among other biometric measures. The calculation of PA measures during the assessment period requires less than 50% of missing data.

8.1.5 Ultrasound measures (if applicable)

A subset of study sites will be selected to perform evaluation of treatment efficacy using the US joint images from the Joint Tissue Activity and Damage Examination (JADE) Protocol in Musculoskeletal Ultrasound (MSKUS) and/or Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). Participants at designated and MSKUS-experienced sites who are in

Arm A (prophylactic treatment), meet enrollment criteria and are >17 years of age at enrollment will have the option to participate in the US sub-study, performed according to the Schedule of Assessments (Table 1). Assessments will include the following indicators of joint health:

- Changes in synovial hypertrophy
- Changes in cartilage thickness
- Changes in synovial hyperaemia, as observed by power Doppler (JADE)

The US joint images will be scanned and sent to the third-party imaging CRO for evaluation of the indicators listed above, using two blinded readers with separate adjudication for disagreements.

8.1.6 Future scientific research

Serum and plasma samples, as well as unused backup samples, will be archived for testing by the central laboratory for future scientific research (eg, immunology assays, further coagulation assays, clarification of any clinical or laboratory AE, viral analysis). This is optional, and only participants who have consented for sample collection and use of unused samples are to be used for future research and will have the samples archived.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examination

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 CRF.

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. Vital signs should also be taken at any unscheduled visits.

8.2.3 Clinical safety laboratory assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA 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 CRF. 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 and/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 CRF.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or 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 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 Adverse event of special interest

An adverse event of special interest (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.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP;
  - Pregnancy will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])
- Symptomatic overdose (serious or nonserious) with IMP/non-investigational medicinal product (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.

8.3.1.1 Other compound specific AESI(s)

Compound specific AESIs include the following:

- 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 Common Terminology Criteria for Adverse Events (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.

8.3.2 Time period and frequency for collecting AE and SAE information

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

All SAEs and 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.

8.3.3 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs, 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.

8.3.4 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 AESIs (as defined in Section 8.3), 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 given in Appendix 3 (Section 10.3).

8.3.5 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

Adverse events that are considered expected will be specified in the reference safety information.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements

8.3.6 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention, and until the final safety Follow-up Visit or phone call.

If a pregnancy is reported, the Investigator should inform the Sponsor (or representative) within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.7 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.

8.3.8 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, Adverse Events Definitions for Recording, Evaluating, and Reporting) should be reported as an SAE. All bleeding episodes after signature of the ICF will be captured in the ePD that the participant and/or the participant's parents/caregivers will be maintaining throughout the study period (if a bleed occurs during the screening period, before the baseline visit, it will be recorded in the eCRF).

8.3.9 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 CRF.

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 in Arm A and Arm B 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 Section 10.9. Washout prior to the BIVV001 Day 1 dose administration is at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. The washout period for subjects in abbreviated PK sampling may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor

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.

If a participant has a bleed during the PK time period above, the participant should enter the bleed into the ePD, contact the Investigator as soon as possible and follow the criteria given in Section 10.9.

Arm A: Prophylaxis Treatment regimen

Participants 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 6.1.2.1).

See Table 2 for all participants except participants in the sequential PK subgroup.

If a participant has a bleed during the PK time period above, the participant should enter the bleed into the ePD and contact the Investigator as soon as possible.

Sequential PK Subgroup (Subgroup of Arm A Participants Only)

A minimum of 16 participants from Arm A will enroll in the Sequential PK Subgroup to ensure that a minimum of 13 participants complete the PK sampling as required for the estimation of the terminal half-life, as follows:

- Dosing at Day 1: A single dose of 50 IU/kg of BIVV001 under medical supervision (using a partial vial and actual potency dosing (see Section 6.1.2.1).
- Sampling for PK profiling beginning at Day 1:
  Pre-injection and 15 (±3) minutes, 3 hours (±15 minutes), 24 (±2) hours, 72 (±5) hours [Day 4], 168 (±5) hours [Day 8], 240 (±5) hours [Day 11], and 336 (±5) hours [Day 15] from the start of the injection.

Participants with pre-planned surgery participating in the PK subgroup should not enter the surgery subgroup until repeat PK sampling has been completed 26 weeks following the BIVV001 Day 1 PK profiling. If the surgery was performed before repeat PK sampling has been completed, then the participant will continue the study and replaced in PK subgroup.

Repeat PK profiling will be conducted at 26 weeks. Participants should attend the visit at trough. If the participant is unable to conduct repeat PK at Week 26, he/she should return to clinic for PK as soon as possible before Week 39.

- Dosing for repeat BIVV001 profiling: single dose of 50 IU/kg of BIVV001 (using a partial vial and actual potency dosing, see Section 6.1.2.1).
- Sampling for repeat BIVV001 profiling:
  Pre-injection and 15 (±3) minutes, 3 hours (±15 minutes), 24 (±2) hours, 72 (±5) hours [Day 4], 168 (±5) hours [Day 8], 240 (±5) hours [Day 11], and 336 (±5) hours [Day 15] from the start of the injection.

Participants in the Sequential PK subgroup may need to miss their regular BIVV001 dose due to the repeat 240 and 336 hour PK sampling; the dose immediately missed should be administered just after the 336 hour PK sample has been drawn. Participants in the sequential PK subgroup will not receive BIVV001 at Week 2 and Week 27 (or 1 week after the repeat PK). The participant will then revert to his previous dosing schedule.

If a participant has a bleed during the PK time period above, the participant should enter the bleed into the ePD and contact the Investigator as soon as possible. Instructions for repeat washout and PK sampling are provided in Section 10.9.

Arm B –On-demand switch to prophylaxis treatment regimen

Participants in Arm B will receive a Day 1 dose of BIVV001, and have abbreviated BIVV001 PK profiling as follows (see Table 2):

- Dosing at BIVV001 Day 1: single dose of BIVV001 50 IU/kg administered under medical supervision, (using a partial vial and actual potency dosing, see Section 6.1.2.1).

Abbreviated sampling beginning at BIVV001 Day 1:

- Pre-injection and 15 (±3) minutes, 3 hours (±15 minutes), 24 hours (±2) hours [Day 2], 72 (±5) hours [Day 4], and 168 (±5) hours [Day 8] from the start of the injection.

For all participants, PK assessments will be based on FVIII activity levels determined by one-stage clotting assay and two-stage chromogenic assay performed at all scheduled visits.

Pharmacokinetic assessments will be conducted on varying schedules, according to participants' group assignments. All participants will undergo PK sampling at Day 1. Participants in Arms A and B will have trough and peak sampling at all scheduled visits subsequent to Day 1. A subgroup of participants in Arm A (n=16) will undergo extensive PK sampling and a repeat PK sampling at Week 26.

Participants in the PK subgroup will be replaced if they do not complete PK sampling for the Day 1 and the repeat PK profiling. Refer to Section 10.8 for PK sampling completion criteria.

The following summarizes the PK assessments:

- Abbreviated pharmacokinetic sampling or sequential pharmacokinetic sampling, will be used to estimate PK parameters, including but not limited to the following :
  - Maximum activity (C_{max}), Elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CLss), Accumulation index (AI), Area under the activity-time curve (AUC), Volume of distribution at steady state (Vss), Mean residence time (MRT), Incremental recovery (IR), Trough activity (C_{trough}) and time above 1% FVIII activity.
- Trough and peak measurements (1-stage aPTT and chromogenic assays) for Arm A, and Arm B (post week 26):
  - Trough measurement: pre-injection.
  - Dosing: single dose of 50 IU/kg BIVV001 administered (using a partial vial and actual potency dosing, see Section 6.1.2.1).

Peak measurement: 15 (±3) minutes from the start of the injection.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are 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 (67).

Where local regulations and EC allow approval, for participants whose factor VIII genotype is not known, an optional sample will be collected at Baseline 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 may withdraw consent and request to have their 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.

8.8.1 Immunogenicity assessments

8.8.1.1 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.

8.8.1.2 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.

8.9 Healthcare resource utilization

Healthcare resource utilization (HRU) associated with medical encounters and attributable to Hemophilia A will be collected in the CRF 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 Section 10.14.17. Medical resource utilization data associated with medical encounters will be collected in the CRF 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

The primary endpoint of ABR will be analyzed using an estimation approach. The mean ABR and one-sided 97.5% confidence interval will be estimated using a Negative-Binomial regression model for the weekly prophylaxis treatment arm (Arm A). If the upper limit of the confidence interval is less than or equal to 6, the weekly prophylaxis treatment regimen will be considered to provide adequate bleeding control.

As a key secondary endpoint, an intra-patient comparison of ABR between BIVV001 weekly prophylaxis treatment and historical prophylaxis treatment for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221 will be performed using a Negative-Binomial regression model under the following statistical hypotheses:

H0 (null): Paired ABR difference (BIVV001 prophylaxis – historical prophylaxis) $\geq$ M versus H1 (alternative): Paired ABR difference (BIVV001 prophylaxis – historical prophylaxis) $<$ M

where M is the non-inferiority margin. The null hypothesis will be declared if the upper bound of the one-sided 97.5% CI is less than 4. If non-inferiority is achieved, then superiority will be evaluated sequentially using a Negative-Binomial regression model as specified above. The paired ABR ratio and 95% CI will be estimated using the FAS. The null hypothesis that the paired ABR ratio (BIVV001 prophylaxis: historical prophylaxis) is $\geq$1 will be tested against the alternative hypothesis that the ABR ratio is <1. Superiority will be declared if the upper bound of the one-sided 97.5% confidence interval is less than 1.

In addition, the 3 secondary endpoints – change from baseline to Week 52 in Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, and HJHS total score – will be analyzed via mixed-effects model repeated measures (MMRM).

9.2 SAMPLE SIZE DETERMINATION

The sample size was estimated to rule out a greater-than-acceptable risk of immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 participants in the prophylaxis arm is expected to provide 104 evaluable participants with at least 50 EDs. An ED is defined as a 24-hour period in which one or more BIVV001 injections are given. If $\leq$2 participants out of 104 evaluable participants develop an inhibitor, then the upper bound of an exact 95% confidence interval would exclude 6.8%, a threshold determined at the FDA Factor VIII Inhibitor Workshop that was held in 2003. Approximately 124 participants who are currently on a prophylaxis treatment regimen will enroll in Arm A, a 52-week prophylaxis arm, of which approximately 16 participants will be enrolled in the sequential PK subgroup. In addition, approximately 26 participants who are currently on an on-demand treatment regimen will enroll in Arm B and will receive BIVV001 on-demand for 26 weeks followed by weekly prophylaxis for 26 weeks. Thus, the overall sample size is approximately 150 subjects (ie, 124 in Arm A and 26 in Arm B).

The primary efficacy objective of this study is to evaluate the efficacy of BIVV001 weekly prophylaxis as estimated by the mean ABR and one-sided 97.5% CI in Arm A. Based on currently marketed FVIII products, mean ABR during clinical trials typically ranges from 2 to 5 bleeds per year but can be as high as 6 bleeding episodes per year (1, 2, 3, 4, 5, 6, 7). This indicates that while the ABR is typically low with adequate treatment, there is variability in clinical bleeding phenotype with some severe hemophilia A participants having higher bleeding rates than others. In order to show adequate control of bleeding consistent with currently marketed FVIII products, and to account for this variability, a clinically meaningful treatment effect may be claimed if the upper bound of the confidence interval of the estimated ABR is less than or equal to 6. In a Phase 3 study of rFVIIIFc, the mean ABR for an individualized prophylaxis arm was 2.9 and the dispersion factor was estimated at 2.3 (REF: data on file). Based on 2000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 participants will provide at least 90% power for the upper bound of the one-sided 97.5% confidence interval to exclude an ABR greater than 6, assuming a 15% drop out rate.

For the key secondary efficacy endpoint, an intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR will be performed using non-inferiority testing for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221. The non-inferiority margin was estimated based on the known treatment effect between on-demand and prophylaxis treatment. A meta-analysis of Phase 3 registrational studies for recombinant FVIII products that include both on-demand and prophylaxis treatment arms estimated an average reduction of 31 bleeds per year between on-demand and prophylaxis treatment regimens (5, 7, 8, 9, 6, 10, 11). The lower bound of this treatment effect was 27 bleeds per year. Using a fixed margin approach to maintain a substantial amount (85%) of the treatment effect results in a non-inferiority margin of 4. Further details on the meta-analysis and derivation of the non-inferiority margin will be specified in the statistical analysis plan. For a non-inferiority test of the null hypothesis (median difference in ABR exceeds or is equal to non-inferiority margin) versus the alternative hypothesis (median difference in ABR is less than non-inferiority margin), a sample size of 63 achieves 90% power to detect non-inferiority using a one-sided paired Wilcoxon Signed Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is 4. Without prior knowledge of the standard deviation of the paired differences, a conservative estimate of 10 was assumed. In order to account for drop-out and the use of the Per Protocol Set, at least 75 participants who have completed at least 6 months of participation in observational Study 242HA201/OBS16221 will be enrolled in Arm A.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 13):

Table 13 - Populations for analyses

Population	Description
All-Enrolled Analysis Set	All participants who were enrolled in the study, regardless of whether they were dosed with study drug or not. Participants will be considered enrolled when the Investigator has verified that they are eligible according to the criteria in Section 5 of the protocol. Participant disposition and enrollment summaries will be based on the All-Enrolled Analysis Set.
Full Analysis Set	All participants who receive at least one dose of study drug.
Per Protocol Set	A subset of the Full Analysis Set including participants who do not have important protocol deviations potentially impacting efficacy.
Safety Analysis Set	The safety analysis set 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.
Sequential Pharmacokinetic Subgroup	All participants who have evaluable PK profiles for both the Baseline and Repeat PK profiles, as determined by the PK scientist.
Surgery Subgroup	All participants who have undergone major surgery after the first dose of study drug.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Data for bleeding episodes will be collected by each participant via an electronic diary or, in the case of bleeding episodes occurring and/or treated at the study site, on the electronic case report form and will include type of bleed, location of bleed, and treatment dates, if applicable. This information will be used to derive the primary and related secondary efficacy endpoints.

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

All primary analyses of bleeding endpoints will be based on treated bleeding episodes consistent with ISTH criteria (61) using a standardized definition, as follows. A bleeding episode 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 less than or equal to 72 hours from the previous injection will be considered 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 more than 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 treated and untreated bleeds and the timing of prophylactic and bleed treatments (see Section 8.1.1.1).

In addition, an analysis of all bleeding episodes (including untreated bleeds) will be performed. The definition of all bleeds will follow the ISTH criteria, except that untreated bleeds will be counted based on the date and time of the bleed itself, as described in the SAP.

9.4.1 Efficacy analyses

The primary analysis of all primary, secondary, and exploratory efficacy endpoints will be based on the Full Analysis Set. The primary analysis of the key secondary endpoint will be based on the Per Protocol Set, consistent with guidelines for non-inferiority testing. In general, continuous variables will be summarized by descriptive statistics, including mean, median, SD, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category.

All analyses and summaries relating to bleeding and consumption will be based on the efficacy period (specified in SAP); data collected during the PK and surgical/rehabilitation periods (major and minor) will not be included.

All other efficacy analyses will be based on the treatment regimen period (specified in SAP), excluding data that occurs during any major surgical/rehabilitation period to avoid confounding the treatment effect.

9.4.1.1 Primary efficacy endpoint

The primary analysis of the primary endpoint will estimate the mean ABR and one sided 97.5% CI using a Negative Binomial regression model for the weekly prophylaxis arm (Arm A). If the upper limit of the CI is less than or equal to 6, the weekly prophylaxis treatment regimen will be considered to provide adequate control. A bleeding episode is counted in the primary analysis if it was treated. All types of bleeding episodes (spontaneous, traumatic, and unknown) will be included in determining the annualized number. The observed ABR for each individual participant will be calculated as the total number of bleeding episodes experienced by a participant divided by the total number of days in the respective efficacy period for each treatment regimen, multiplied by 365.25.

Sensitivity and subgroup analyses of the primary endpoint will be described in the Statistical Analysis Plan.

9.4.1.2 Key secondary efficacy endpoints

The key secondary efficacy endpoint will be analyzed for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline using the Per Protocol Set. The paired differences in ABR between BIVV001 weekly prophylaxis treatment and historical prophylaxis will be analyzed by using a Negative-Binomial regression model. Non-inferiority will be established if the upper bound of the one-sided 97.5% CI is less than 4. If non-inferiority is achieved, superiority will be evaluated sequentially using the Full Analysis Set. As a supportive analysis, the non-inferiority analysis will also be performed using the Wilcoxon signed rank test. Specifically, the median of the paired differences in ABR between BIVV001 weekly prophylaxis and historical prophylaxis will be tested using a Wilcoxon Signed Rank test, using the Per Protocol Set. The null hypothesis that the median difference is ≥4 will be tested against the alternative hypothesis that the median difference is <4. The null hypothesis will be rejected if $p<0.025$, establishing non-inferiority of BIVV001 weekly prophylaxis treatment to historical prophylaxis.

In addition, the MMRM will be conducted on each of the 3 endpoints (ie, Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, and HJHS Total Score) in Arm A, excluding visits that are coincidental with a major surgical/rehabilitation period. The MMRM model will include the baseline value of Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, HJHS total score as a covariate and visit as a fixed effect, respectively. An unstructured variance-covariance matrix within a subject will be used. The adjusted mean change in Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, HJHS total score from baseline to Week 52, along with its 95% CI, will be estimated by the MMRM model, respectively. A sensitivity analysis will be performed on the participants who roll over from lead-in observational study using the same MMRM model for the 3 endpoints as described above.

9.4.1.3 Other secondary efficacy endpoints

Annualized bleeding rate will be summarized descriptively by type of bleed (spontaneous, traumatic, or unknown) and location of bleed (joint, muscle, internal, or skin/mucosa) by study arm and treatment regimen. The summary of ABR by type and the summary of ABR by location will also be presented by age group (12-17 years, ≥18 years) for the weekly prophylaxis arm (Arm A) based on the FAS. ABR will also be summarized descriptively for all bleeding episodes, including untreated bleeding episodes, by study arm and treatment regimen.

The consumption of BIVV001 will be annualized and summarized by study arm and treatment regimen.

The number of injections and total dose of BIVV001 (IU/kg) to treat a bleeding episode will be summarized by study arm and treatment regimen 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 by study arm and treatment regimen as the number and percentage of bleeding episodes with each response (excellent, good, moderate, or no response).

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

The number and percentage of participants achieving trough FVIII activity levels above 1%, 5%, 10%, 15%, and 20% will be summarized for Arm A. 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. 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 for Arm A. 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 .

Changes in HJHS domain scores such as swelling and strength from Baseline to Week 52 will be summarized descriptively by visit and by study arm.

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 by visit and by study arm. For Haem-A-QoL, total score and subscale scores will be summarized descriptively by visit and by study arm.

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.

9.4.1.4 Exploratory efficacy endpoints

Analyses of exploratory efficacy endpoints will be described in the Statistical Analysis Plan finalized before database lock.

9.4.1.5 Multiplicity Issue

Type I error for secondary endpoints is controlled through a hierarchical testing framework. The α level is 0.05. Following the estimation approach described for the primary efficacy endpoint (ABR in Arm A), the key and selected secondary endpoints are included in the hierarchy in the following order:

1. Arm A intra-patient comparison non-inferiority (NI): ABR of BIVV001 weekly prophylaxis treatment vs. historical prophylaxis treatment (Section 9.1).
2. Arm A intra-patient comparison superiority: ABR of BIVV001 weekly prophylaxis treatment vs. historical prophylaxis treatment (Section 9.1).
3. Arm A change from Baseline to Week 52: Haem-A-QoL physical health score (Section 9.1).
4. Arm A change from Baseline to Week 52: PROMIS pain intensity 3a (Section 9.1).
5. Arm A change from Baseline to Week 52: HJHS total score (Section 9.1).

No multiplicity adjustment will be made on any secondary efficacy variable other than those mentioned above.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Analysis Set.

All safety analyses will be based on the safety period (specified in SAP). Unless otherwise specified, adverse events and laboratory evaluations occurred during major surgical/rehabilitation periods will not be included in the safety summaries.

Safety will be assessed through descriptive summaries of AEs, laboratory test results, physical examination, and vital signs.

In addition, incidence of inhibitor development will be assessed using an exact 95% confidence interval based on the binomial distribution. For the assessment of inhibitors, 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 of BIVV001. The calculation will also be performed including all participants with a valid inhibitor test following at least 25 EDs and including all participants with a valid inhibitor test, regardless of how many days they were exposed to BIVV001.

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 according to the below definition.

Safety endpoint definitions

Inhibitor development

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.

Embolic and thrombotic events

The following definition will be used for purposes of medical adjudication of the TEAE data resulting from a search conducted using the Embolic and Thrombotic Events SMQ.

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 (MRV), computed tomography venogram (CTV), magnetic resonance angiography (MRA), or computed tomography angiography (CTA) to be included as part of medical adjudication.

An indwelling central venous access device is a well-established risk factor for thrombosis (68) 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 (69) and will not be included as part of medical adjudication.

9.4.3 Pharmacokinetics

FVIII activity measured by one-stage clotting and chromogenic coagulation assay will be used to estimate PK parameters using noncompartmental analysis. Primary PK parameters of FVIII activity (C_{max}, t1/2, CL, CLss, AI, AUC, Vss, MRT, IR, C_{trough}) using the one-stage clotting assay will be estimated. These analyses will be repeated for PK parameters of FVIII activity using the chromogenic coagulation assay. Summary descriptive statistics and individual participant listings will be presented for FVIII activity (using both the one-stage clotting assay and two-stage chromogenic assay) by time point. Mean FVIII activity versus time profiles will be plotted for BIVV001 at both Day 1 and the repeat PK profile. For the abbreviated PK group, baseline PK parameters will be estimated. For the Sequential PK subgroup, geometric means for the intra-subject ratios of baseline BIVV001 to repeat BIVV001 will be provided with 95% confidence intervals for selected PK parameters. Individual PK parameter estimates will be listed for each participant and summarized descriptively by visit (Day 1 and the repeat PK profile).

The population PK analysis will be presented separately from the main clinical study report (CSR). Population PK analysis will be described fully in the population PK analysis plan and will be finalized before database lock.

9.4.4 Immunogenicity analysis

9.4.4.1 Anti-drug antibody

Participant's ADA status (ie, Pre-existing ADA, Treatment-boosted ADA, Unclassified ADA, Treatment-induced ADA, Treatment-emergent ADA [see SAP for definitions]) will be summarized on the safety analysis set. Descriptive statistics (median, 25th/75th quantiles, minimal and maximal) will be used for the analysis ADA titer of different ADA status. The number and percentage of participants with different ADA kinetic status (ie, persistent ADA response, transient ADA responses, and indeterminate ADA response [see SAP for definitions]) will be summarized for the safety analysis set.

9.5 INTERIM ANALYSES

No formal interim analyses are planned.

9.5.1 Data Monitoring Committee (DMC)

There is no DMC in this open-label study, but the study suspension rules (see Section 4.5) will be strictly adhered to throughout the study.

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 ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- 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
- 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

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. The Investigator should address any potential conflicts of interest (eg, financial interest in Bioverativ) with the participant before the participant makes a decision to participate in the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent 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.
- No study procedures other than the informed consent can be performed before the informed consent is signed by the patient and authorized representative.
- 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-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 are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature. The ICF will also contain a separate section for the joint ultrasound sub-study (only at participating sites). The participants will have to check-off agreement to participate/not participate in the sub-study and provide a separate signature.

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 (Global 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.

- 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 (70, 71). Additionally, differential responses to FVIII products may occur in different haplotypes of FVIII that also differ across racial and ethnic groups (72).
- The participant must be informed that his/her 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.
- The participant must be informed that his/her 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.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly 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 clinical trial register (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 CRF 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 closure

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

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 14 will be performed by the central laboratory.

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 4.5 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 14 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	• Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count and differential • Hemoglobin (Hgb) • Hematocrit (HCT)
Clinical chemistry[a]	• Alanine amino transferase (ALT) • Aspartate amino transferase (AST) • Alkaline phosphatase (ALP) • Gamma glutamyl transferase (GGT) • Bilirubin • Blood Urea Nitrogen (BUN) • Creatinine • Glucose [non-fasting] • Total protein • Potassium • Sodium • Chloride
Von Willebrand comprehensive panel	• VWF ristocetin cofactor activity • VWF antigen
Immunogenicity	• Nijmegen modified Bethesda inhibitor assay • ADA • ADA subtype
Coagulation parameters	• Activated partial thromboplastin time (aPTT)
Other tests and assessments	• Ultrasound assessment using the JADE and/or HEAD US protocol (select sites only) • Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • HIV (HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen), HBV (HBV surface antigen [HBsAg], anti-HBV surface antibody and anti-HBV core antibody) and HCV (anti-HCV antibodies) for patients who have been historically negative Follicle stimulating hormone and estradiol (as needed in women of non-child bearing potential only) • CD4 count and viral load (for patients known to be HIV positive)

NOTES :

a All events which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

b Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

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

- Abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), 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 AE or SAE if they fulfill 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.

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.

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.
- The Investigator will also consult the Investigator's Brochure (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.

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 the 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 is not available.
- In rare circumstances, 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 the Study Manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

ACCEPTABLE METHODS[d]
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c.) [Male condoms must be used in addition to hormonal contraception]. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

d) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

e) Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive BIVV001.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the

neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.6. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study

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 (see Section 8.3.1). Treatment of overdoses are described in Section 8.4.

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

10.6 APPENDIX 6: GENETICS

Not applicable.

10.7 APPENDIX 7: 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.

10.8 APPENDIX 8: ASSESSMENTS

Response to treatment: Defined as the number of injections and dose of BIVV001 to treat a bleeding episode, percentage of bleeding episodes treated with a single injection, participant's assessment of response to BIVV001 treatment of individual bleeding episodes using a 4-point response scale, investigator's global assessment of participant's response to BIVV001 treatment using a 4 point response scale.

Investigator's Assessment of Response: Uses a 4 point response scale

Response to Surgery: Investigator's/Surgeon's assessment of participant's response to surgery with BIVV001 using a bleeding response scale when participant has completed the surgical period including a 24 hour post-operative time period.

10.9 APPENDIX 9: 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 48h before Screening inhibitor test to obtain interpretable test results. 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
Day 1 abbreviated PK sampling: Arm A (except sequential PK subgroup) and Arm B	**Washout** ☐ First attempt: Washout of at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product; repeat this washout if participant treats a bleed prior to 96 hours for conventional FVIII product and at least 120 hours for EHL FVIII product (follow second attempt) [a)] ☐ Second attempt: 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 [a)] **PK Sampling** ☐ 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 but prior to completing the PK sampling period, PK sampling will be stopped at the time of the treatment and no repeat PK sampling is required. ☐ The participant should continue with the study schedule.
Sequential PK Sampling: Arm A Sequential PK Subgroup	
Day 1 sequential PK sampling	**Washout** ☐ First attempt: Washout of at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product; repeat this washout if participant treats a bleed prior to 96 hours for conventional FVIII product and at least 120 hours for EHL FVIII product (follow second attempt) ☐ 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.
	PK Sampling ☐ First attempt: PK sampling period with collection of PK samples (Table 3) to 336 hours (Day 15) 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. If the participant treats the bleed prior to collection of the 240-hour (Day 11) sample, a second attempt (repeat) PK sampling period should be conducted. If the participant treats a bleed

	after the collection of the 240-hour (Day 11) sample, no repeat PK sampling is required. ☐ Second attempt: Participants are required to undergo a 336 hour (Day 15) washout from the prior BIVV001 dose, which is then followed by the PK sampling period with collection of PK samples (Table 3) to 336 hours (Day 15). ☐ If the second attempt at PK sampling period fails due to the participant treating a bleed prior to collection of the 240-hour (Day 11) 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.
Week 26 repeat sequential PK sampling	**Washout** ☐ No washout required. Participants should visit clinic 7 (+2) days after previous dose. ☐ If the participant has treated a bleeding episode since his last dose, the scheduled visit should be postponed for 7 (+2) days after previous dose. **PK Sampling** ☐ First attempt: PK sampling period with collection of PK samples (Table 3) to 336 hours (Day 15) 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. If the participant treats the bleed prior to collection of the 240-hour (Day 11) sample, a second attempt (repeat) PK sampling period should be conducted. If the participant treats a bleed after the collection of the 240-hour (Day 11) sample, no repeat PK sampling is required. ☐ Second attempt: Participants are required to undergo a 7 ±1 day washout after previous dose, which is then followed by the PK sampling period with collection of PK samples (Table 3) to 336 hours (Day 15). ☐ If the second attempt at PK sampling period fails due to the participant treating a bleed prior to collection of the 240-hour (Day 11) 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: Arm A (All Participants) and Arm B (All Participants after Week 26)	**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 15-min 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

10.10 APPENDIX 10: 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

10.11 APPENDIX 11: COUNTRY-SPECIFIC REQUIREMENTS

10.11.1 France

Change to the protocol for France only: new text addition is presented as **bold** text and deleted text is presented in ~~crossed~~ text:

Section 1.3 Schedule of Activities (Section 1.3, 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, d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
Pregnancy[n]	X	X		X	X	X	X		X[ii]

[f] This call or visit will occur 14 (+7) days after the last dose of BIVV001, unless the participant enrolls in the open-label extension study. **For female participants in France, a visit must be conducted for purposes of pregnancy testing**.

[ii] The pregnancy test at the Safety Follow up visit is to be performed in France only.

Section 4.4 End of study definition (Section 4.4)

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

- 104 participants have reached 50 exposure days (EDs) and have completed a valid inhibitor test after the 50th ED.
- At least 63 participants in Arm A have at least 6 months of participation in this study and have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline.
- Thirteen participants in the PK subgroup have completed the BIVV001 Day 1 PK profile, and a repeat 14-day BIVV001 PK profile 26 weeks later with adequate estimate of terminal half-life.

If there are participants still ongoing in the study when EOS is declared, they will return to the study for an EOS visit to complete their participation.

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

Section 4.5 Study stopping rules (Section 4.5)

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

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

Section 5.2 Exclusion Criteria (Section 5.2)

The following exclusion criterion has been deleted:

~~E 23. Any specific situation during study implementation/course that may raise ethical considerations~~

The following exclusion criterion has been added:

E25: History of an unprovoked venous thromboembolism, myocardial infarction within 12 months prior to screening, or occlusive cerebral vascular accident within 12 months prior to screening. Patients who have experienced thrombosis associated with indwelling venous access may be enrolled.

10.11.2 Italy

Change to the protocol for Italy only: new text addition is presented as **bold** text and deleted text is presented in ~~crossed~~ text:

Section 5.2 Exclusion Criteria (Section 5.2)

The following exclusion criterion has been replaced:

~~E07 Abnormal renal function, defined as serum creatinine >2.0 mg/dL taken at Screening~~

by:

E07 Impaired renal function, defined as creatinine clearance by Cockcroft-Gault formula <60 mL/min (for ≥18 years) or glomerular filtration rate by Bedside Schwartz formula <60 mL/min/1.73m2 (for <18 years)

Section 1.3 Schedule of Activities (Section 1.3, Table 1)

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

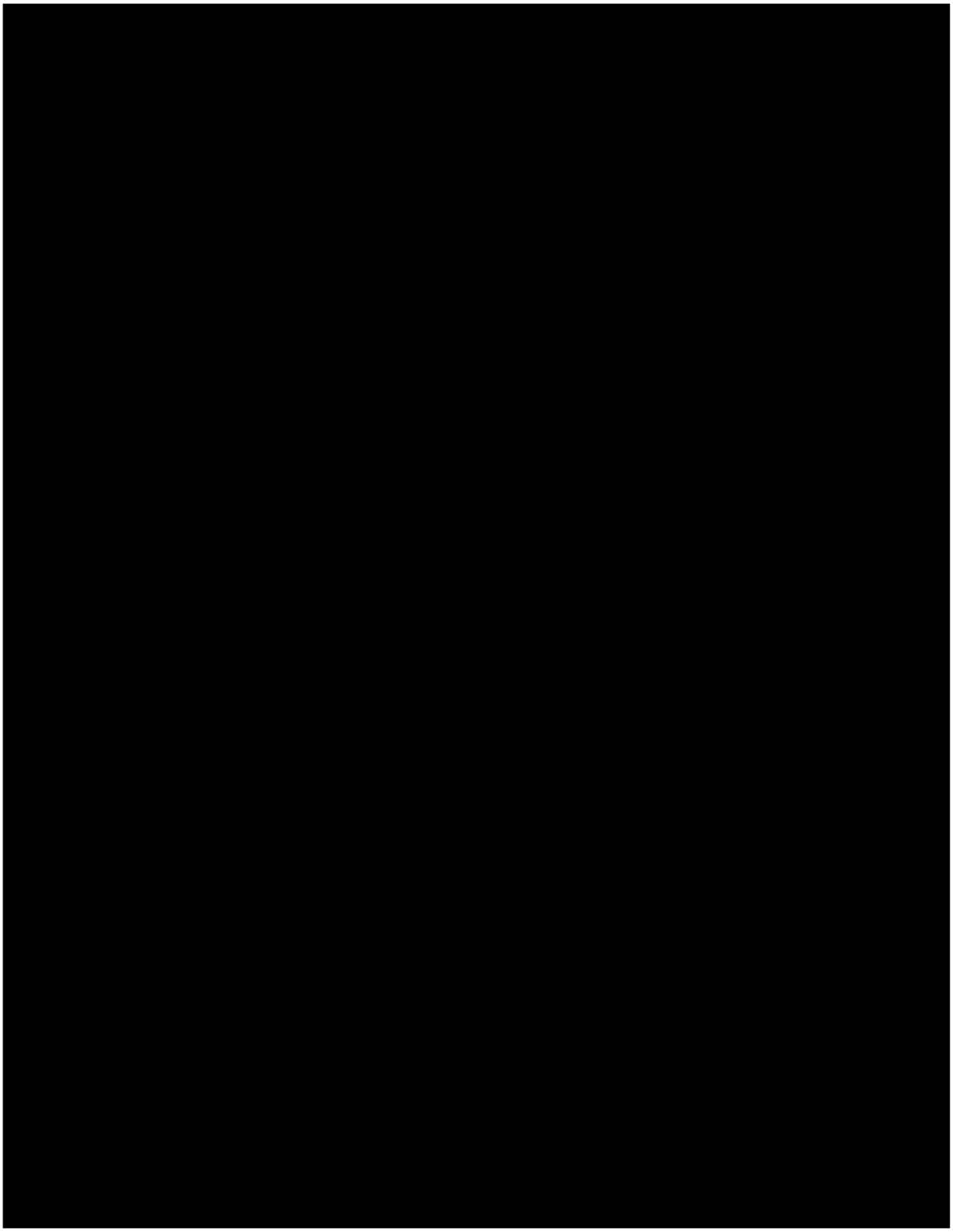
Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c, d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
Height	X	**X**[ii]			**X**[ii]		**X**[ii]		
Physical Exam	X	X	X	**X**	X	**X**	X	X	

ii Only applicable in participants 12-17 years of age

10.12 APPENDIX 12: ABBREVIATIONS

ABR:	Annualized Bleeding Rate
AESI:	adverse event of special interest
AIFA:	Agenzia Italiana del Farmaco
AJBR:	annualized joint bleeding rate
ANSM:	Agence Nationale de Sécurité du Médicament et des Produits de Santé
AUC:	area under the activity time curve
CL:	total clearance
CLss:	total clearance at steady state
C_{max}:	maximum activity
C_{trough}:	trough activity
eCRF:	electronic Case Report Form
ED:	exposure days
EHL:	extended half-life
ePD:	electronic patient diary
FVIII:	factor VIII
HEAD-US:	Hemophilia Early Arthropathy Detection with Ultrasound
HJHS:	Hemophilia Joint Health Score
ISTH:	International Society on Thrombosis and Haemostasis
JADE:	Joint Tissue Activity and Damage Examination
MRT:	mean residence time
NIMP:	non-investigational medicinal product
PGA:	Physician's Global Assessment
PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PK:	pharmacokinetics
PTP:	previously treated patient
QW:	every week
SAE:	serious adverse event
SD:	standard deviation
$t_{1/2}$:	elimination half-life
TESAE:	treatment emergent serious adverse events
Vss:	volume of distribution at steady state

10.13 Appendix 13 Hemophilia Joint Health Score (HJHS)



10.14 Appendix 14: Patient Reported Outcomes

10.14.1 PROMIS-SF v 1.0 Pain Intensity 3a

6 March 2017

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10.14.2 PROMIS-SF v1.0 – Pain Interference 6a

2 June 2016
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10.14.3 PROMIS Pediatric SF v2.0 – Pain Interference 8a

Last Updated: 28 July 2016
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10.14.4 PROMIS-SF v2.0 Physical Function 6b

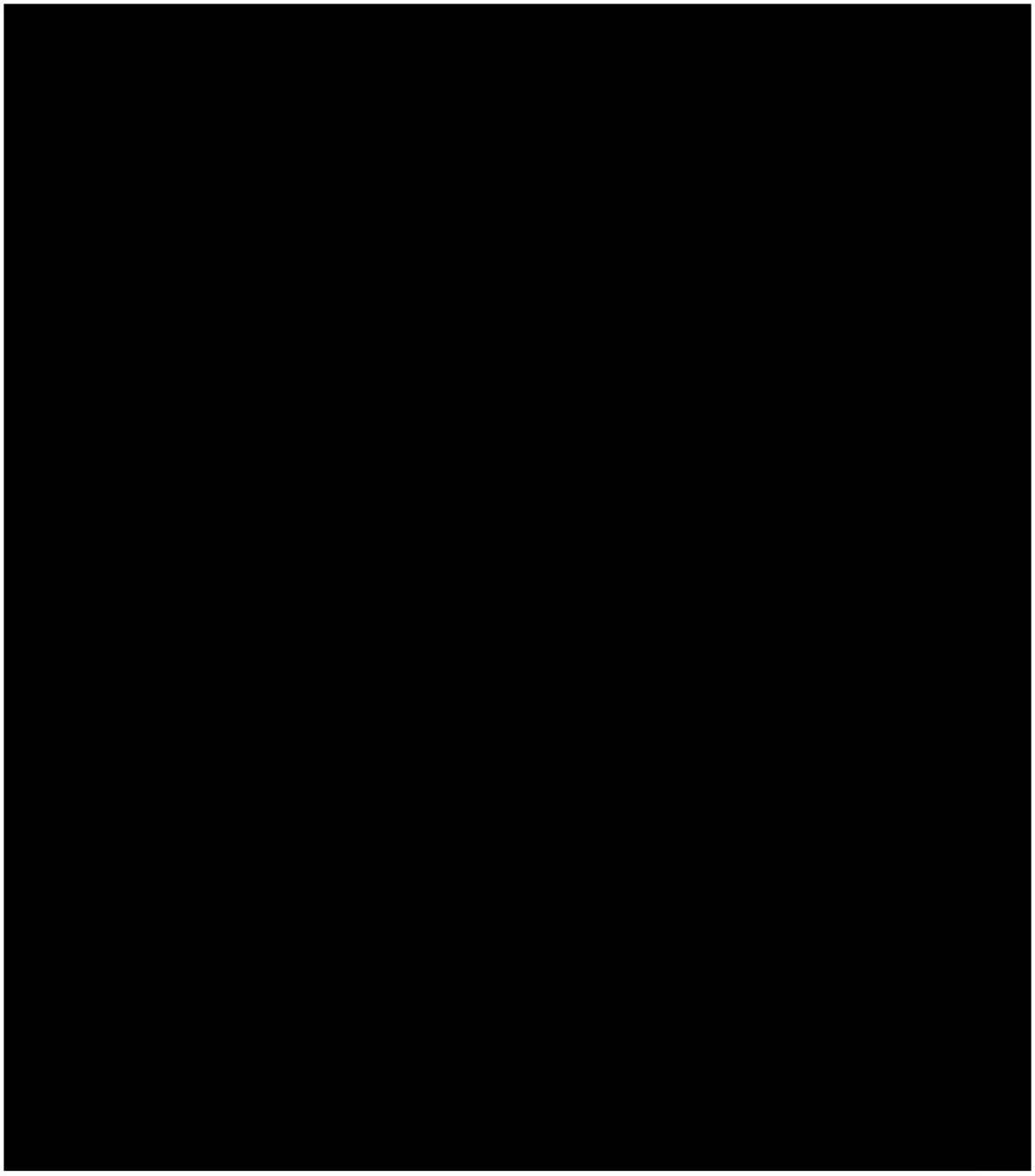
31 July 2018

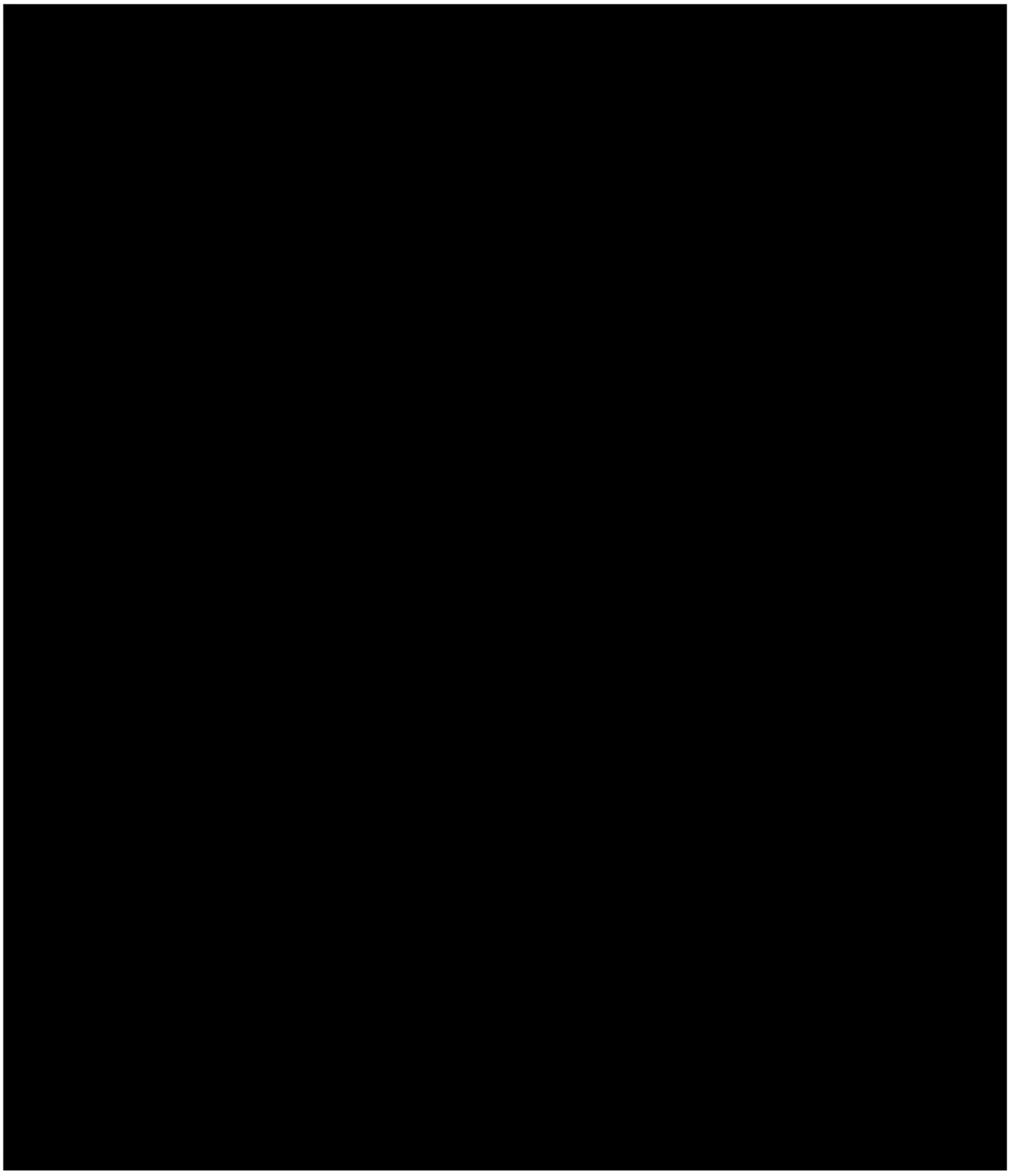
Page 1 of 1

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

 Page 1 of 1

10.14.6 Haem-A-QoL





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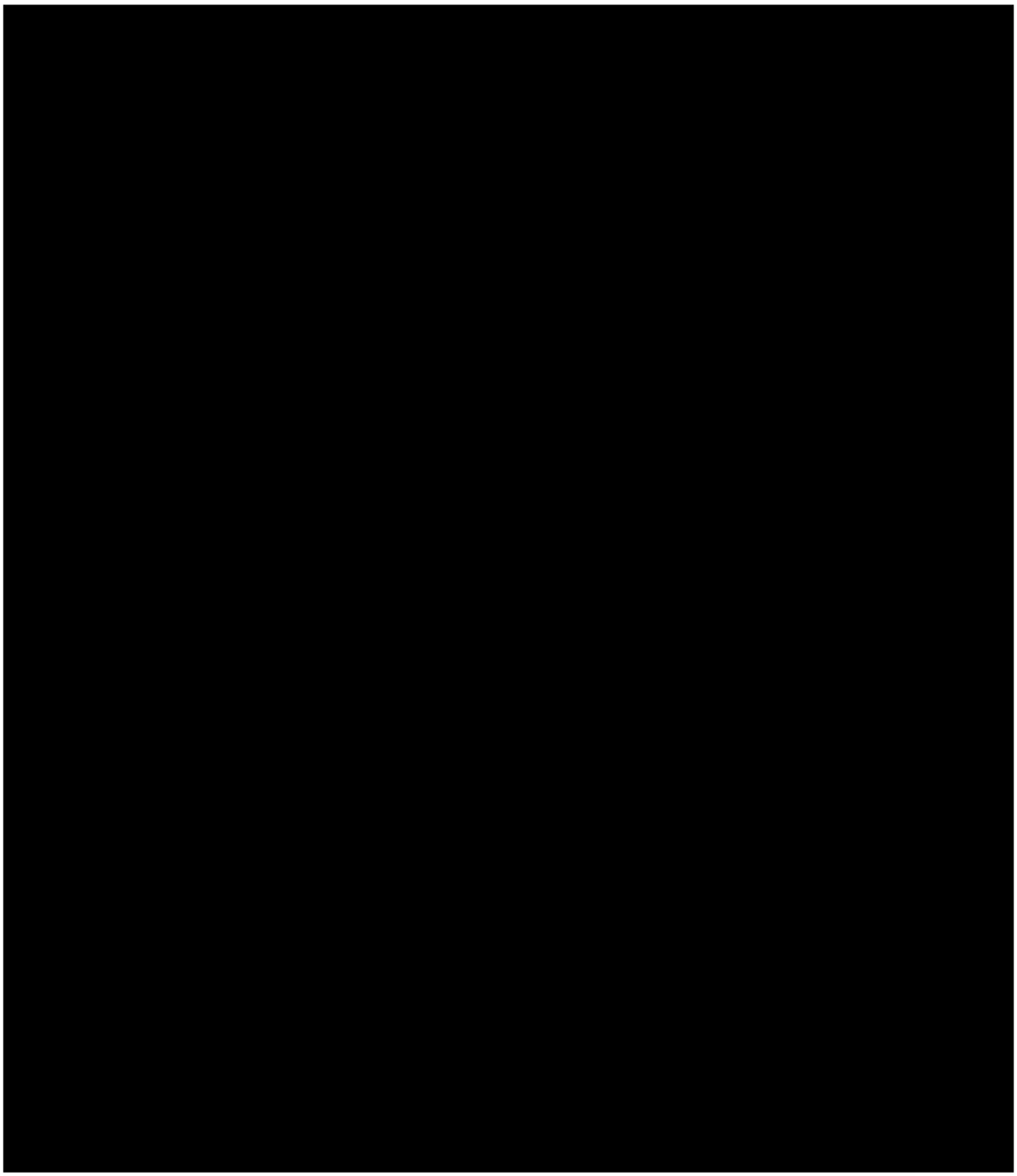

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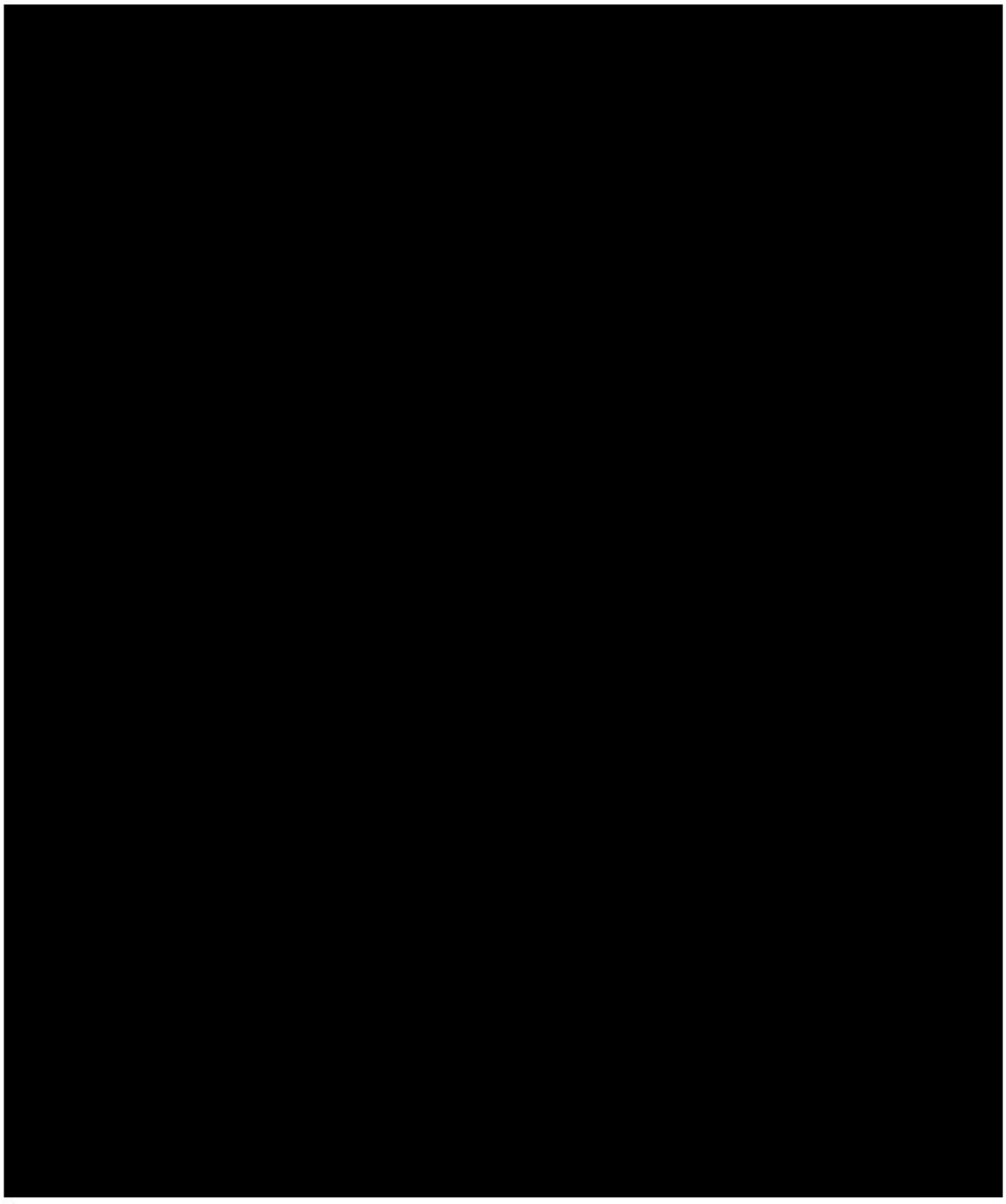

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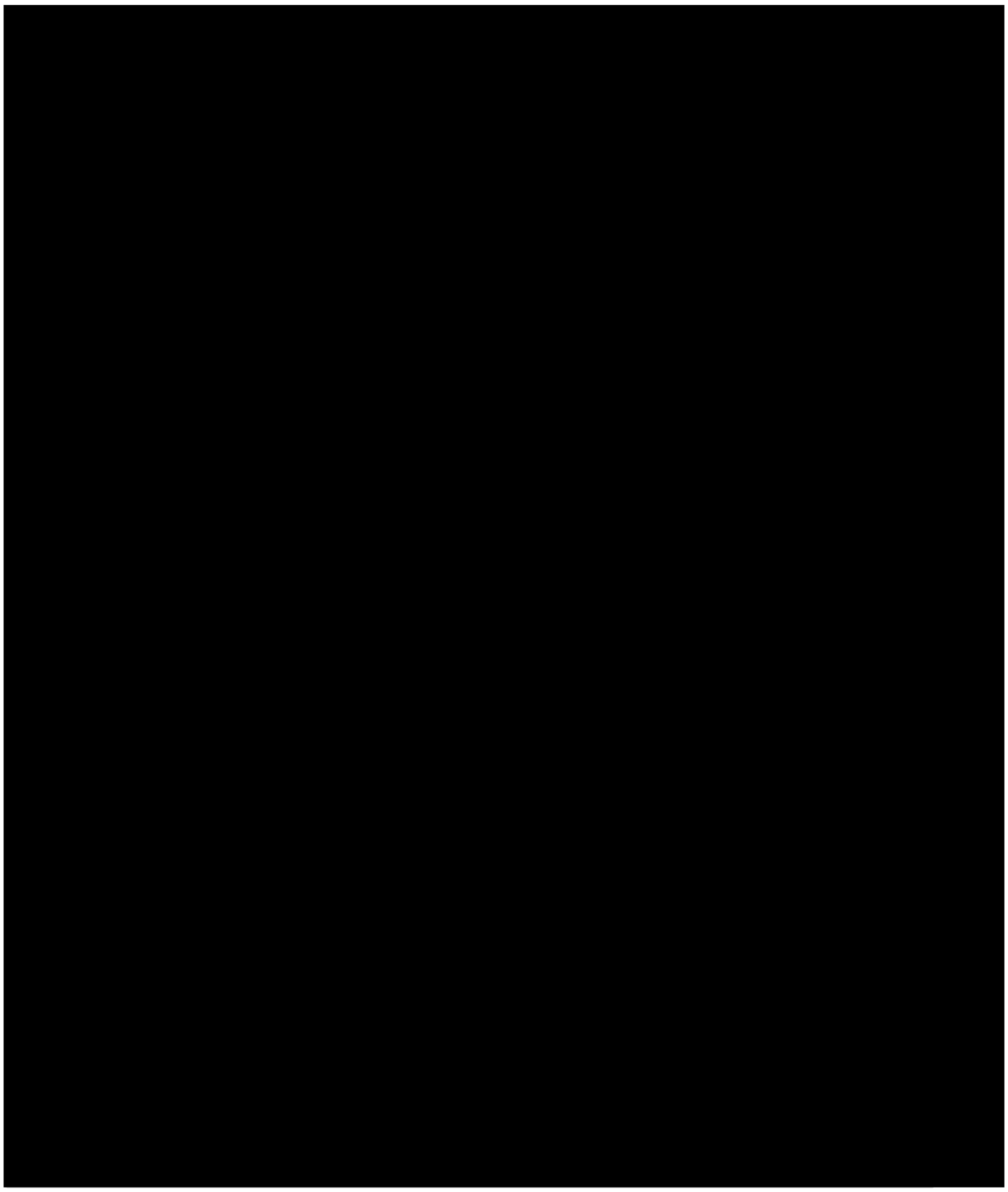

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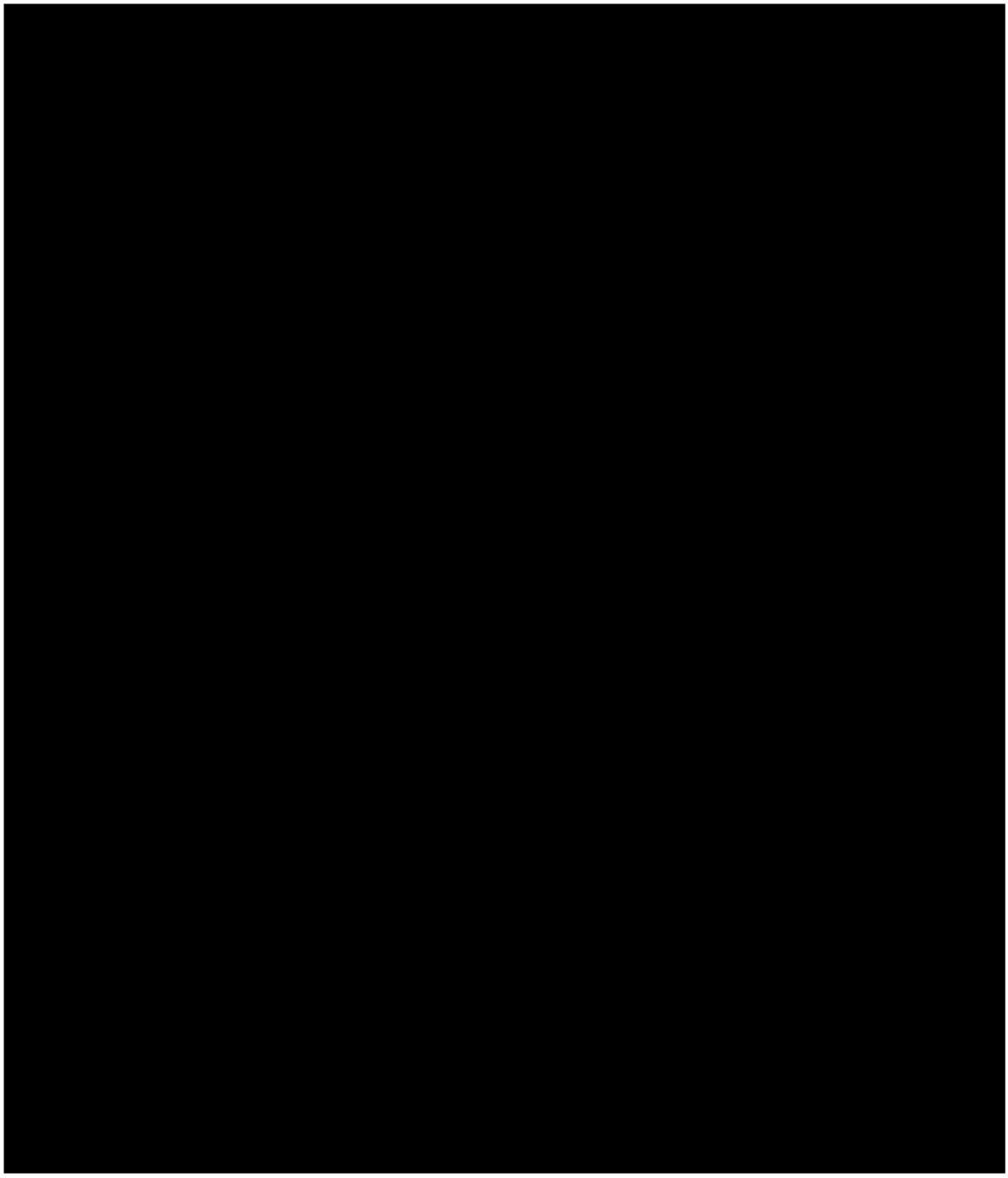

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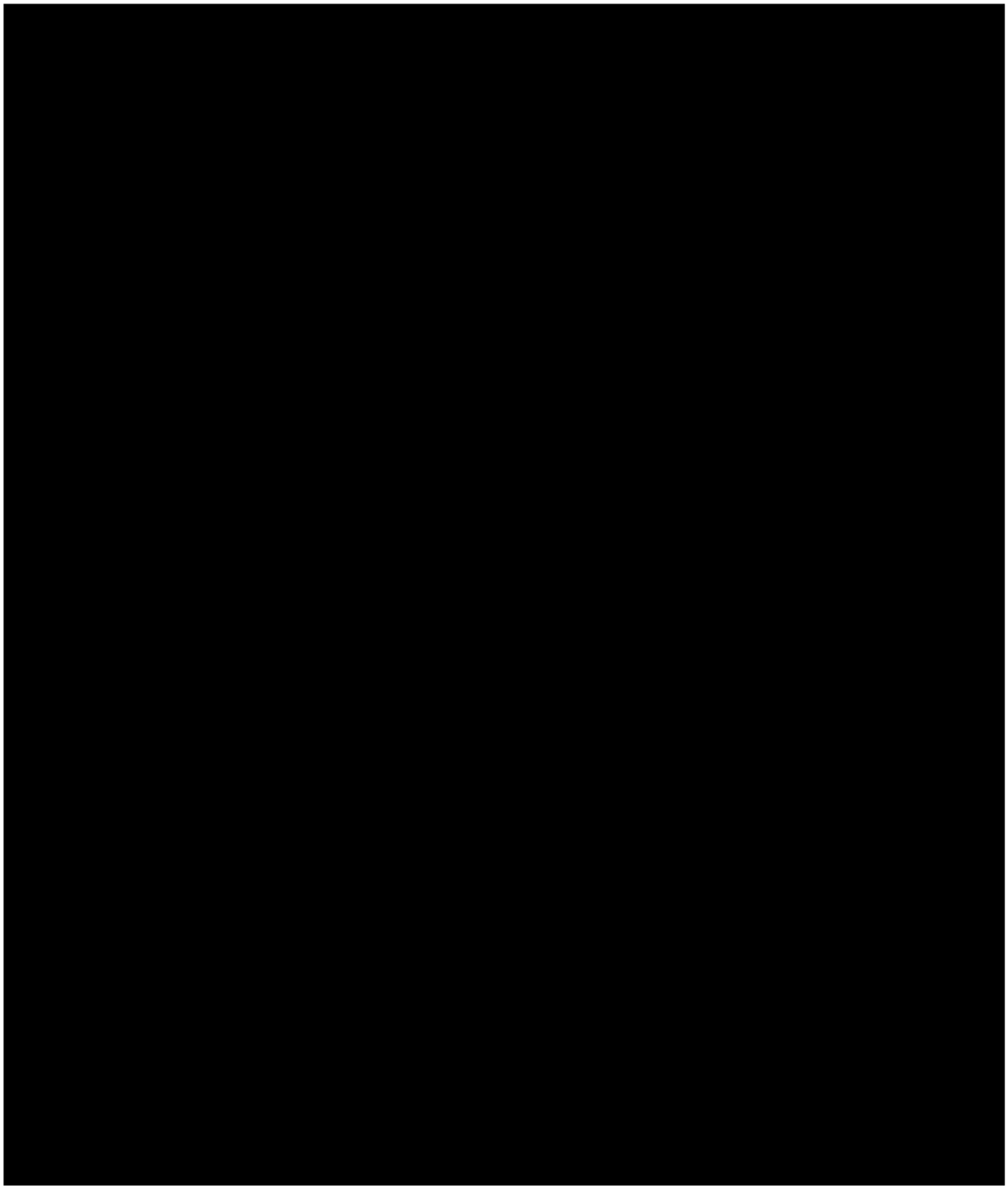

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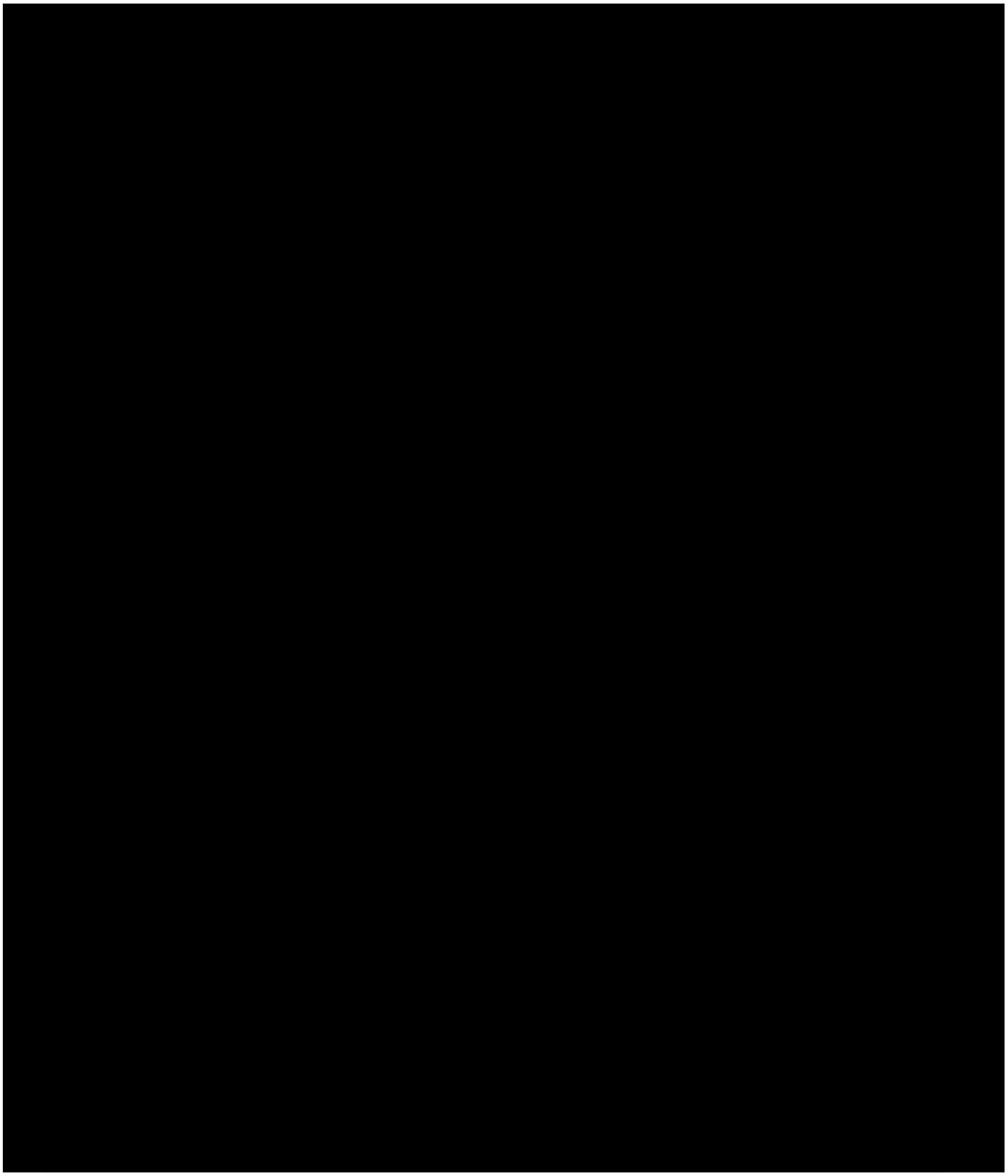
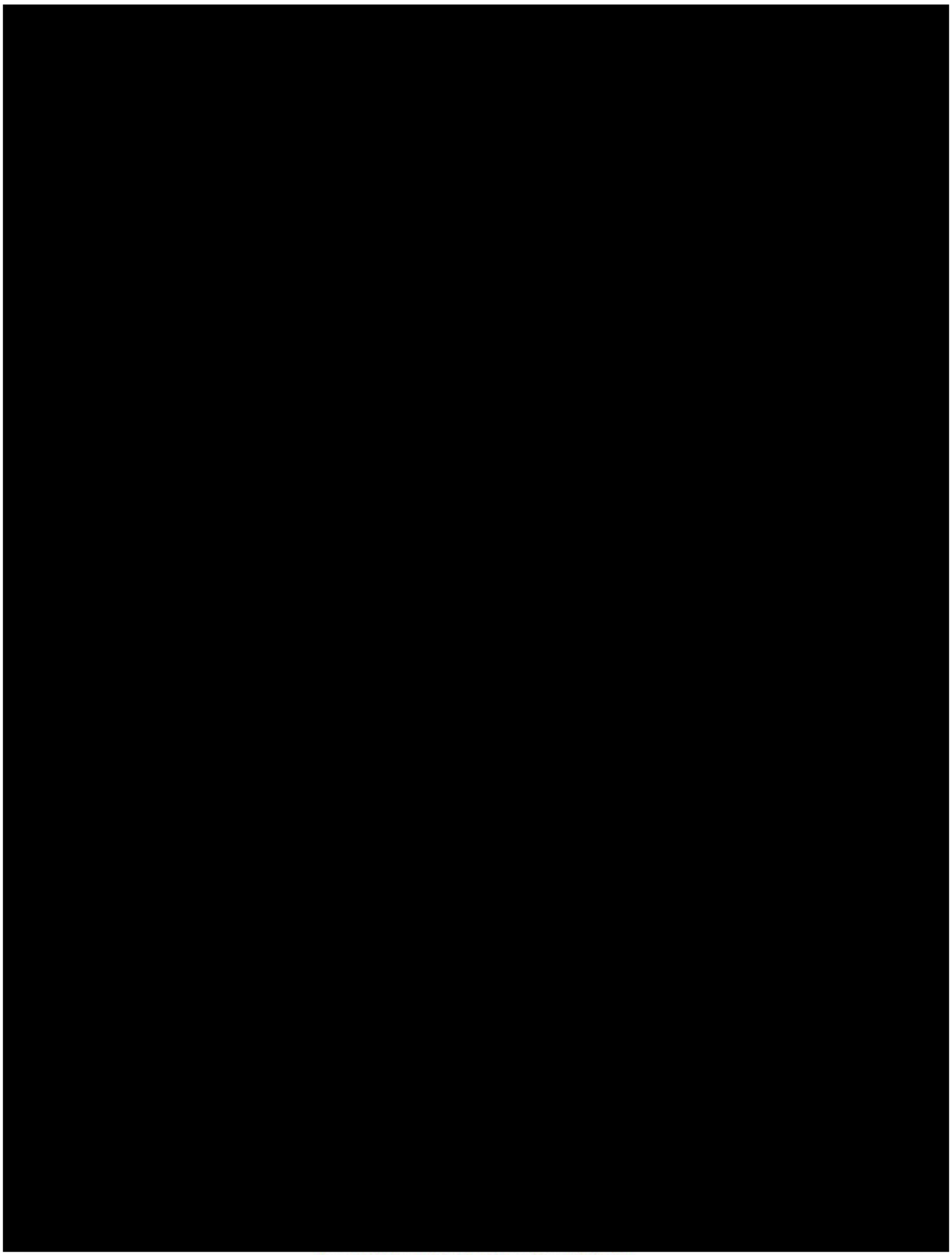
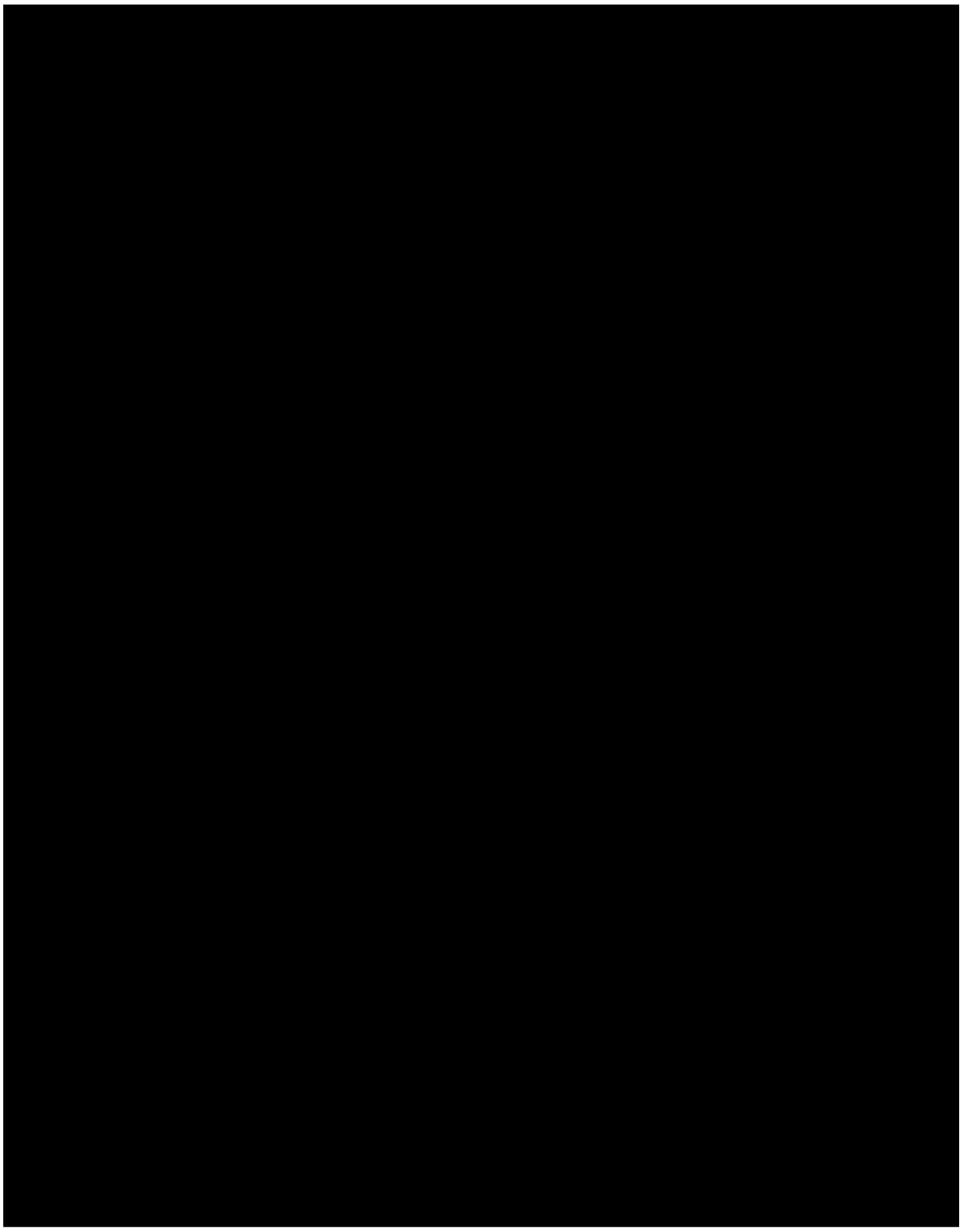
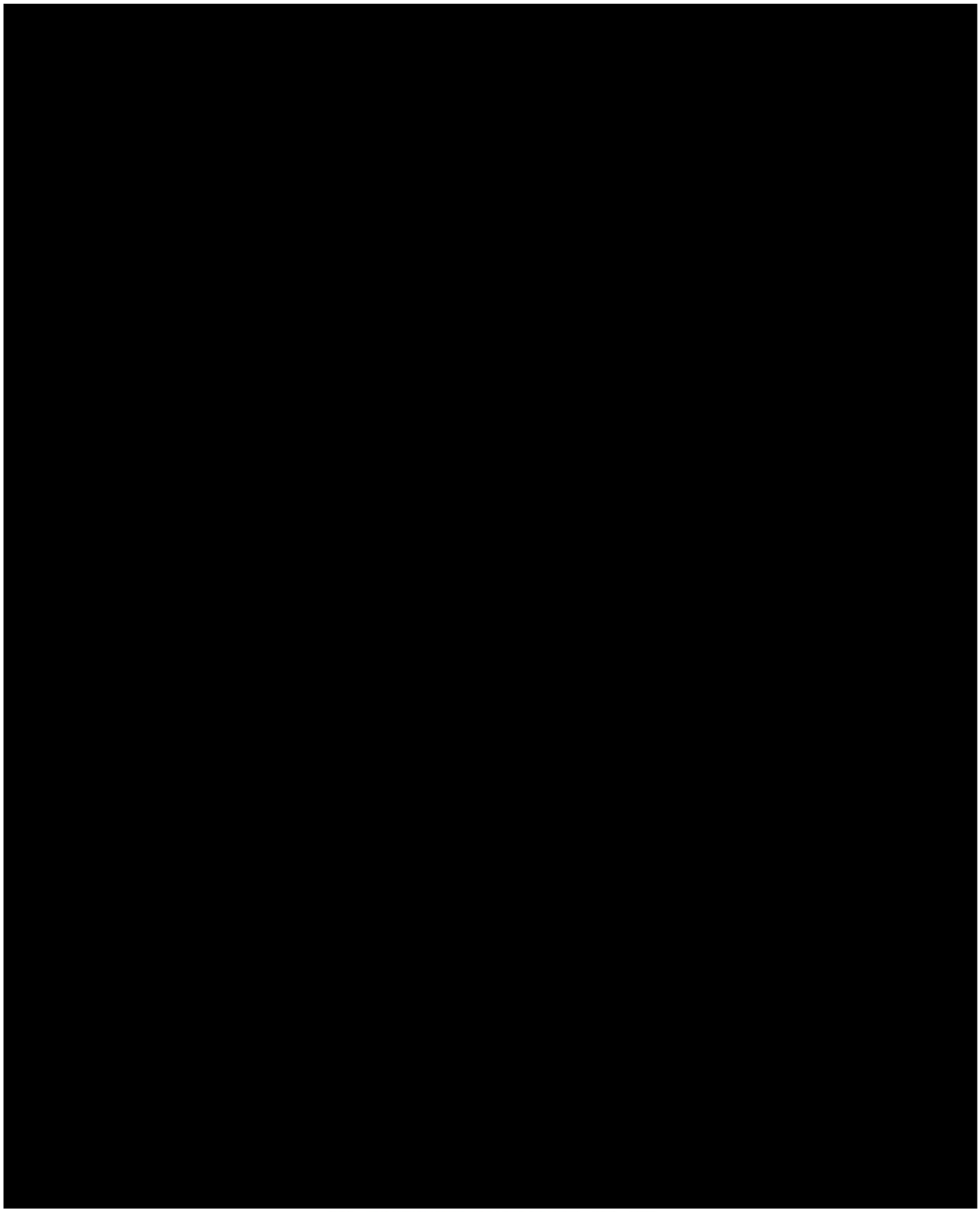
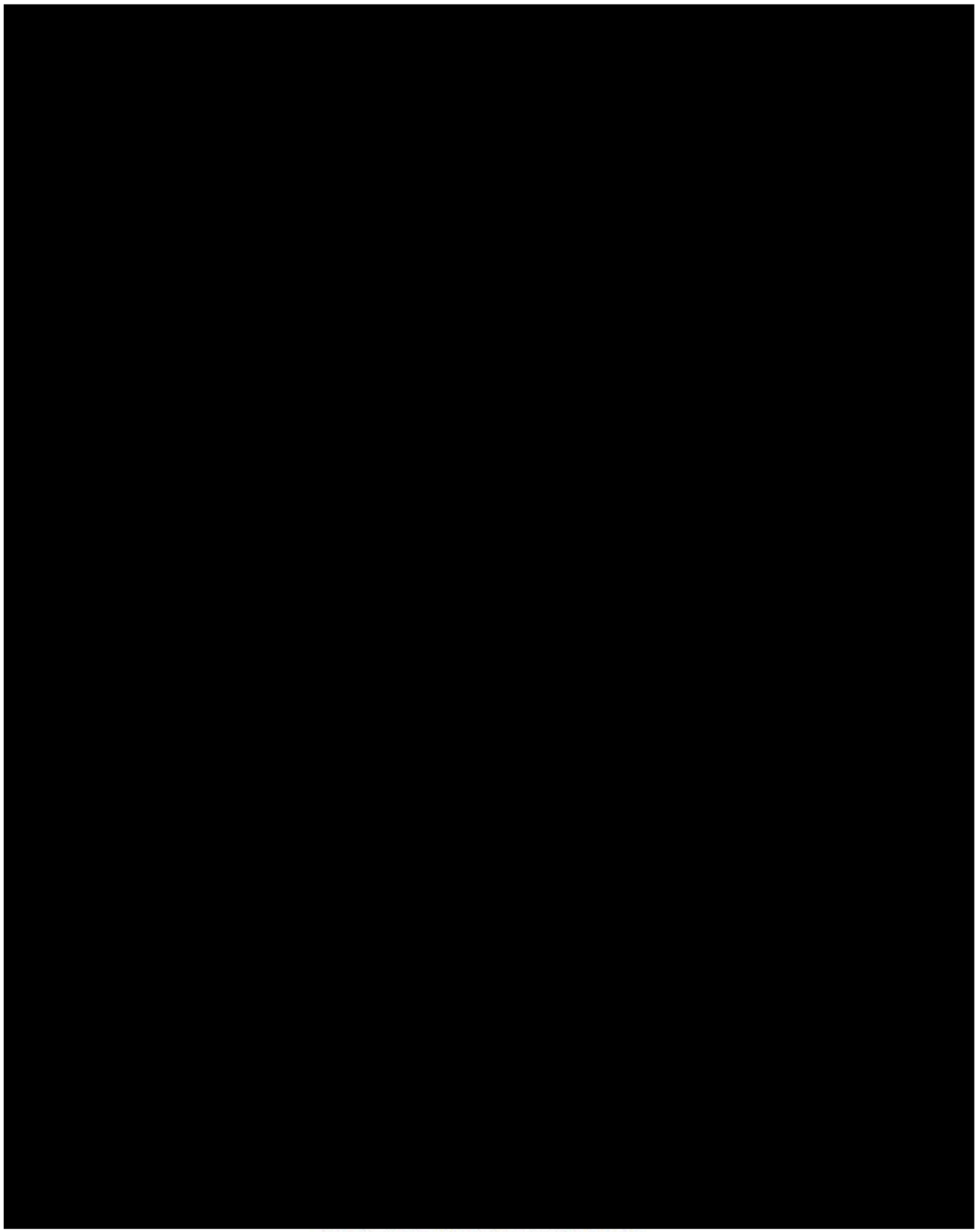
10.14.7 Haemo-QoL 8-12

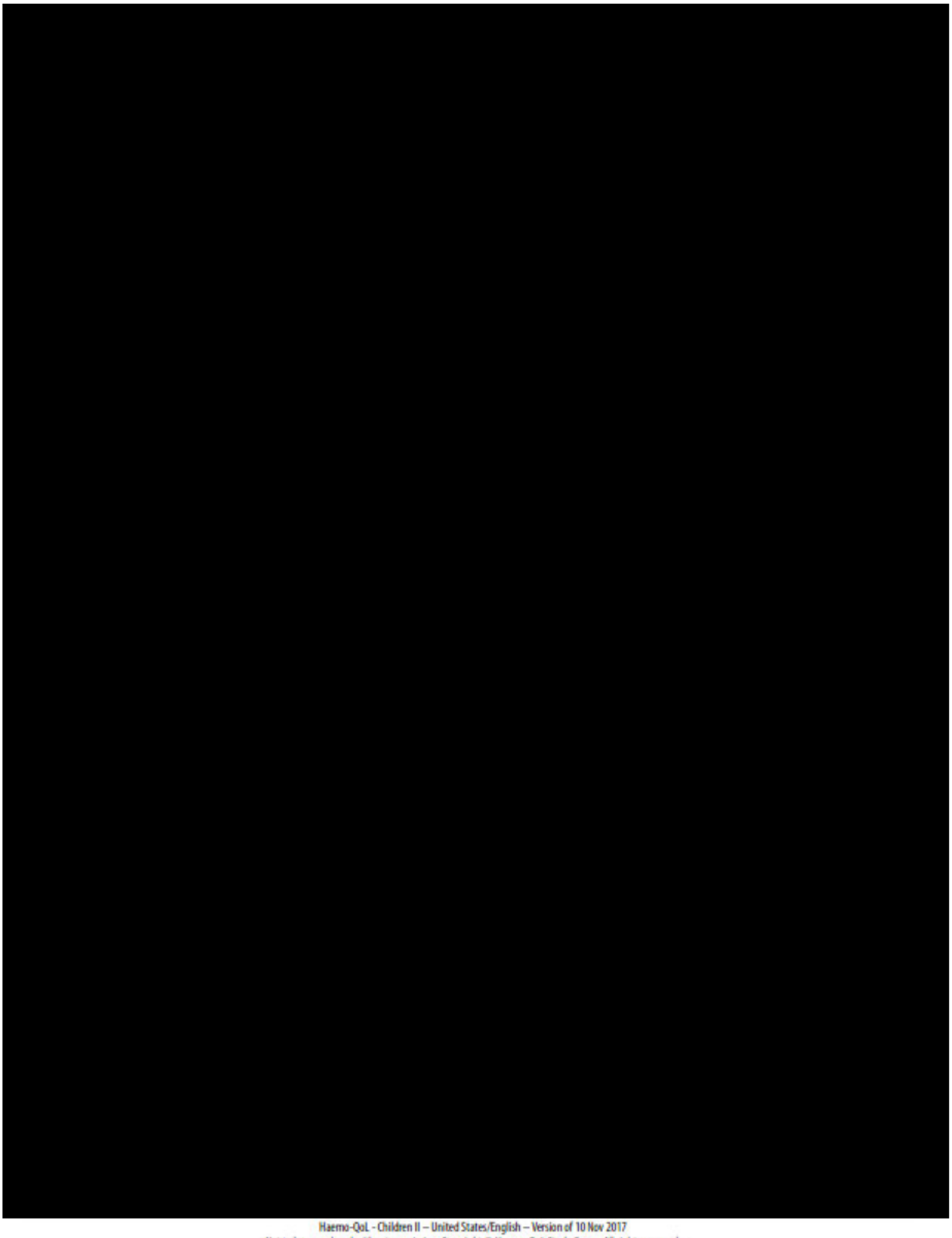


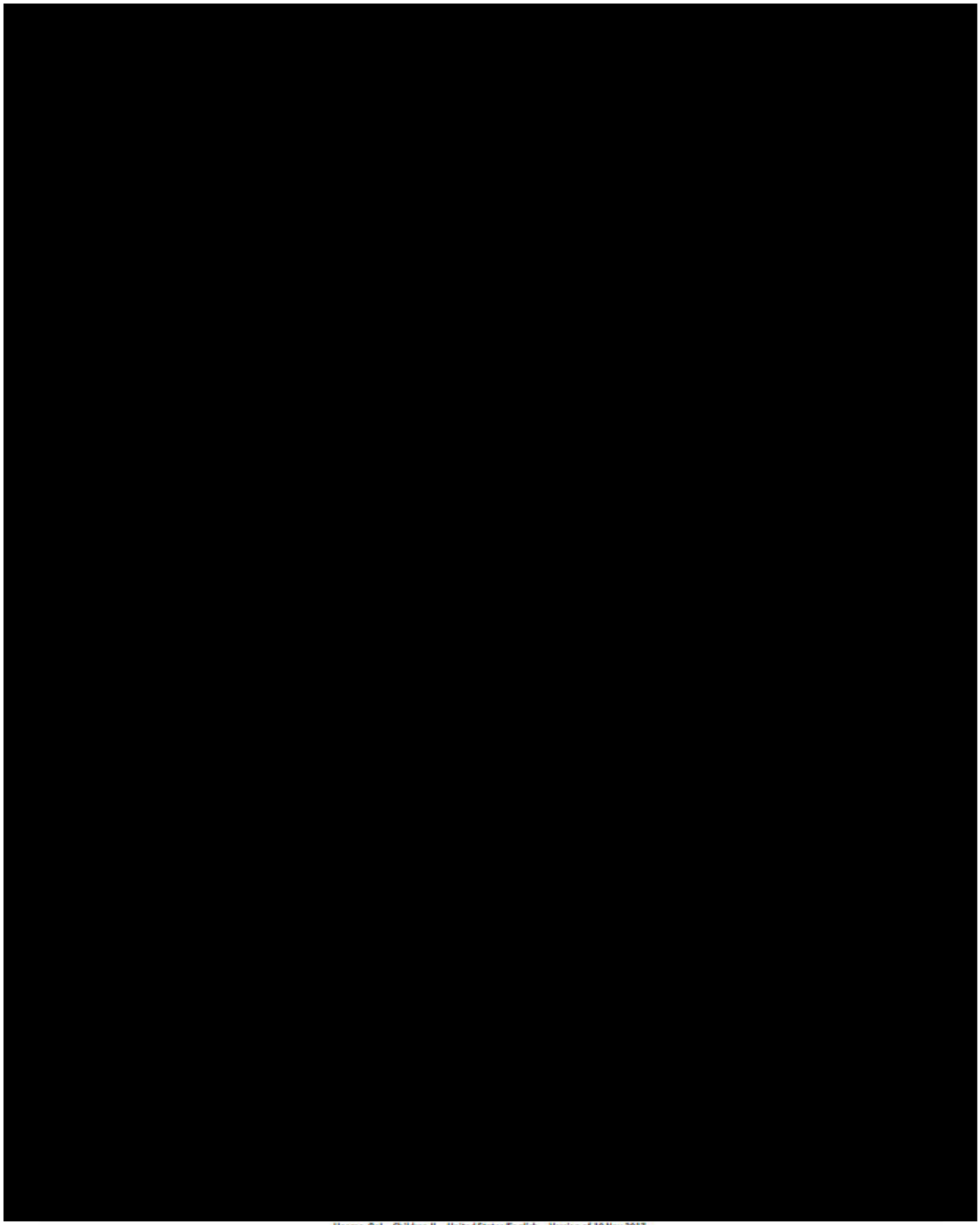


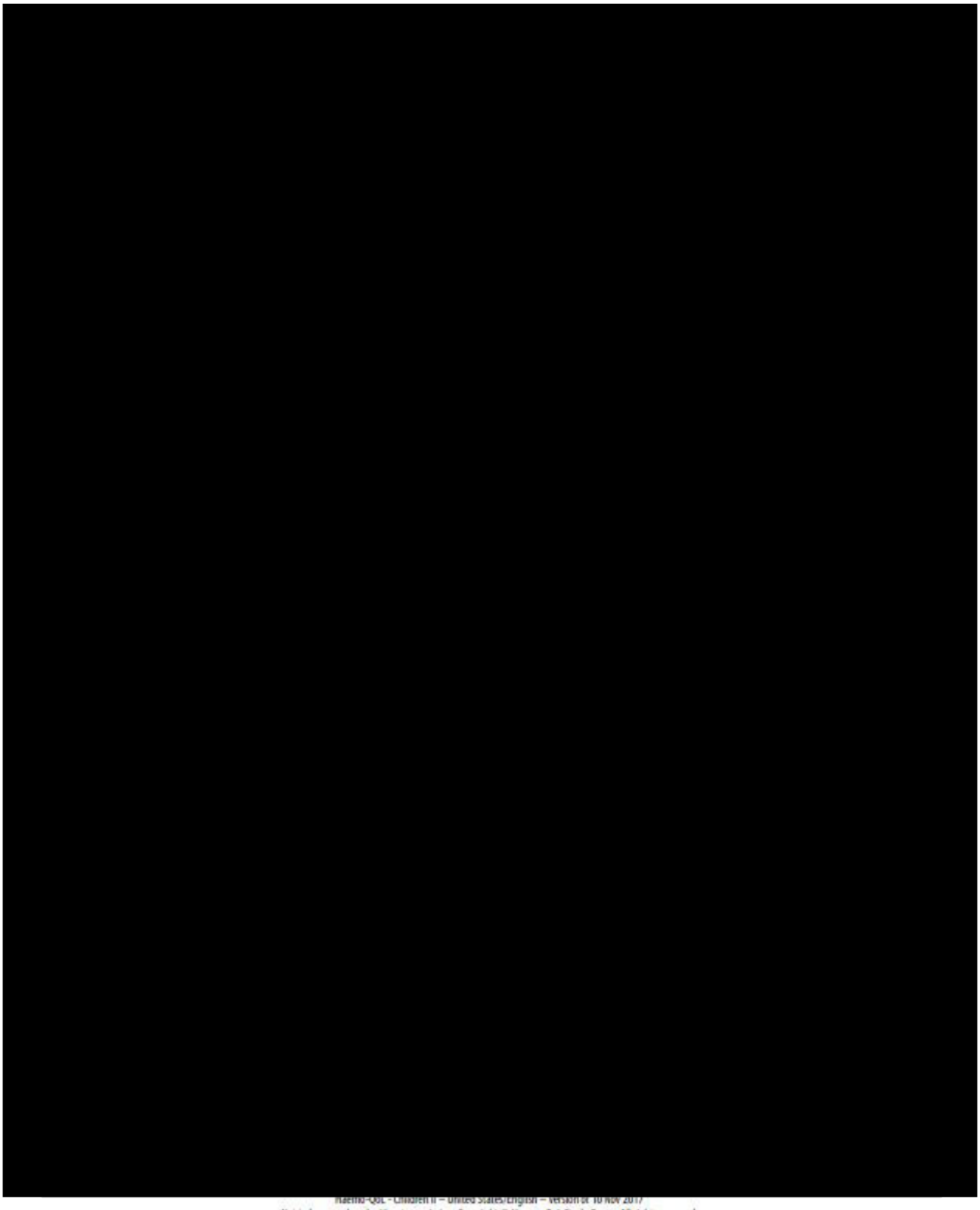












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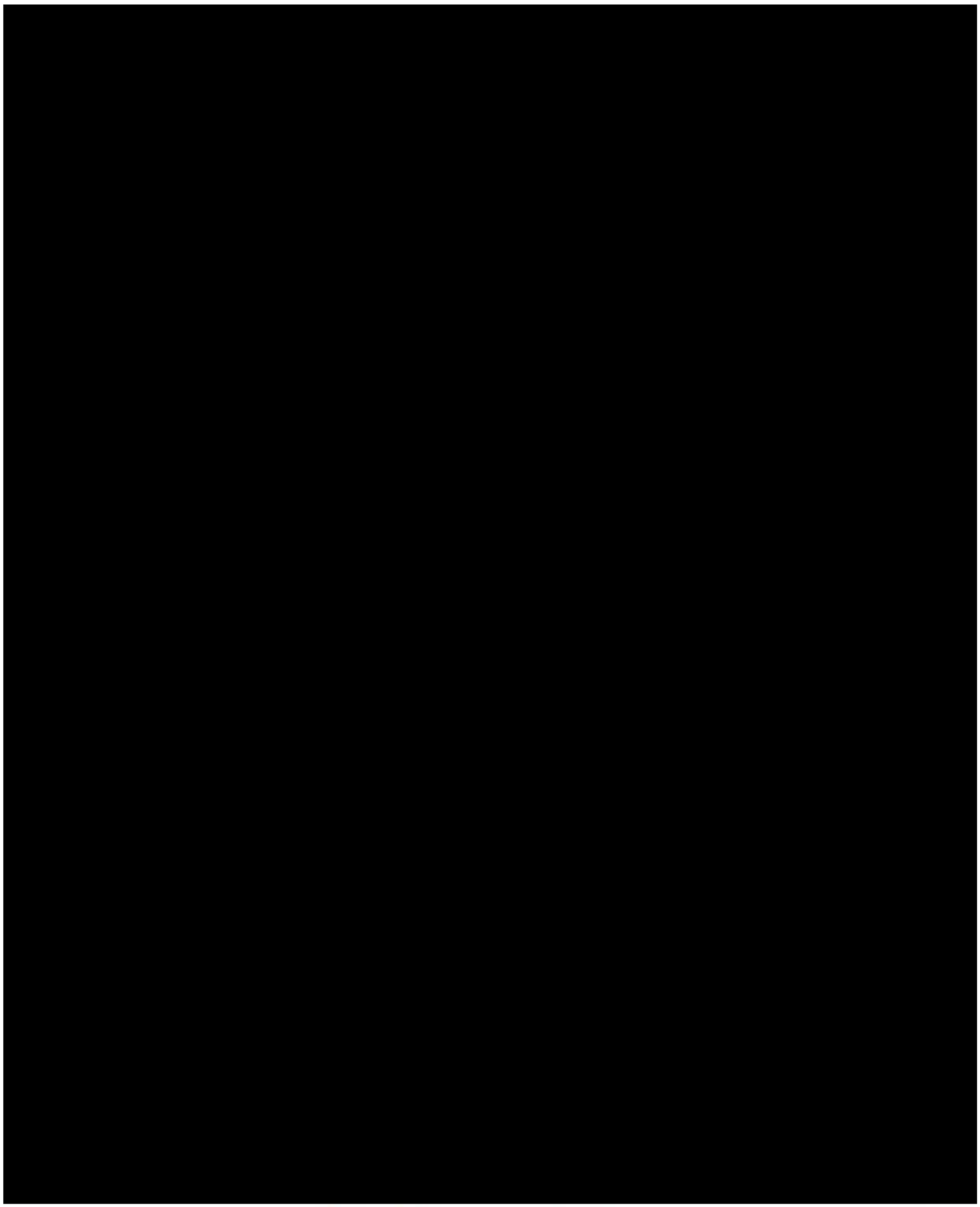

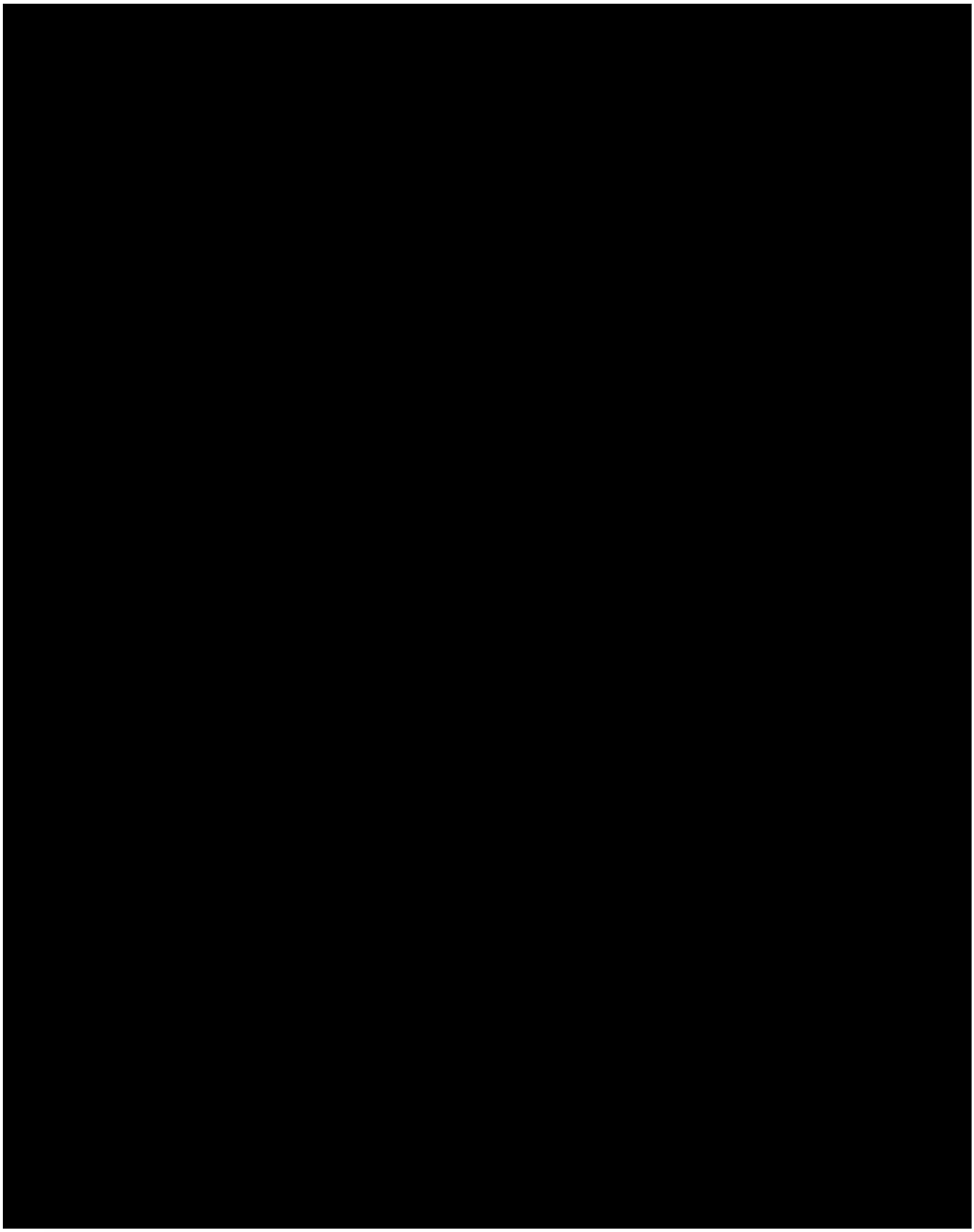

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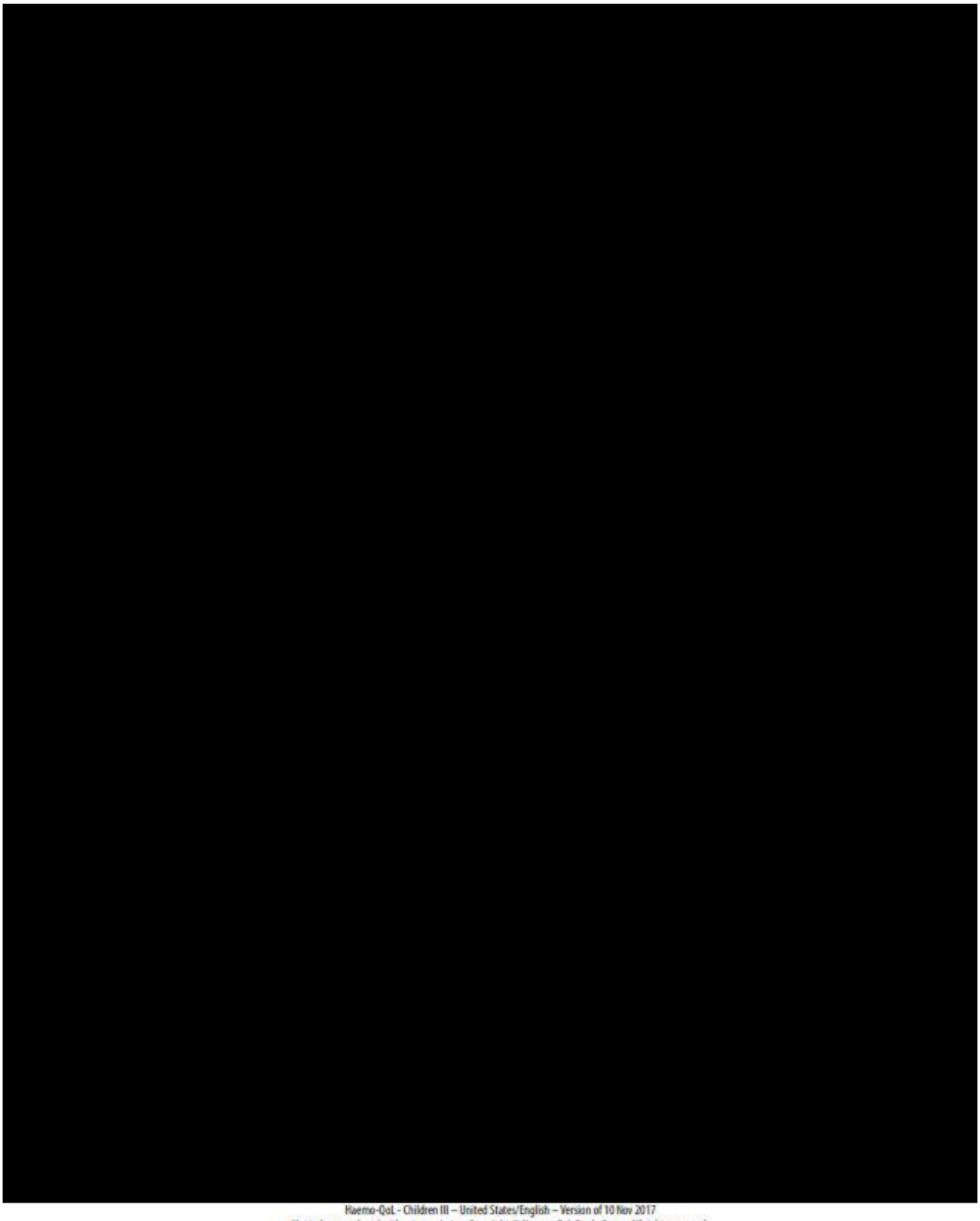

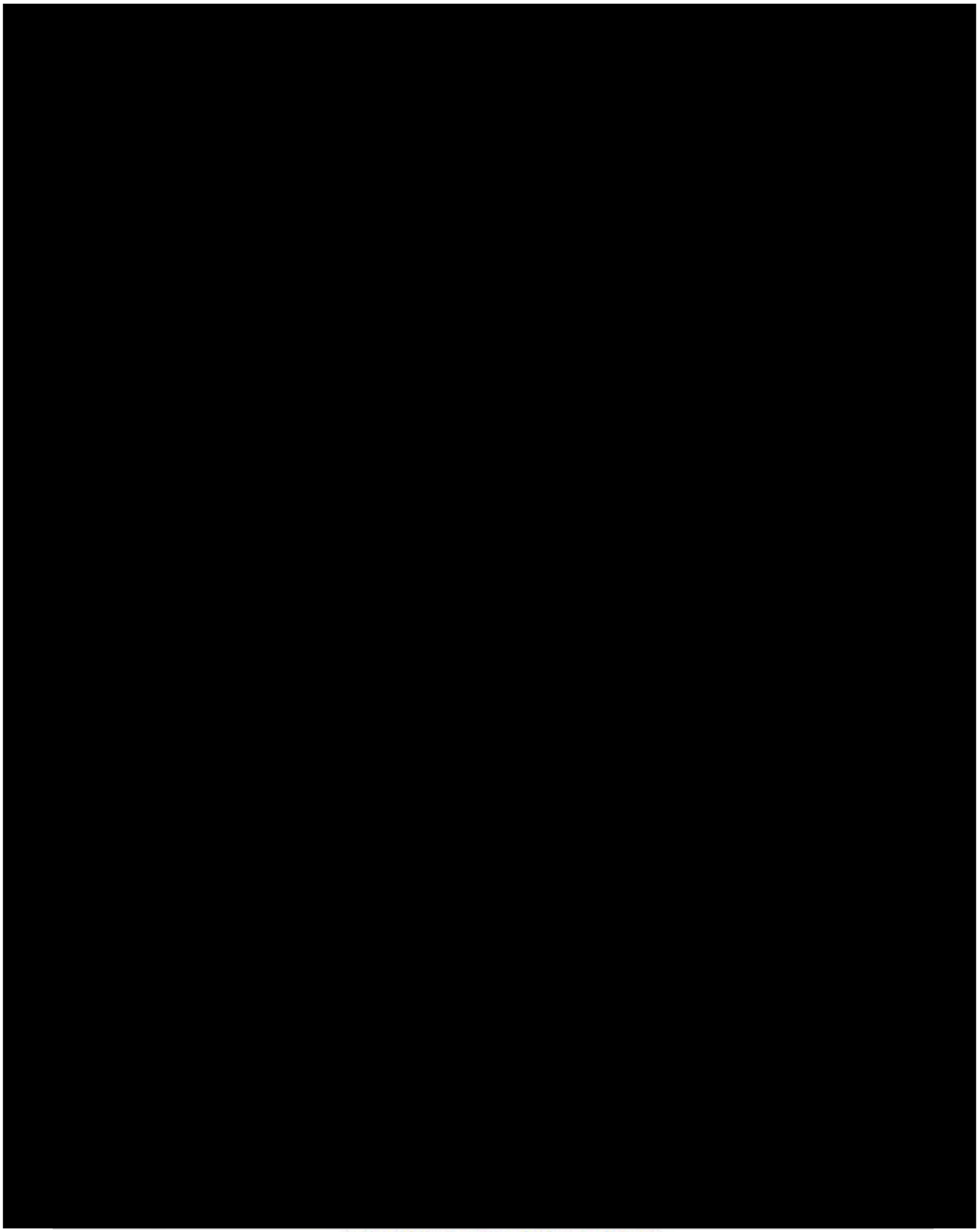

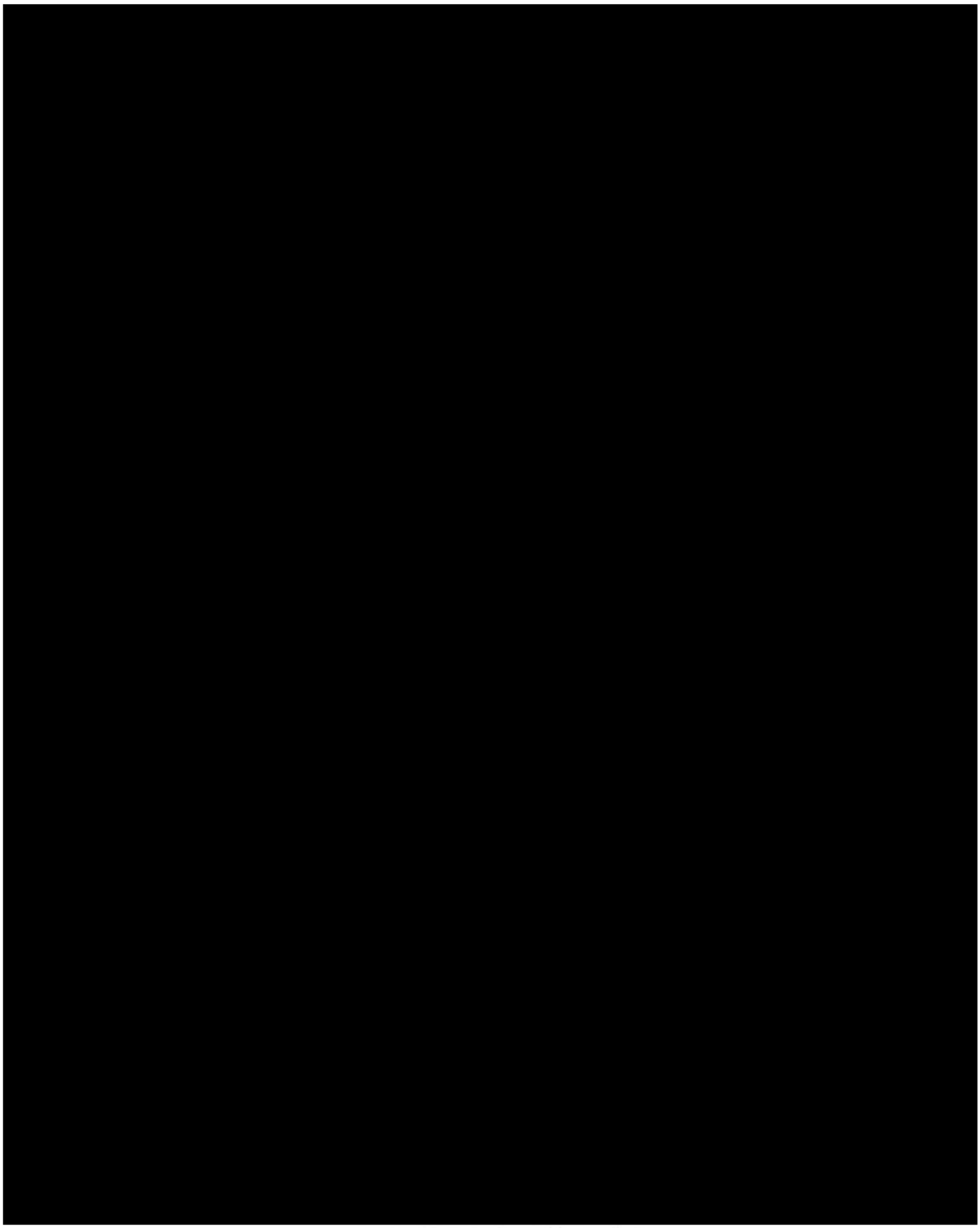

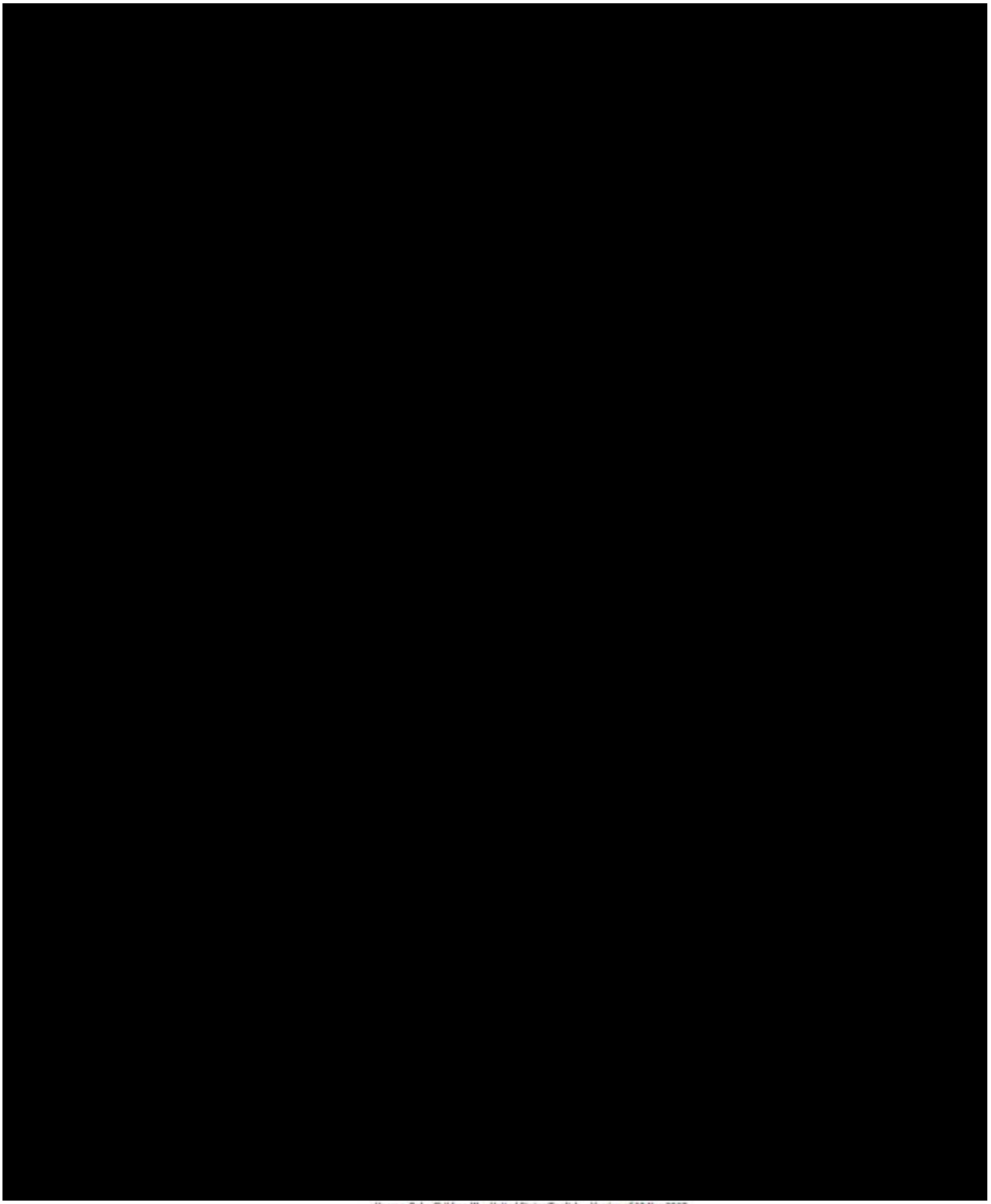

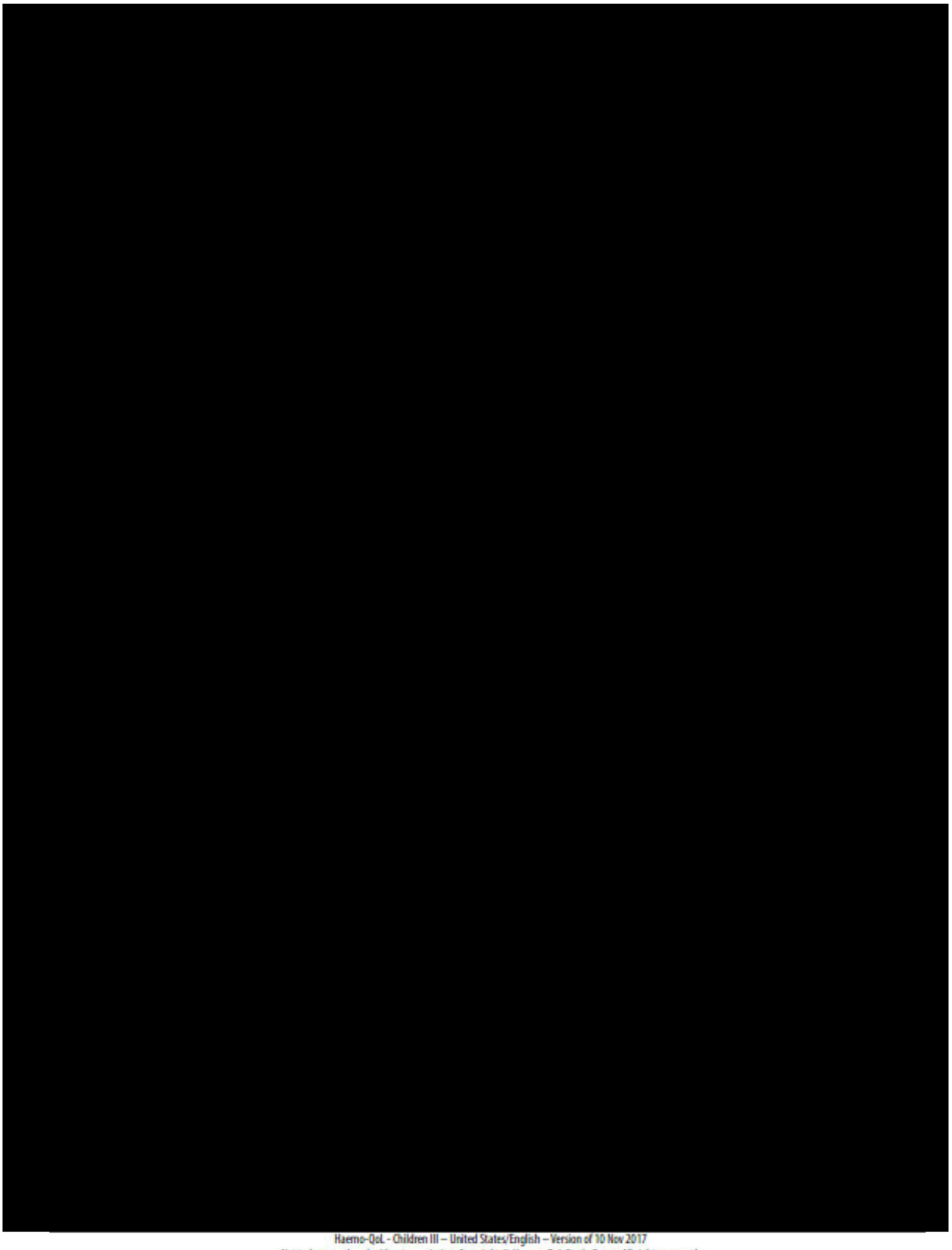

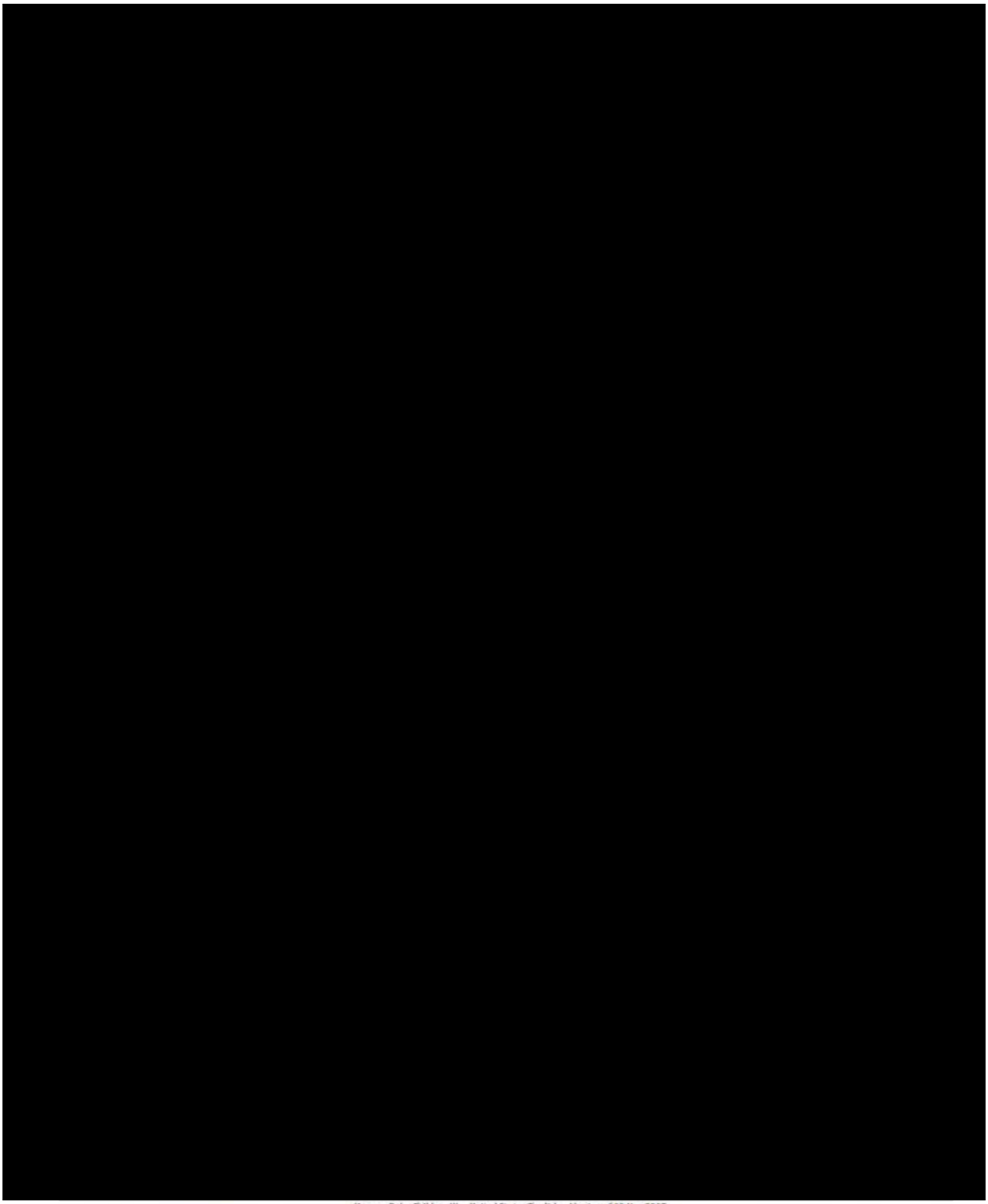

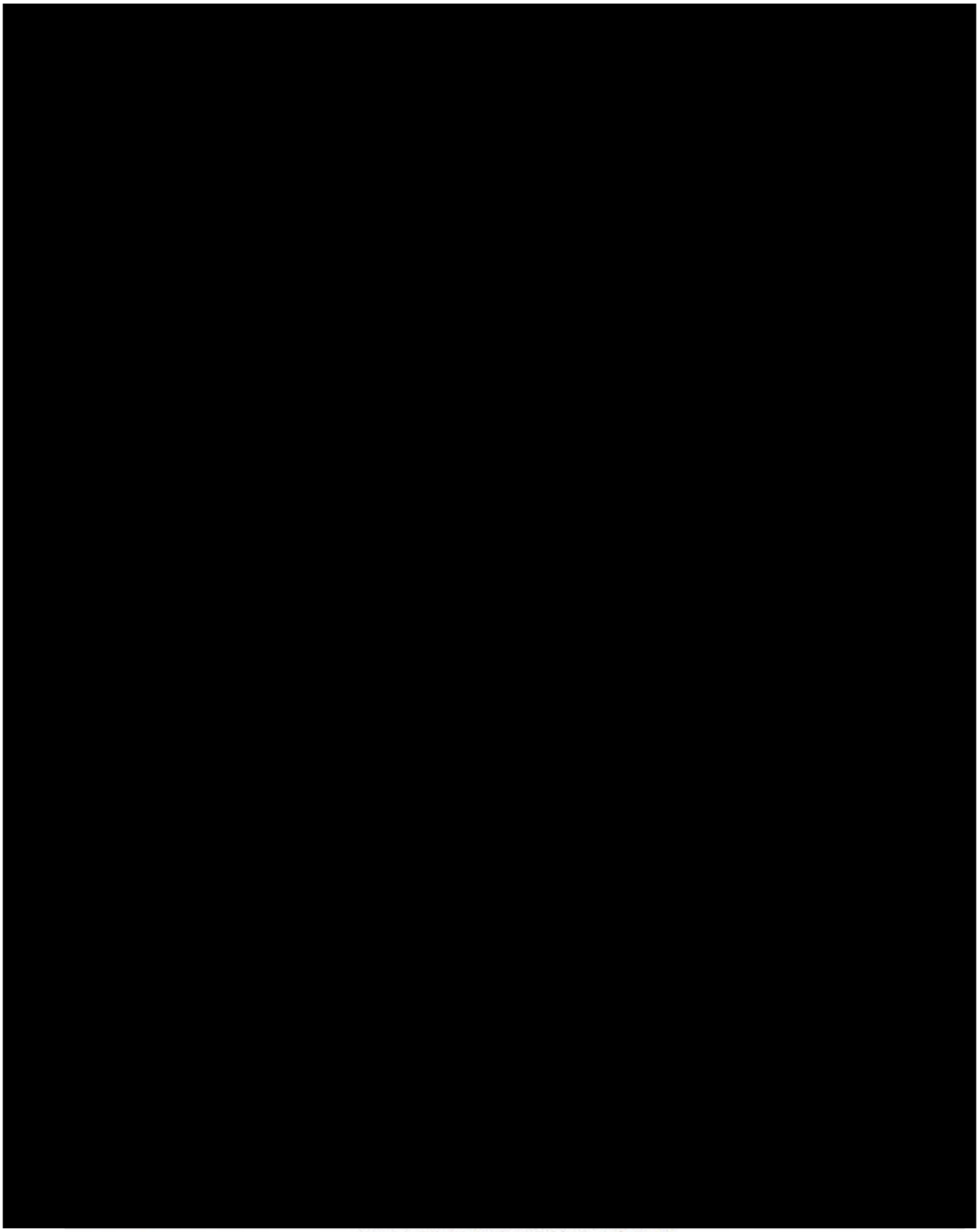

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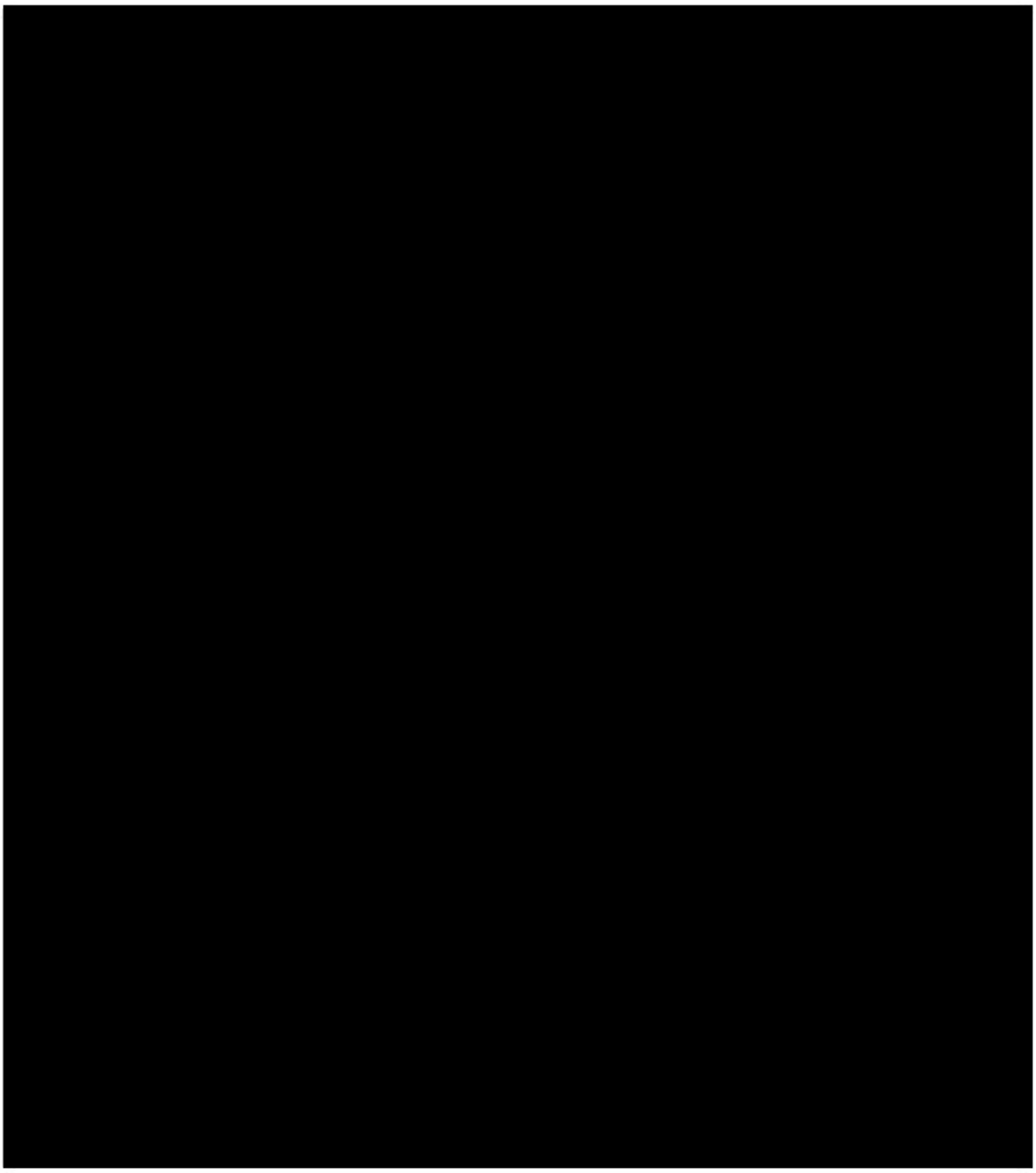

Date : .....

Patient ID: .....

Version 2.0 2015
USA / Canadian Version
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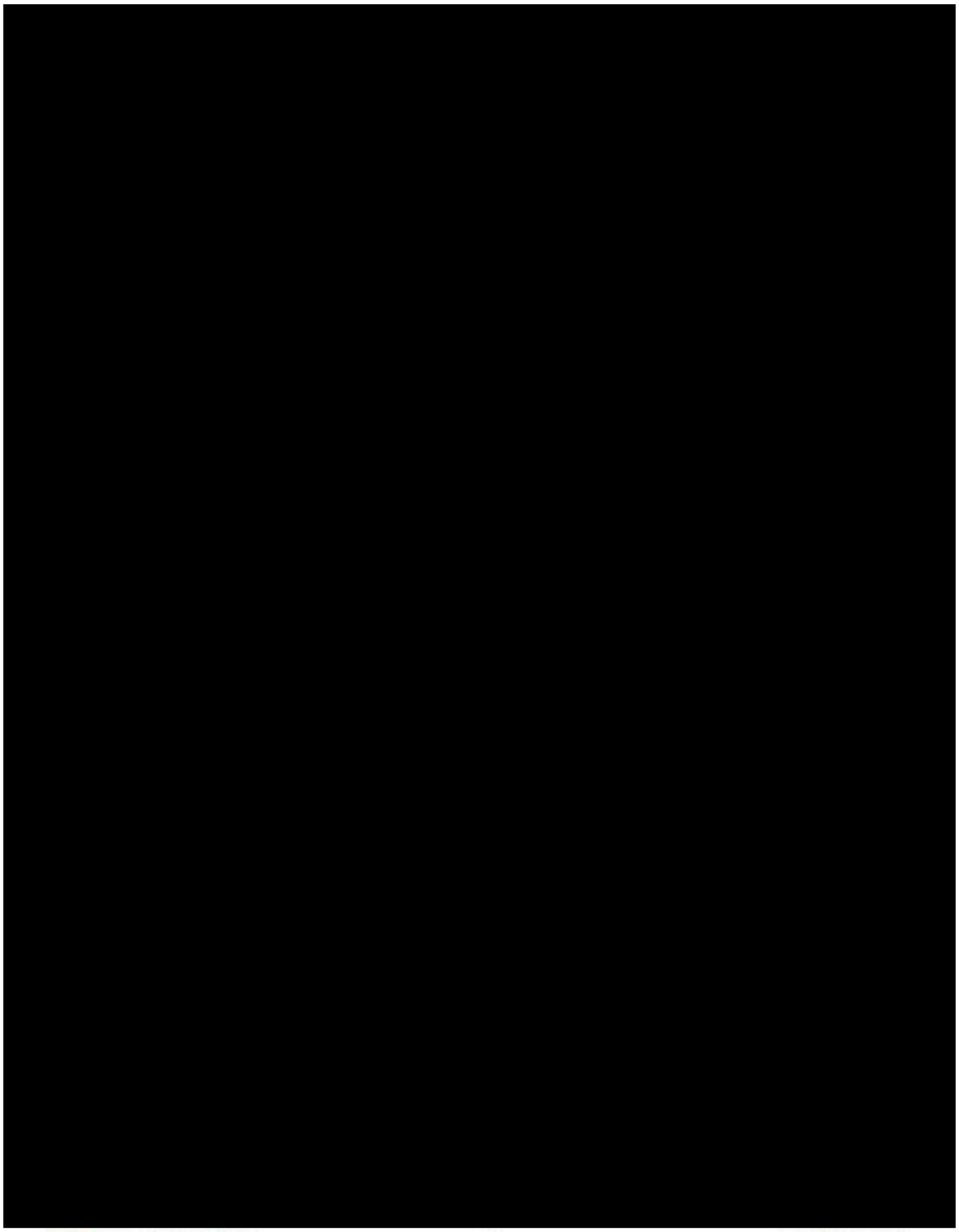
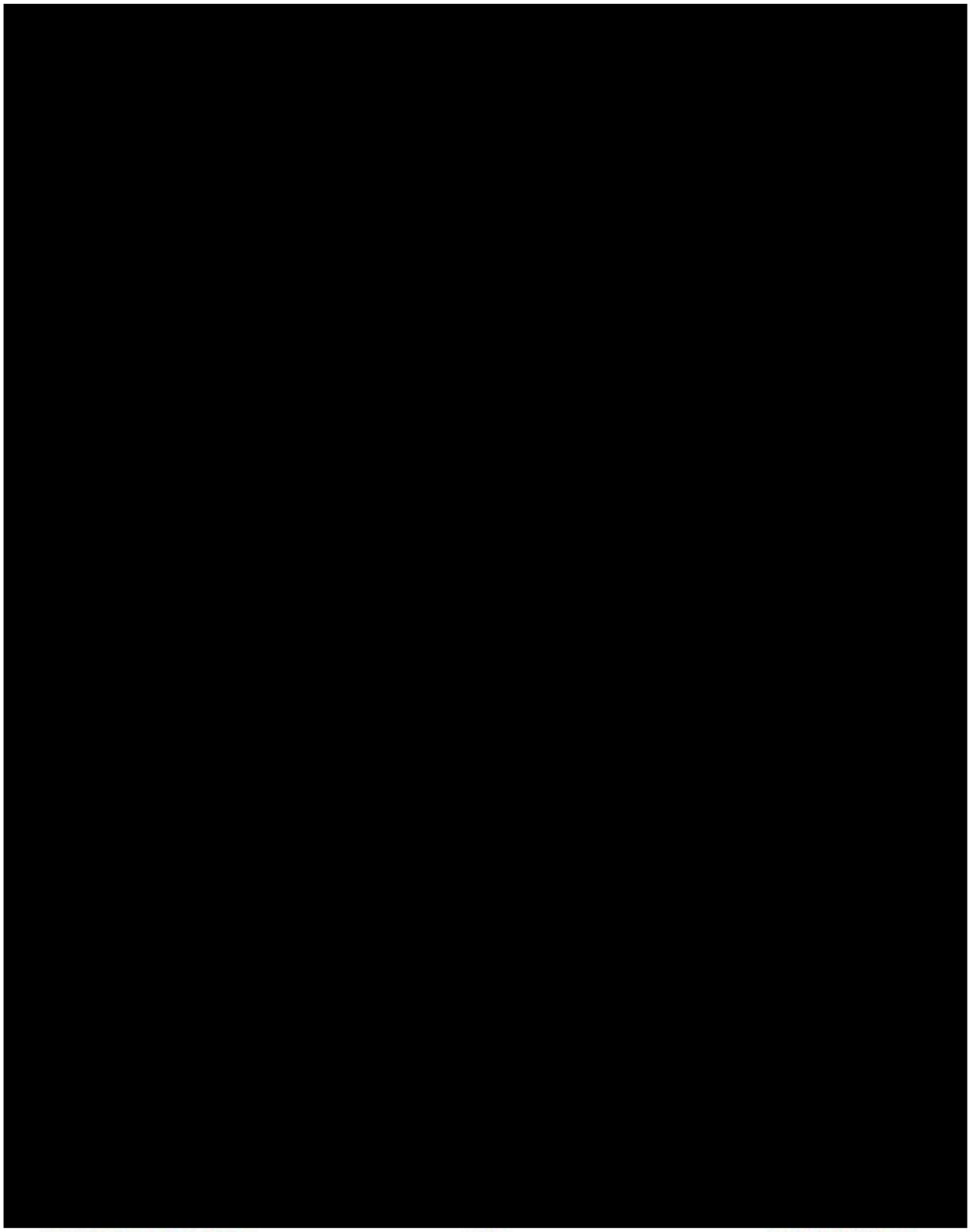
University Medical Centre Utrecht

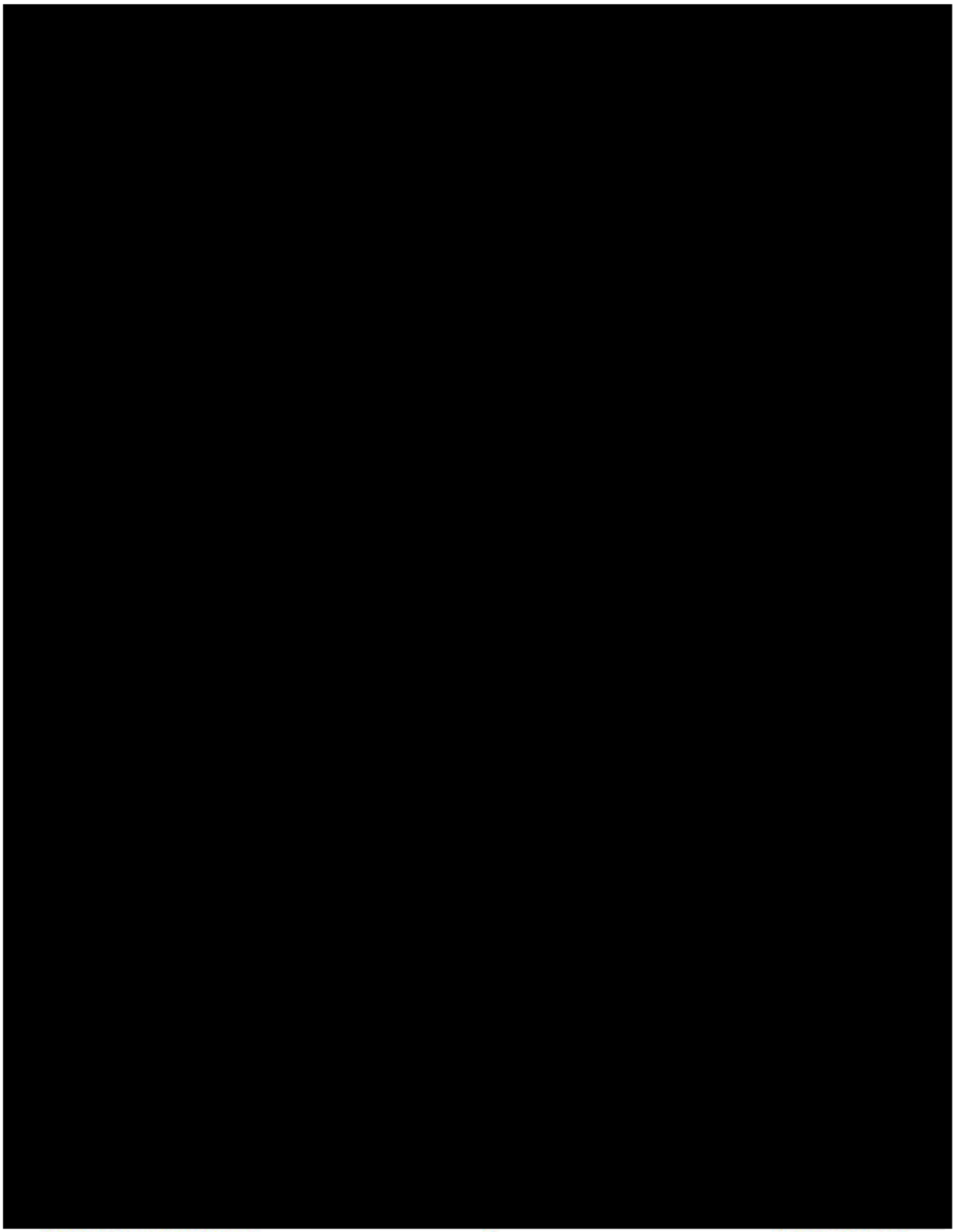
When using this questionnaire, please use the following references:

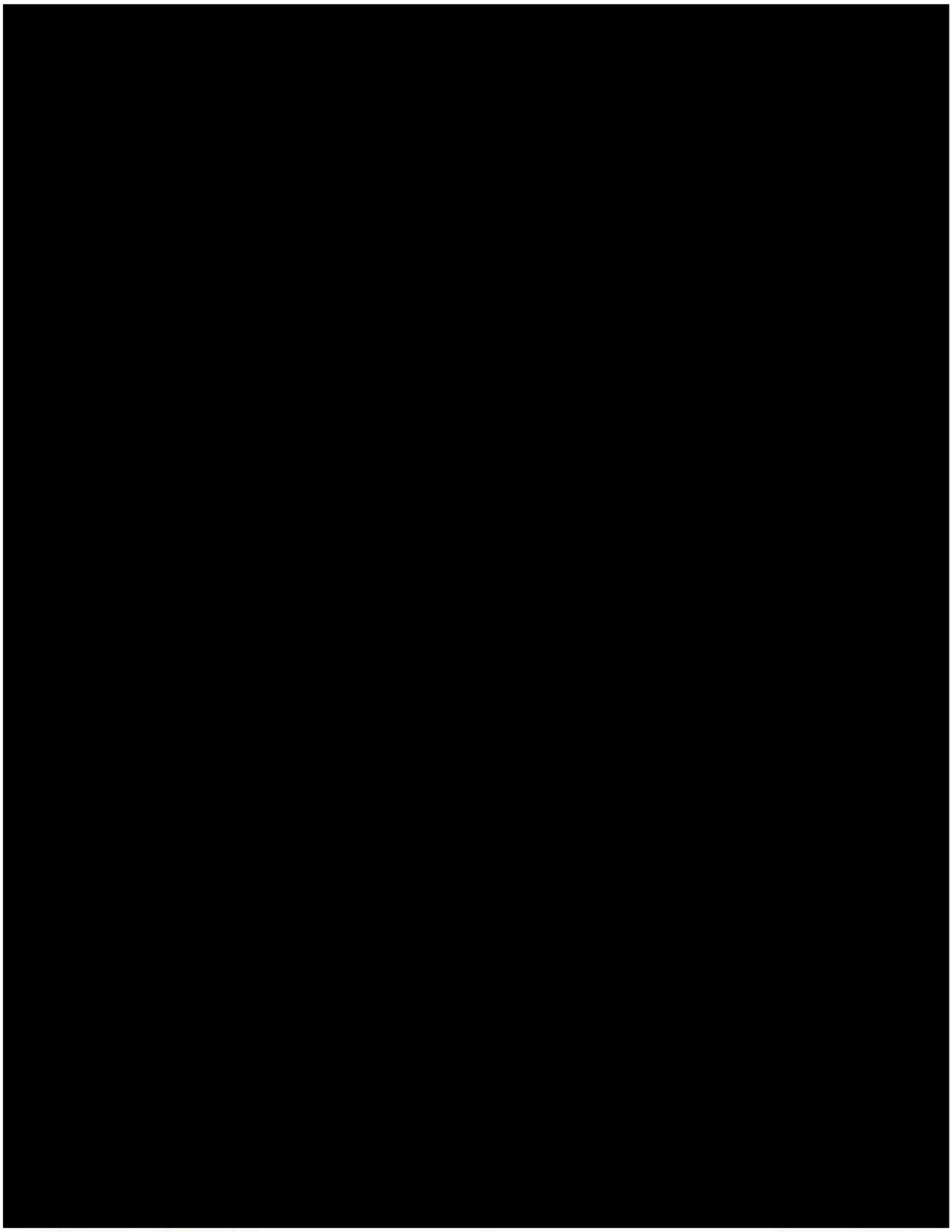
Van Genderen FR, Van Meeteren NLU, Van der Bom JG, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. Haemophilia *2004; 10: 565-71.*

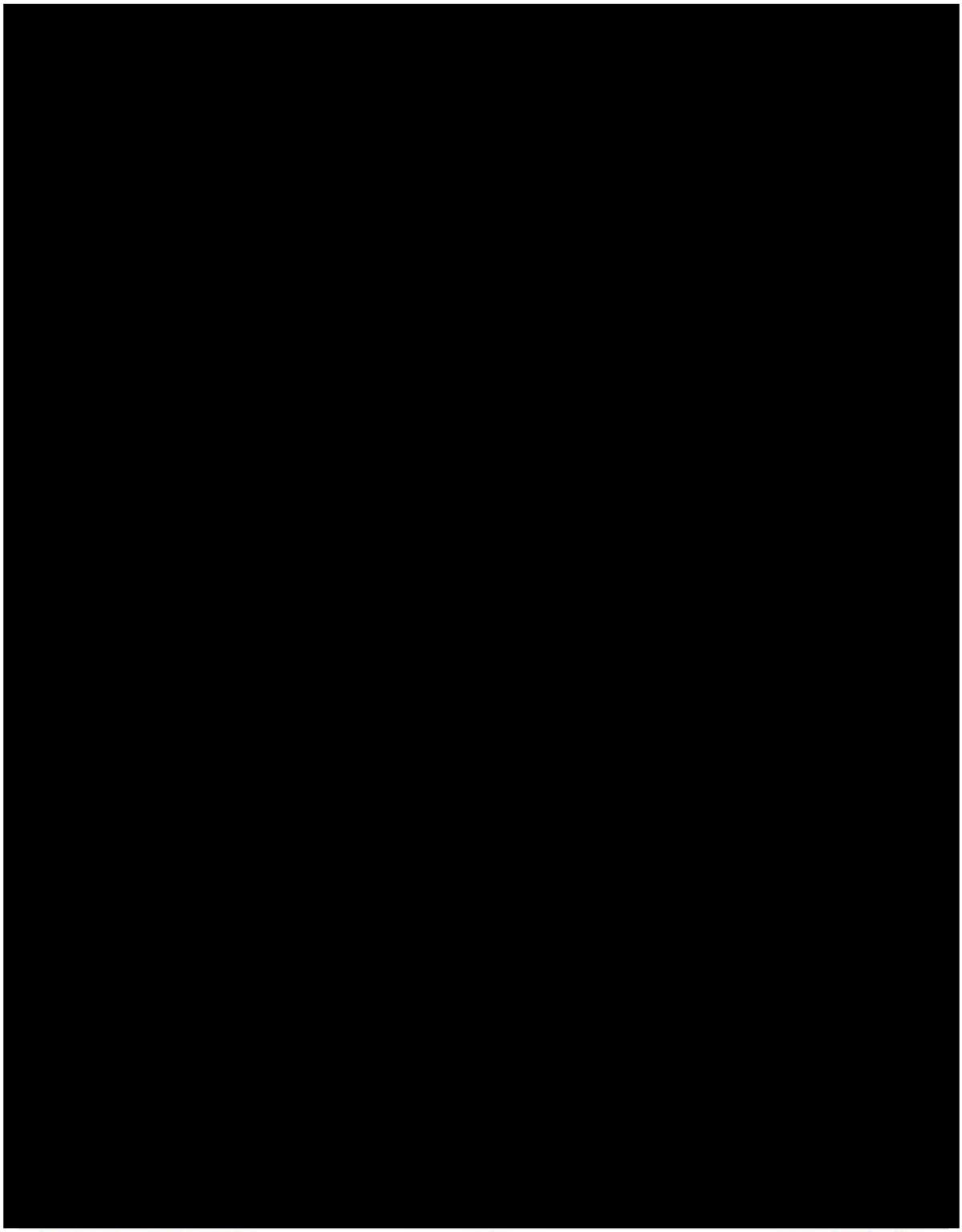
Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM, Van Meeteren NLU. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List (HAL). Haemophilia *2006; 12: 35-46.*

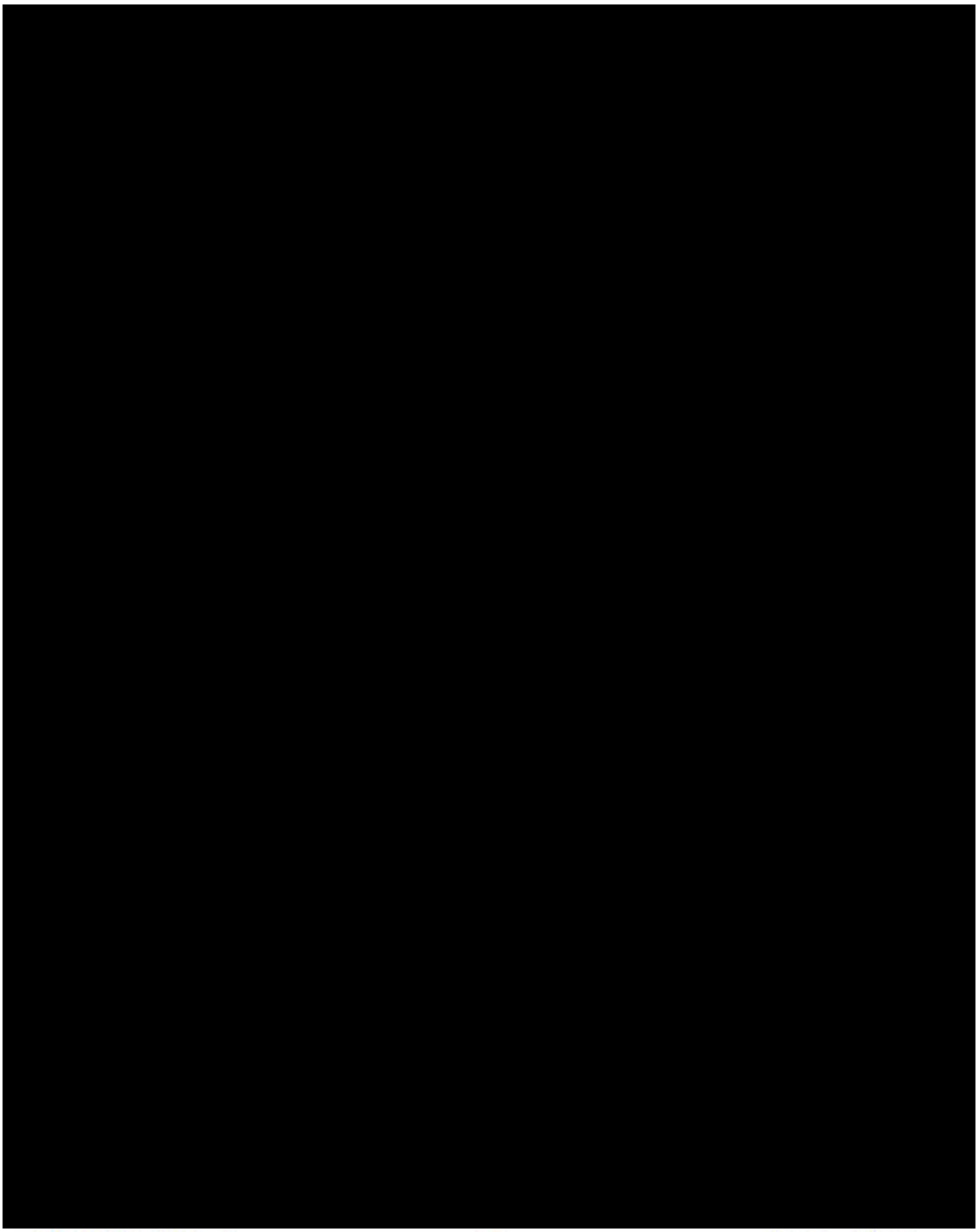


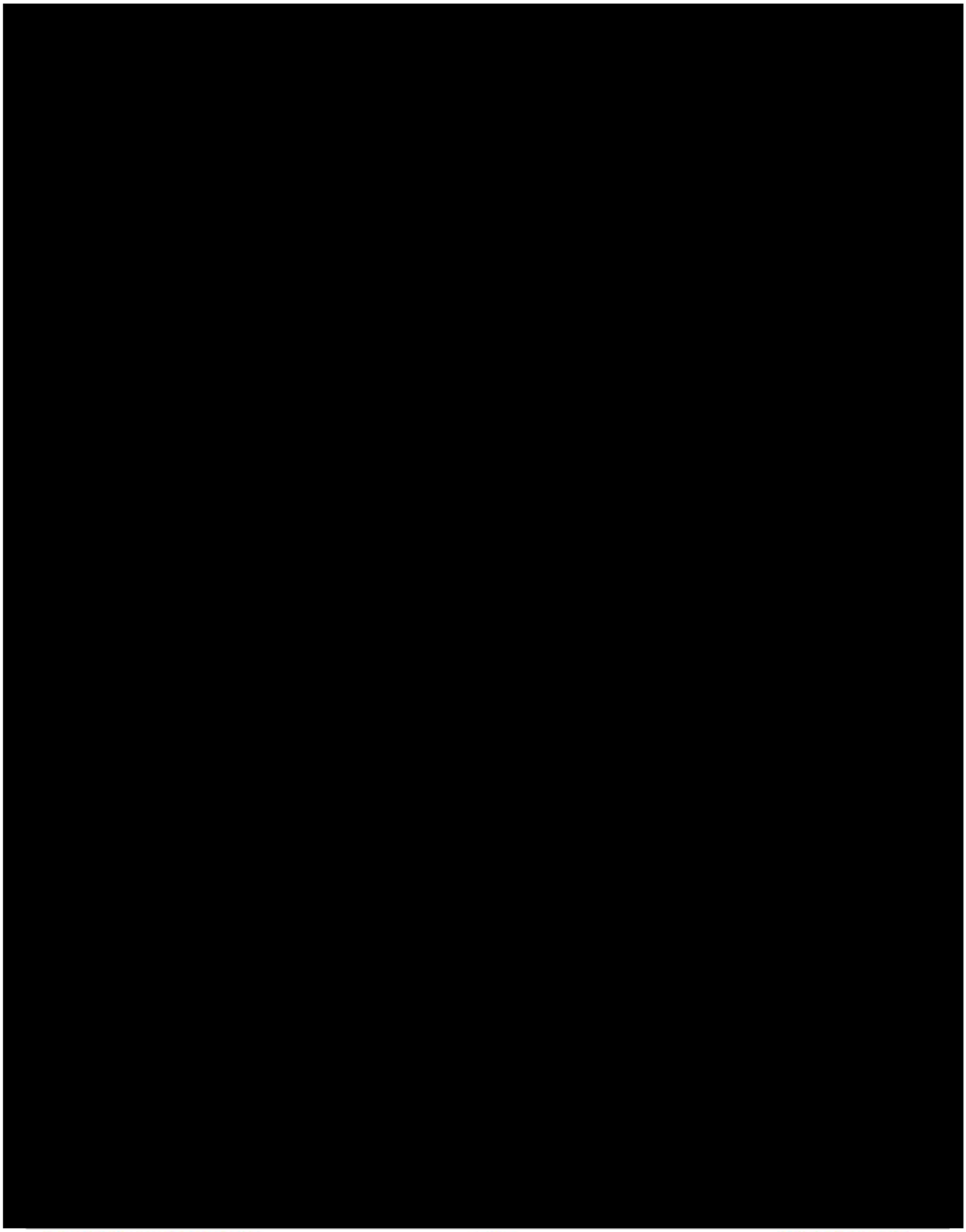


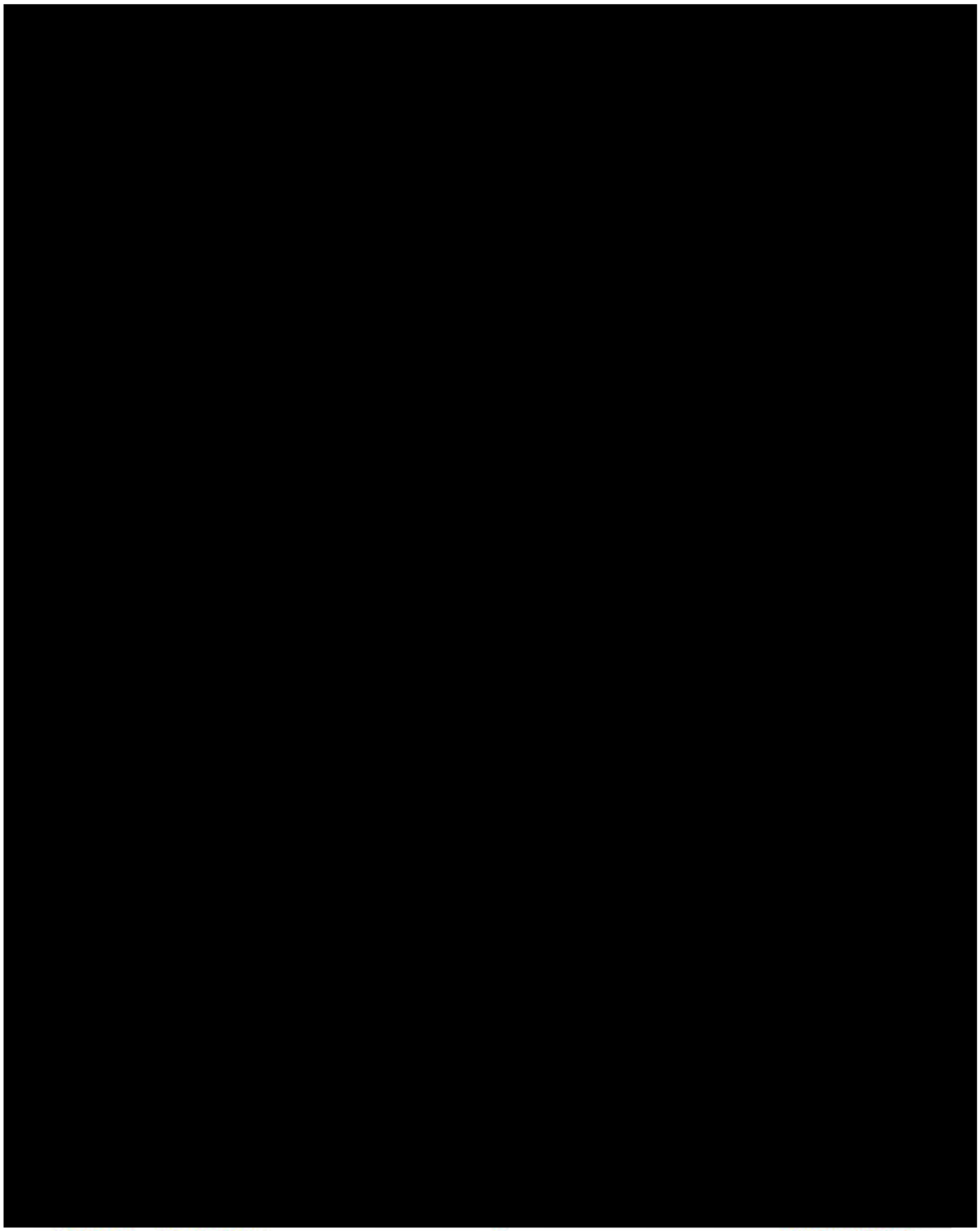


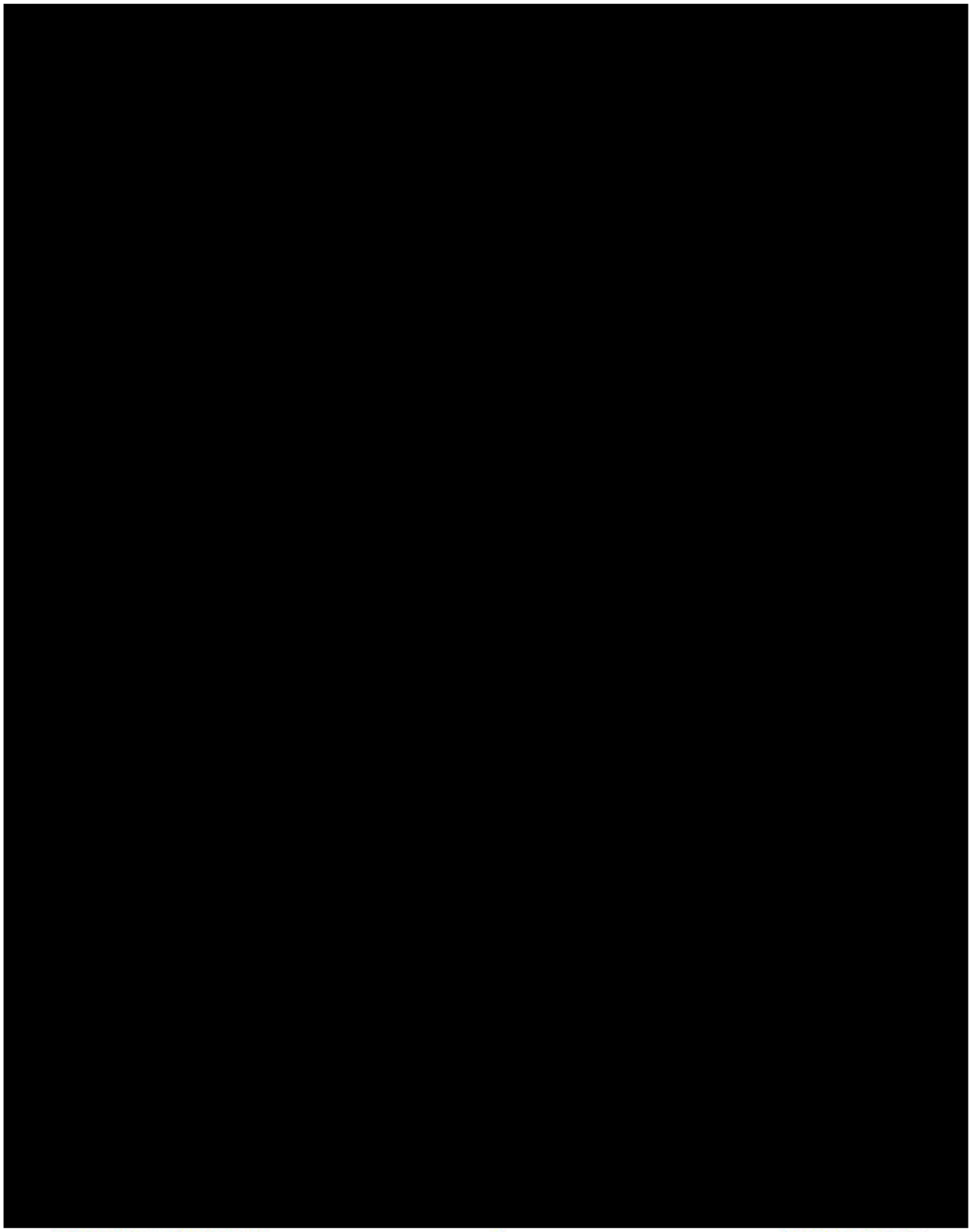












10.14.10 Pediatric Hemophilia Activities List (pedHAL)

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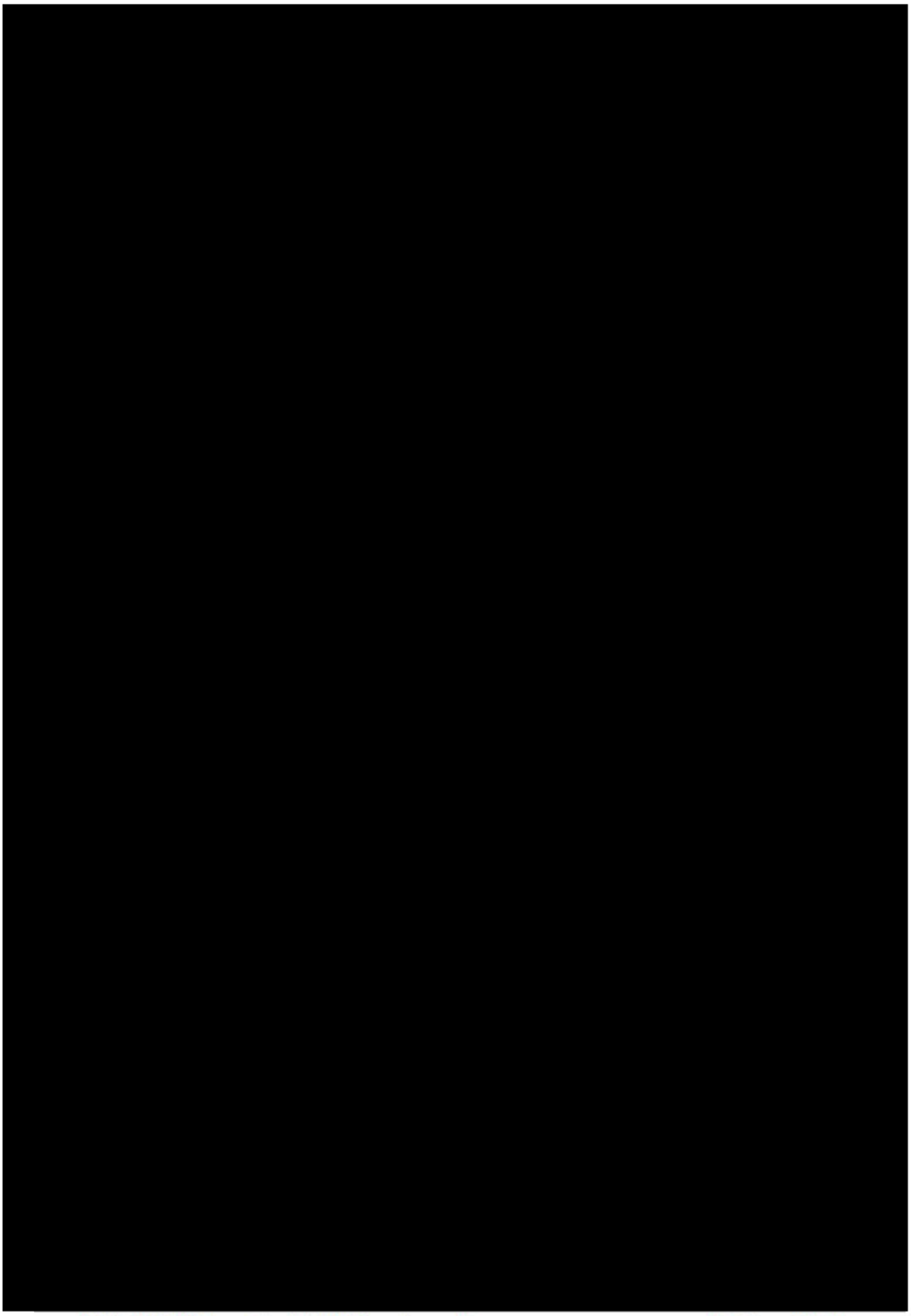
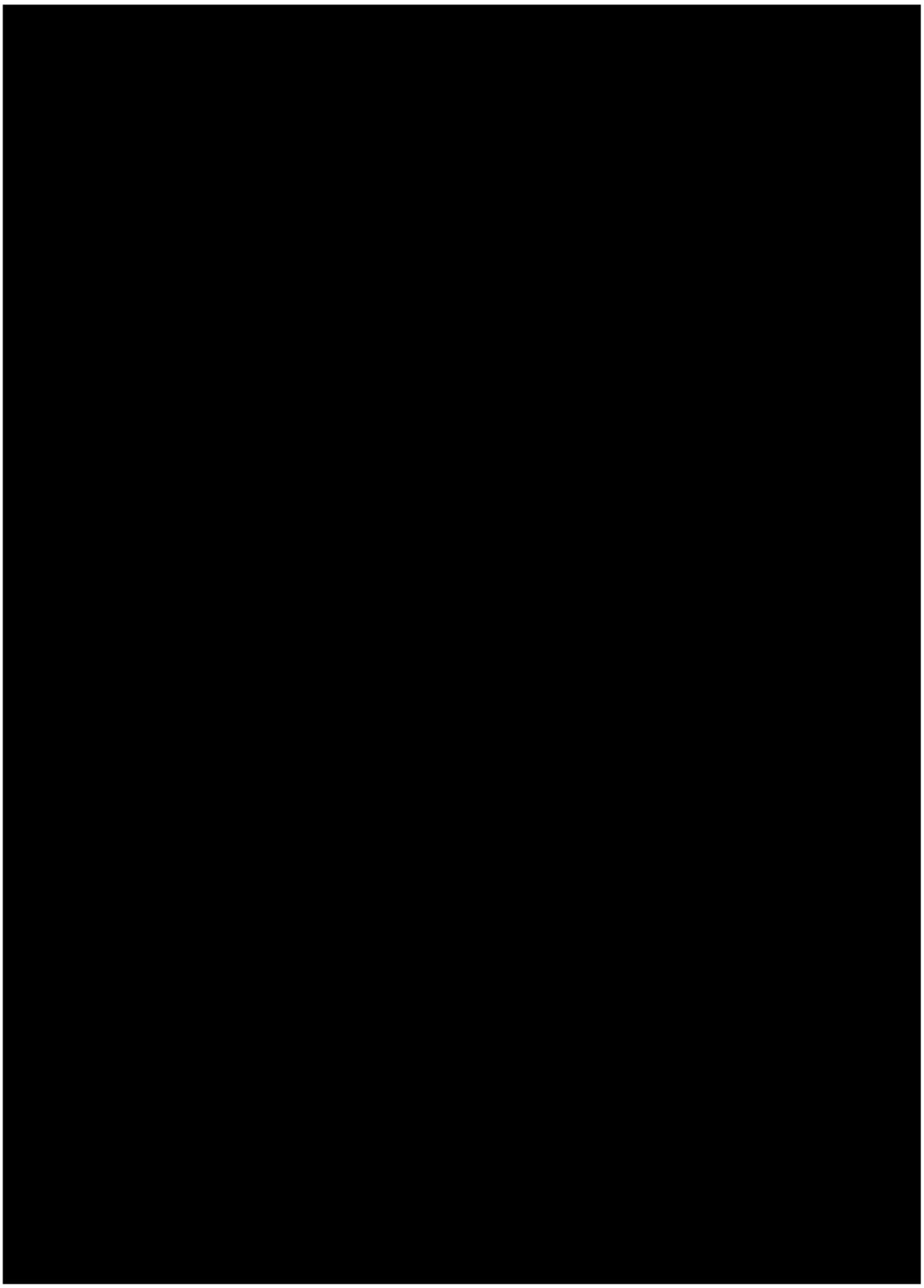
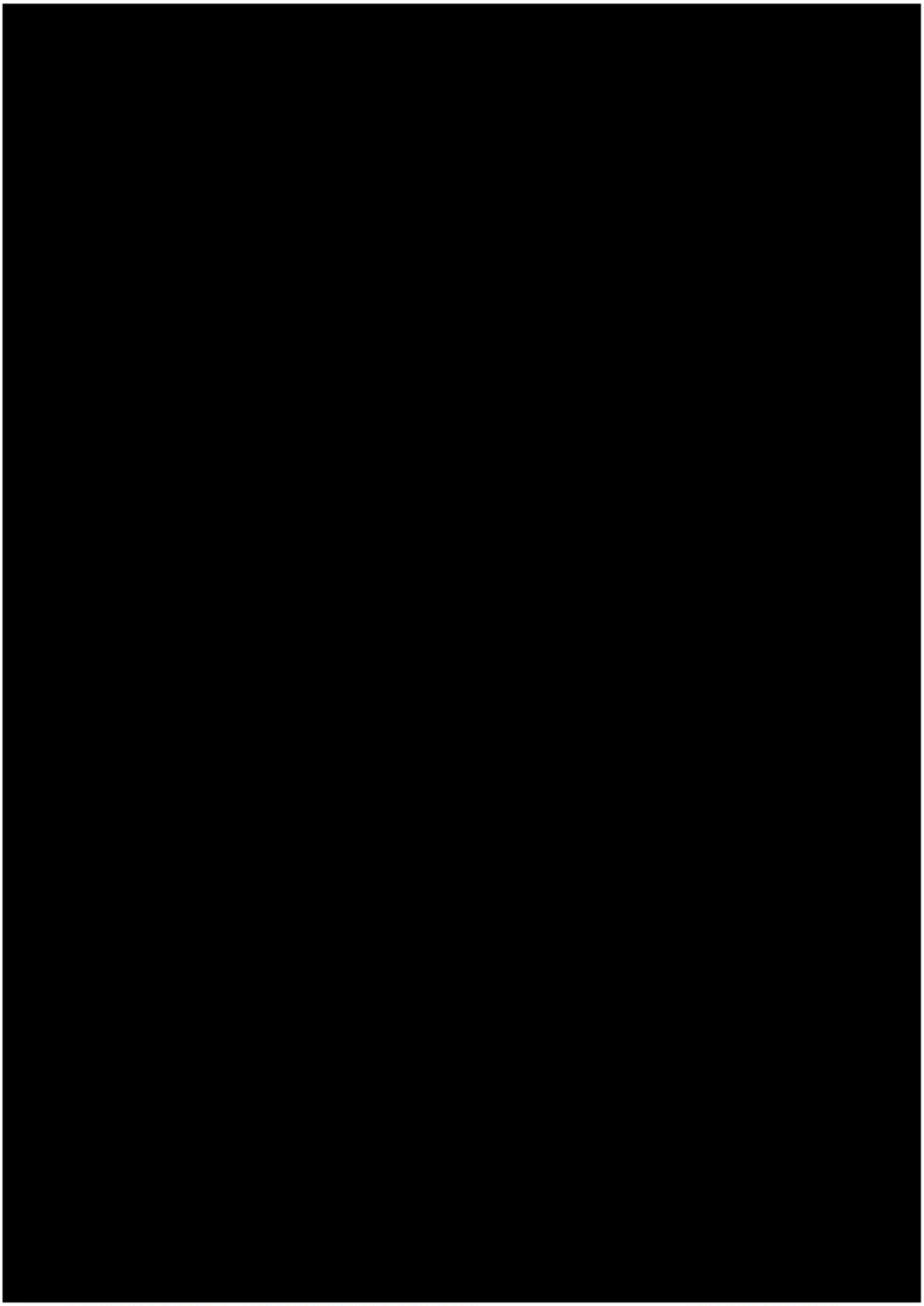
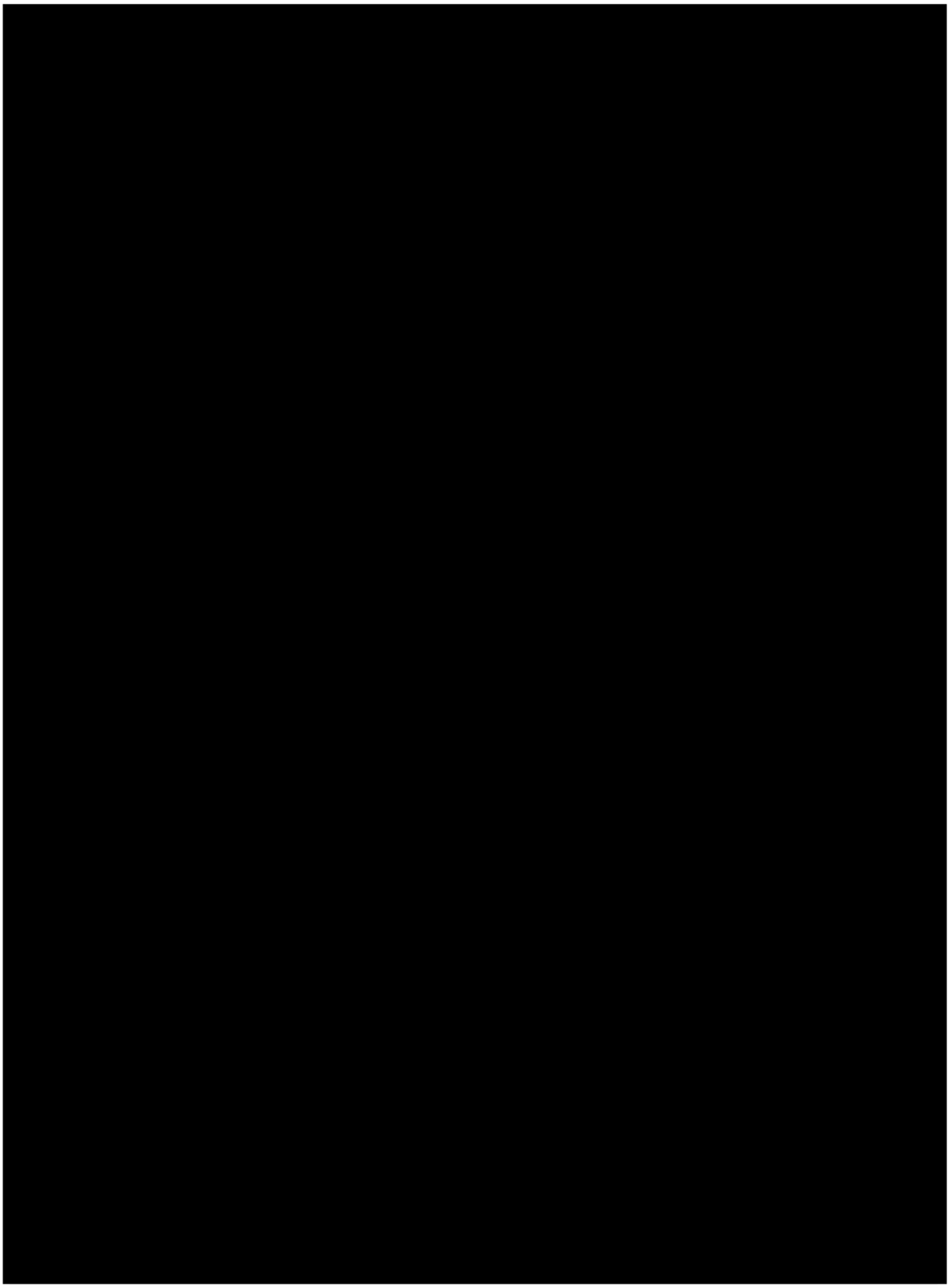
Date of birth :.....

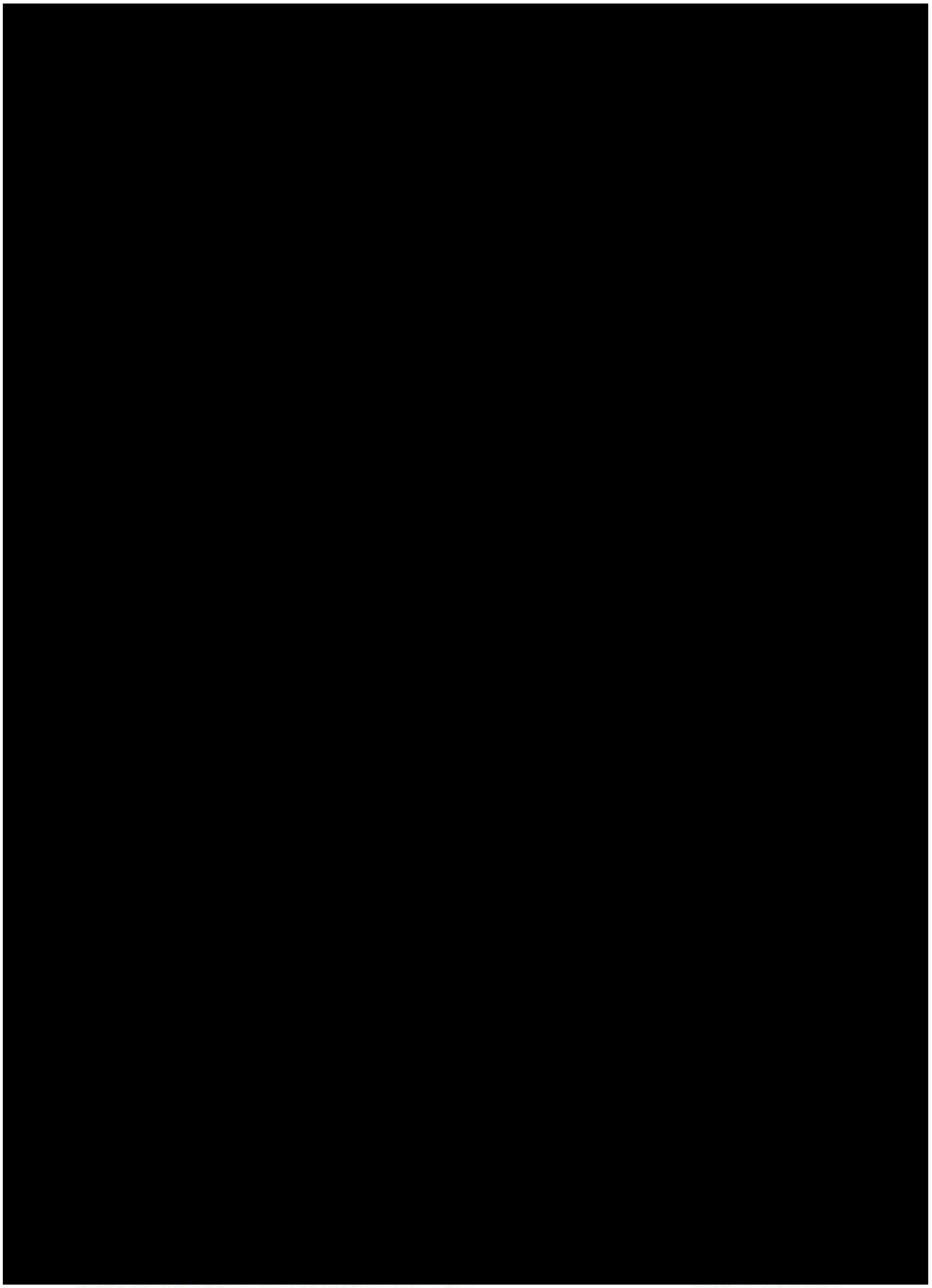
Version 0.12 2015
US/Canadian Version

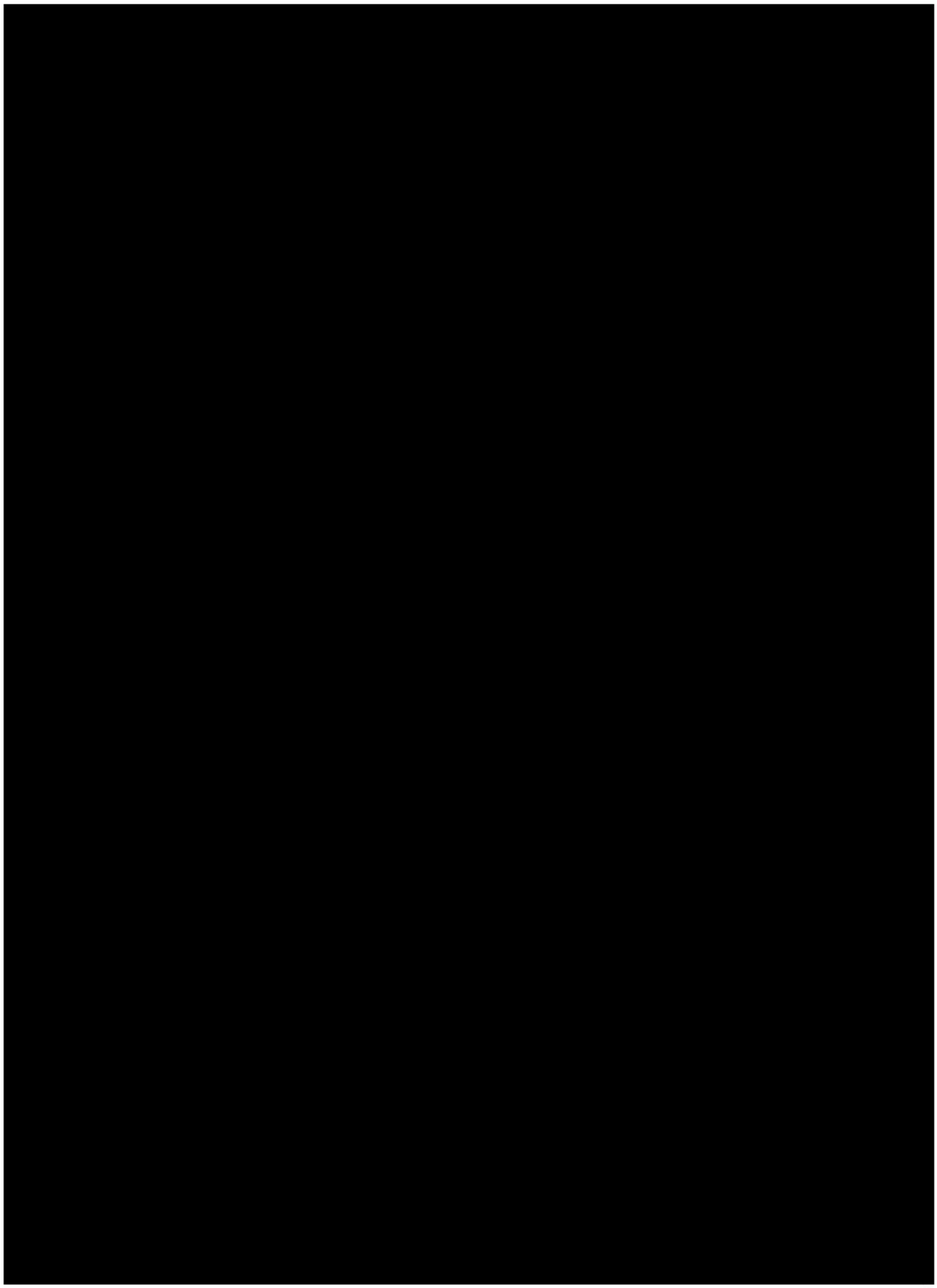


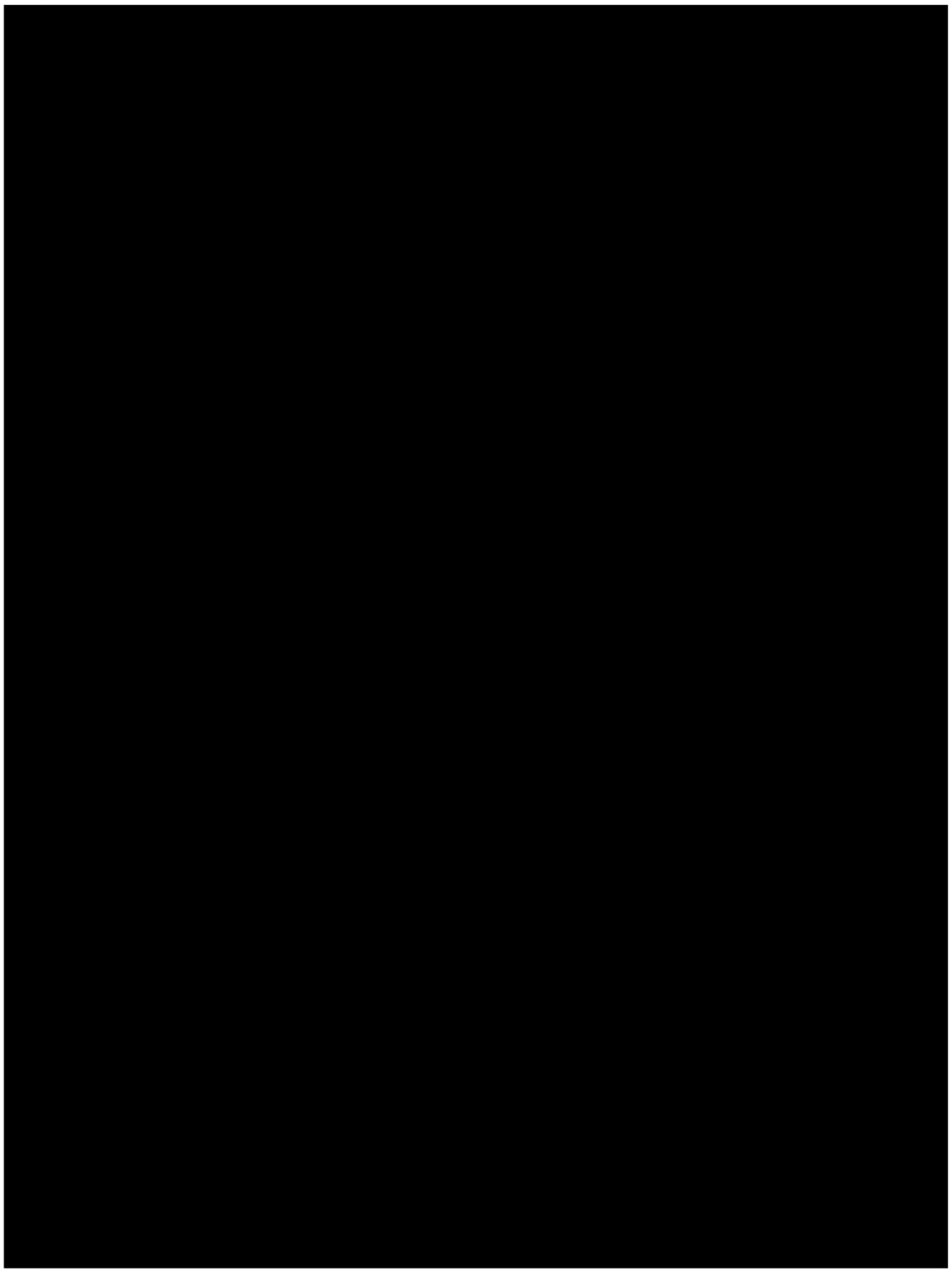


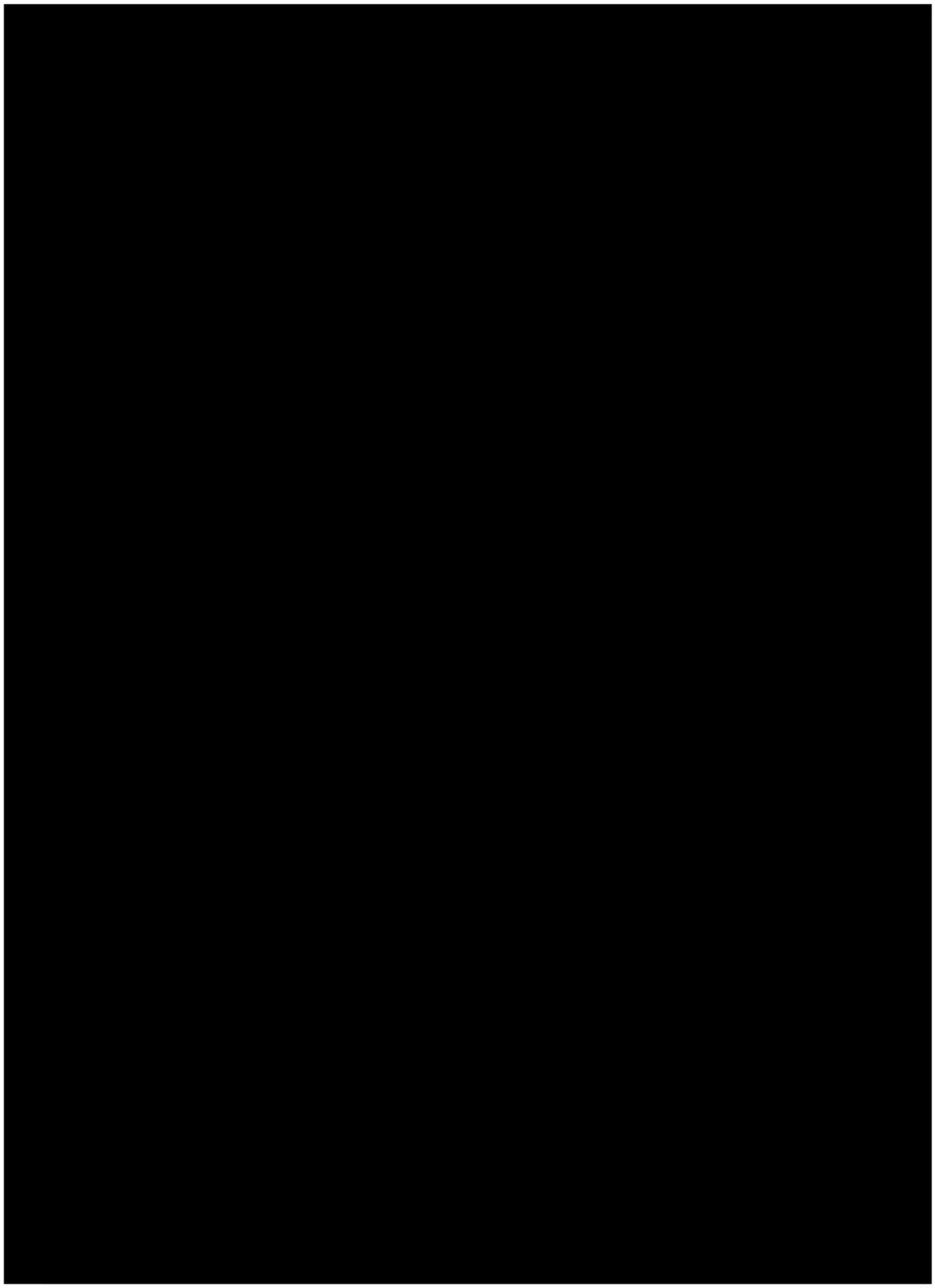


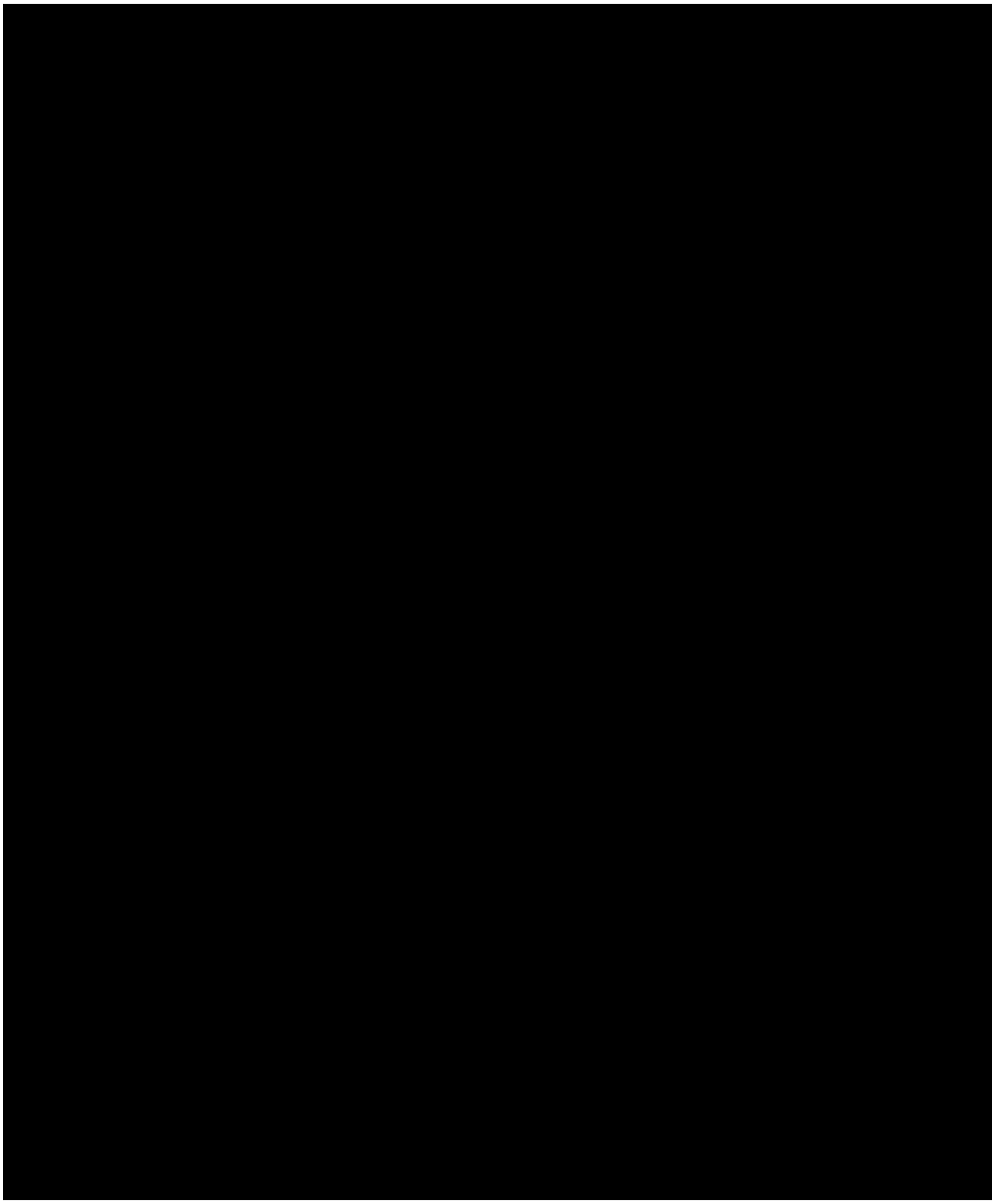


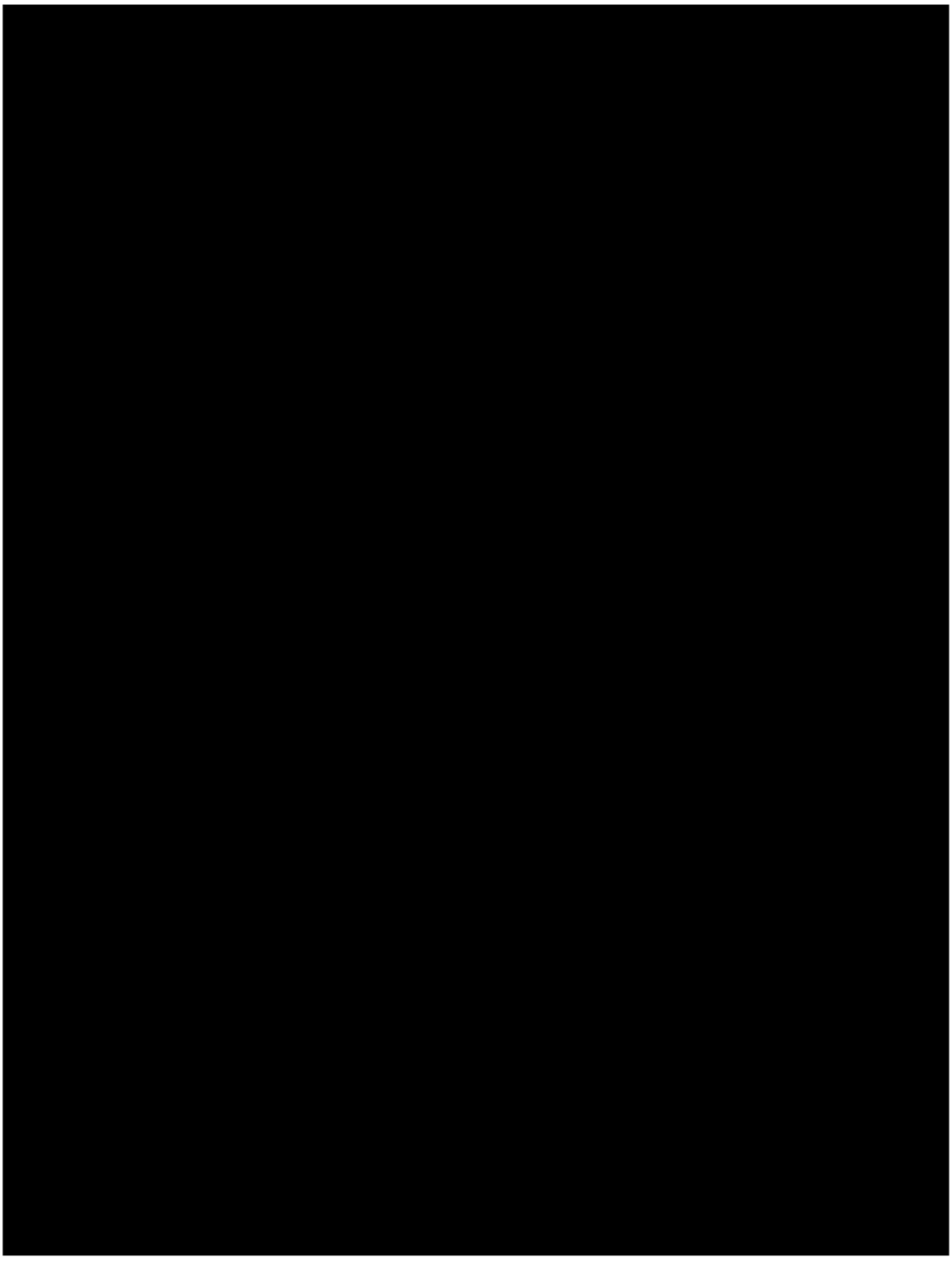


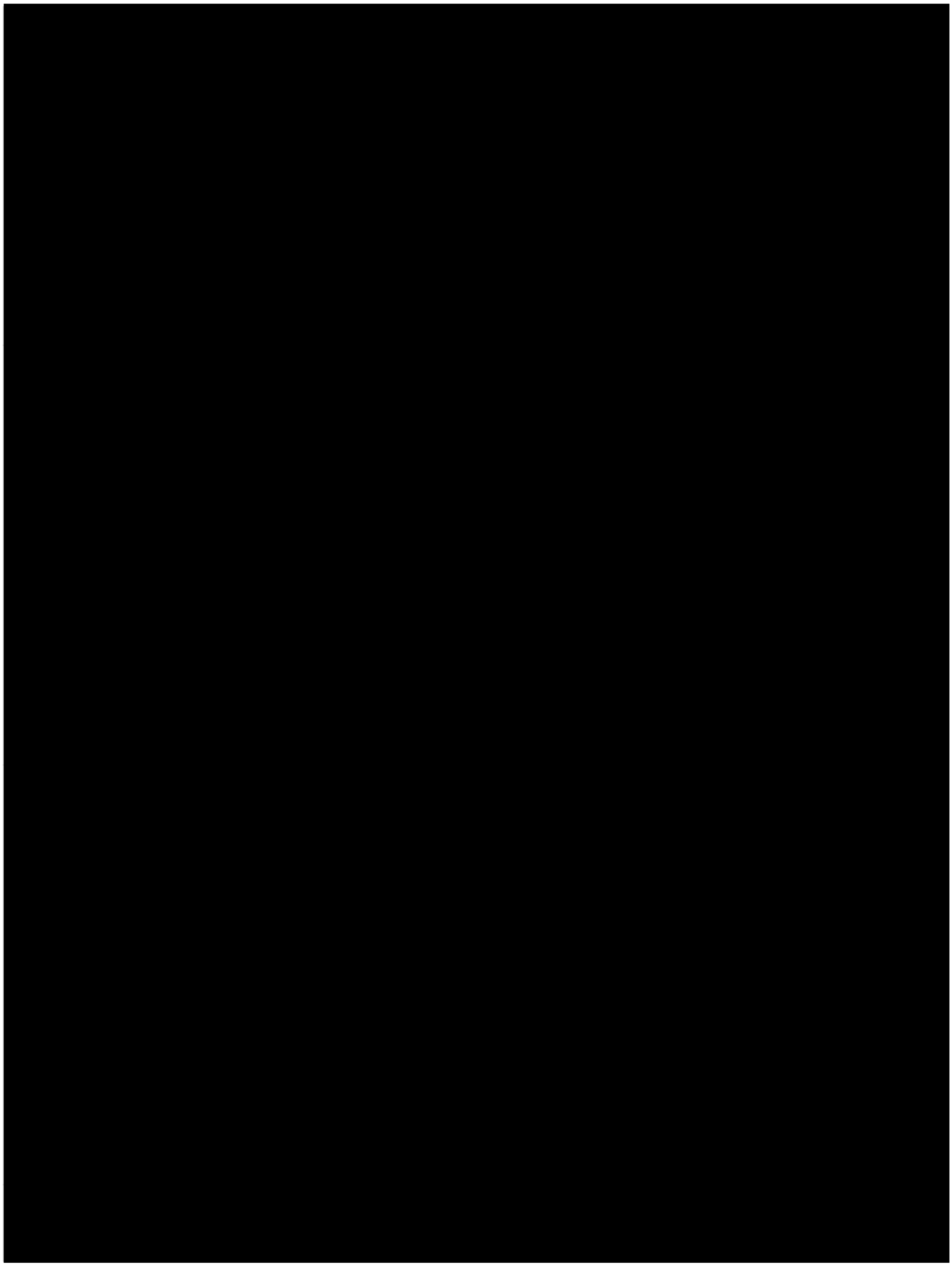


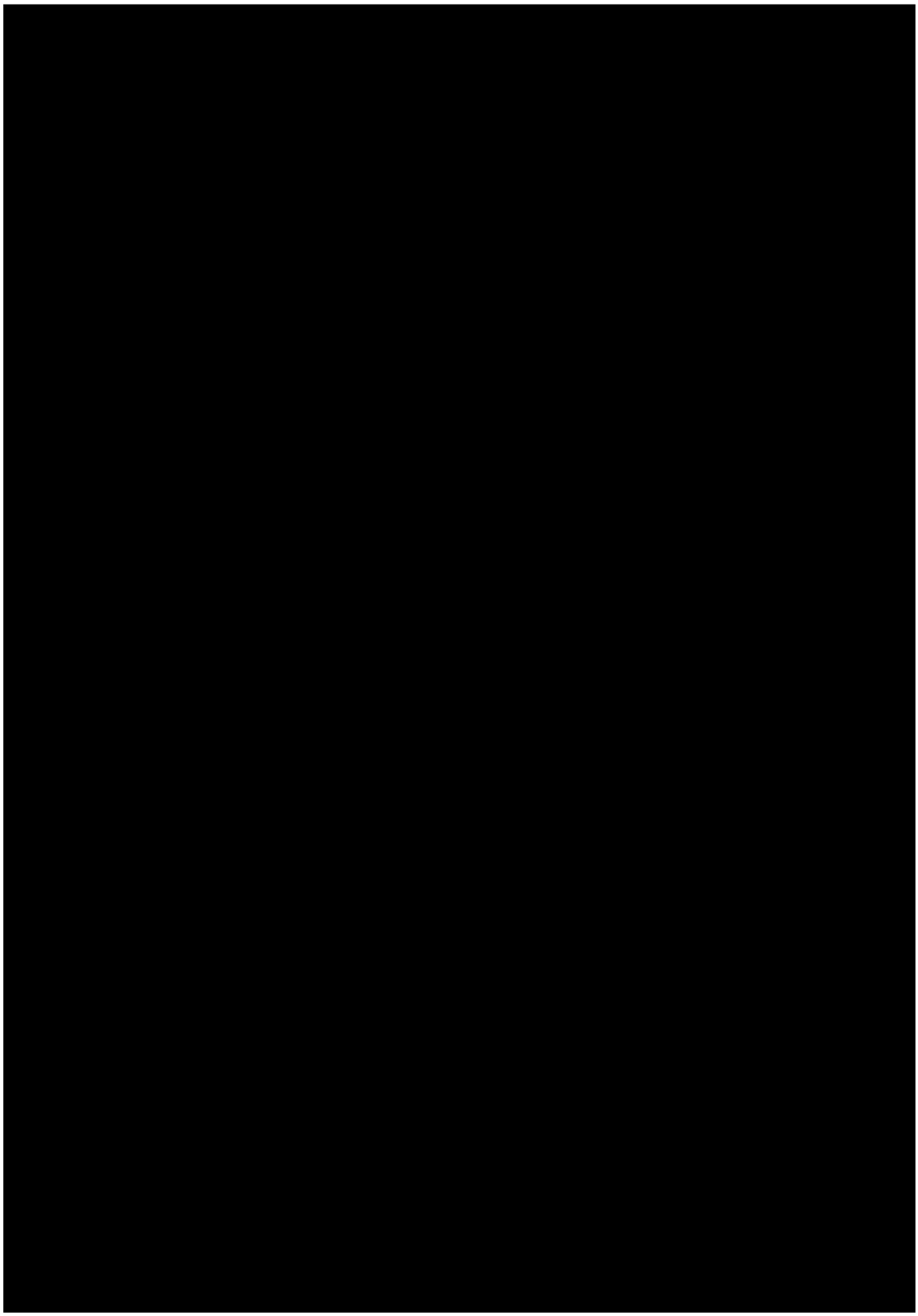


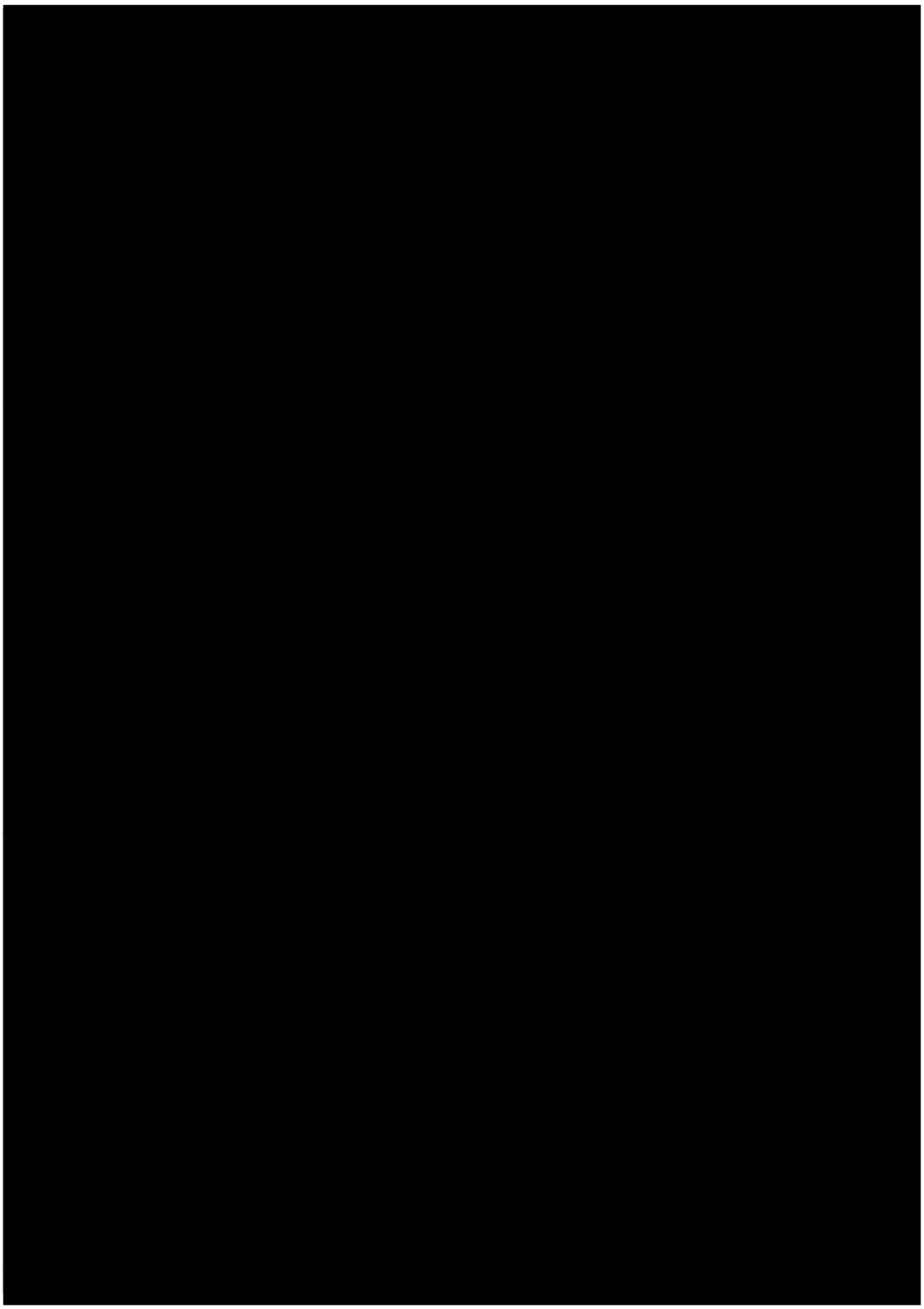


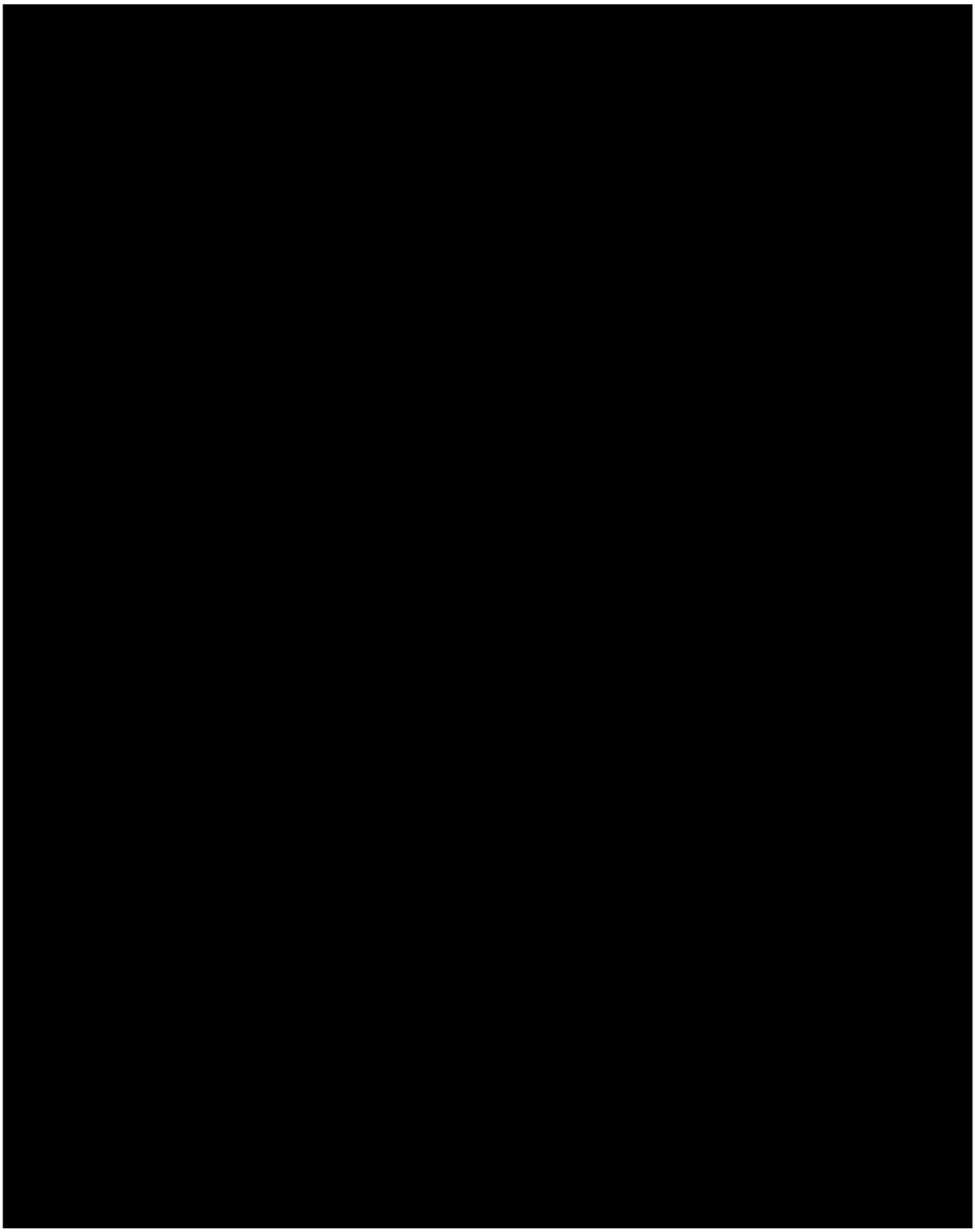












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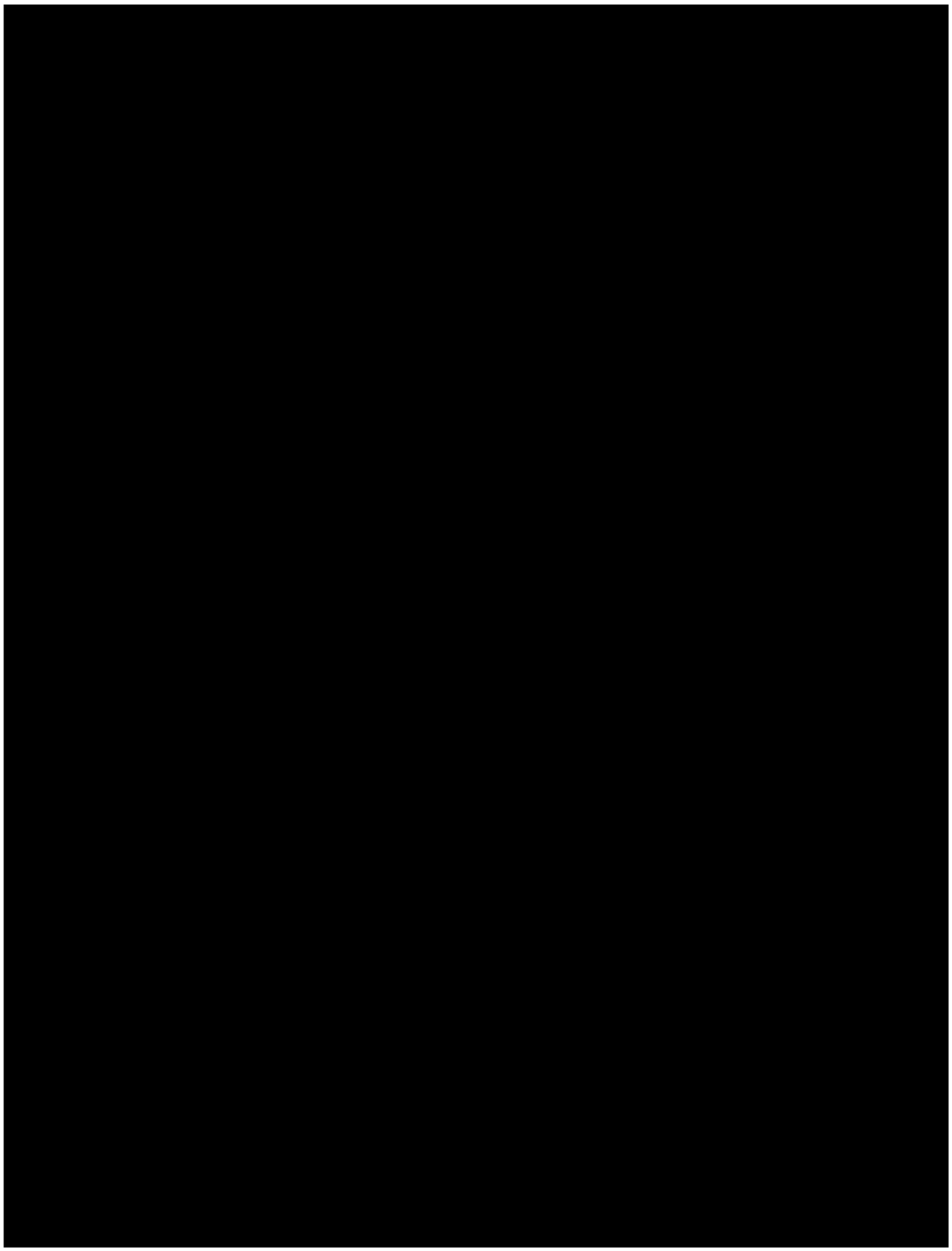
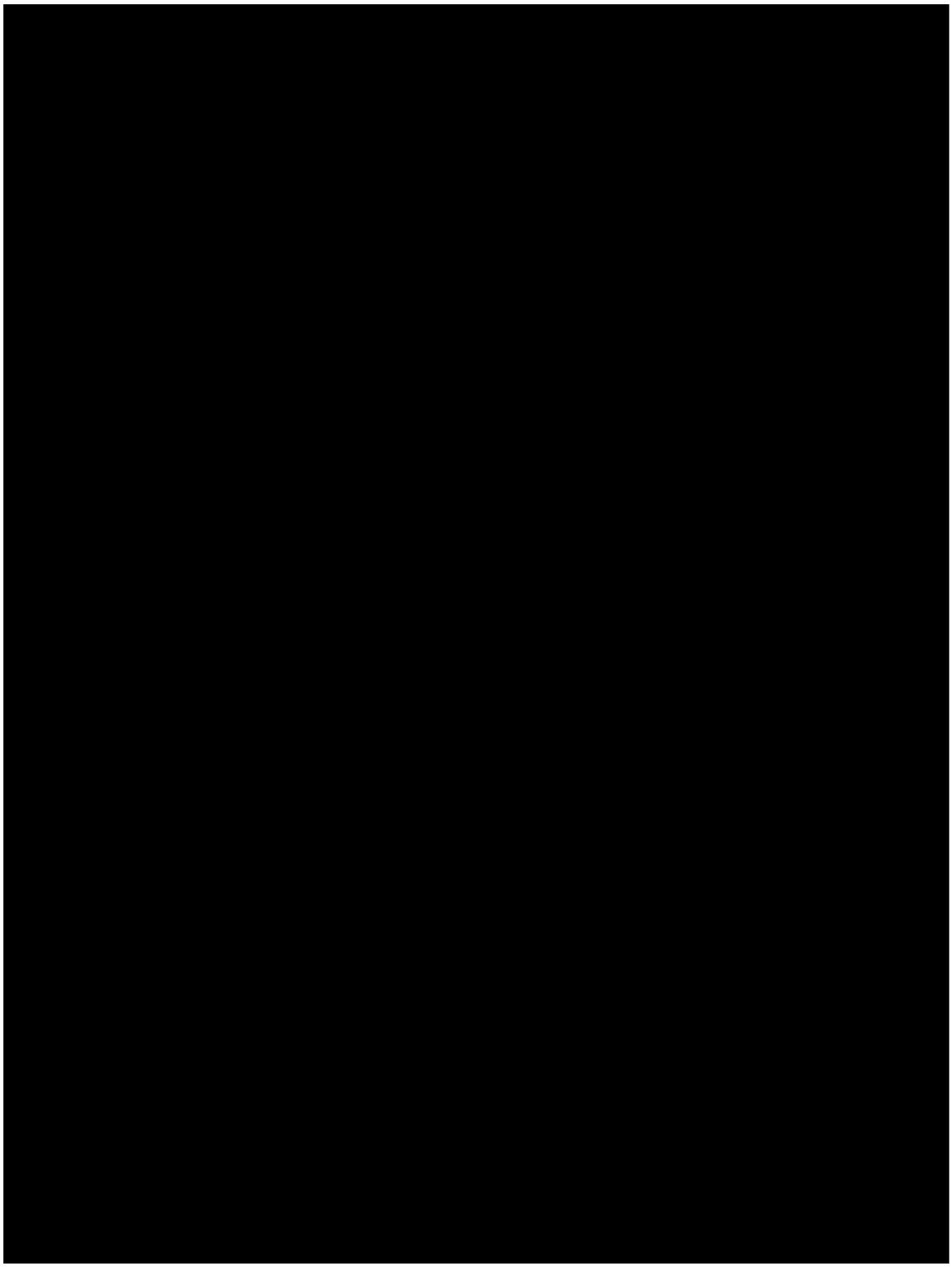
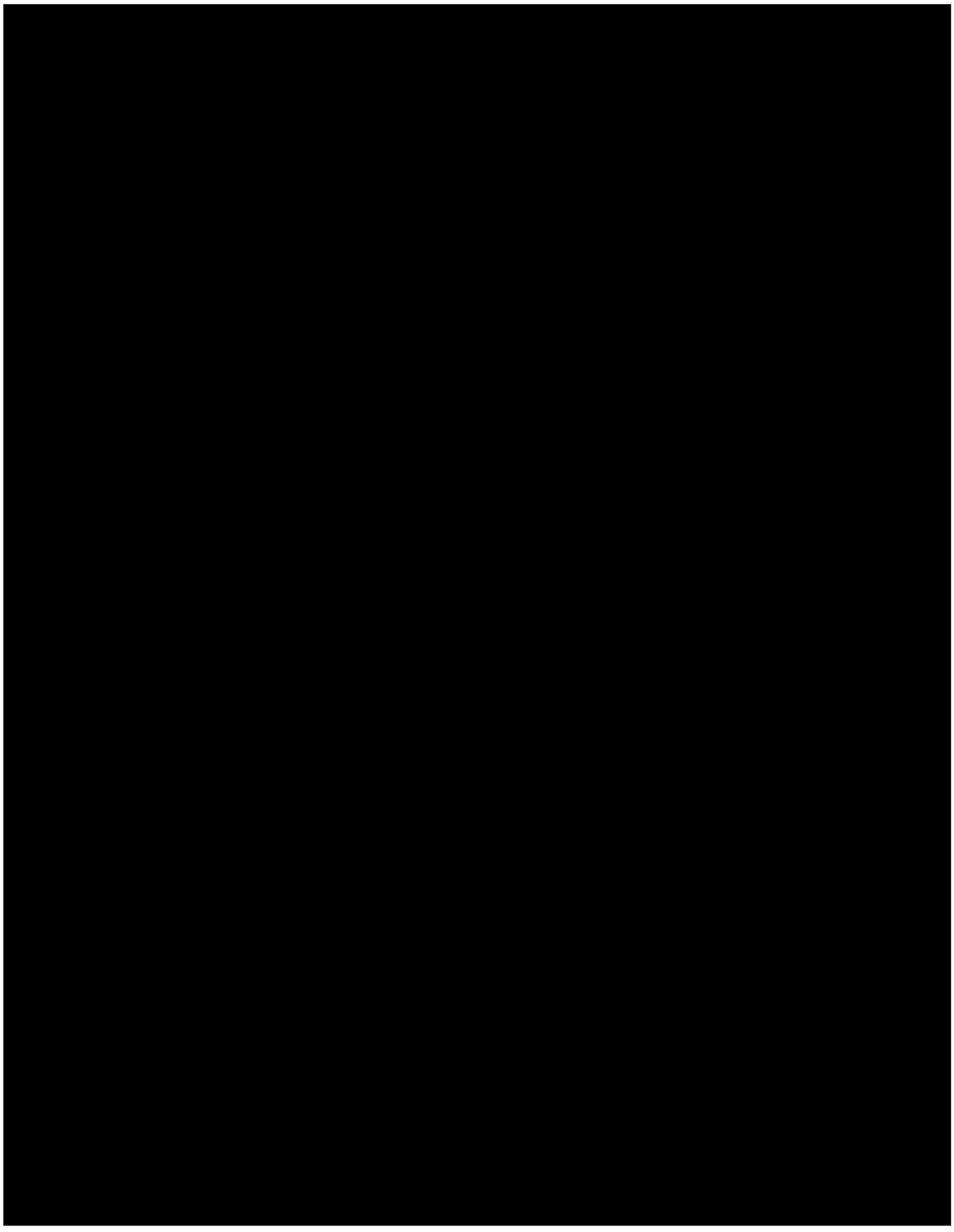
10.14.14 Patient Global Impression of Change (PGIC)

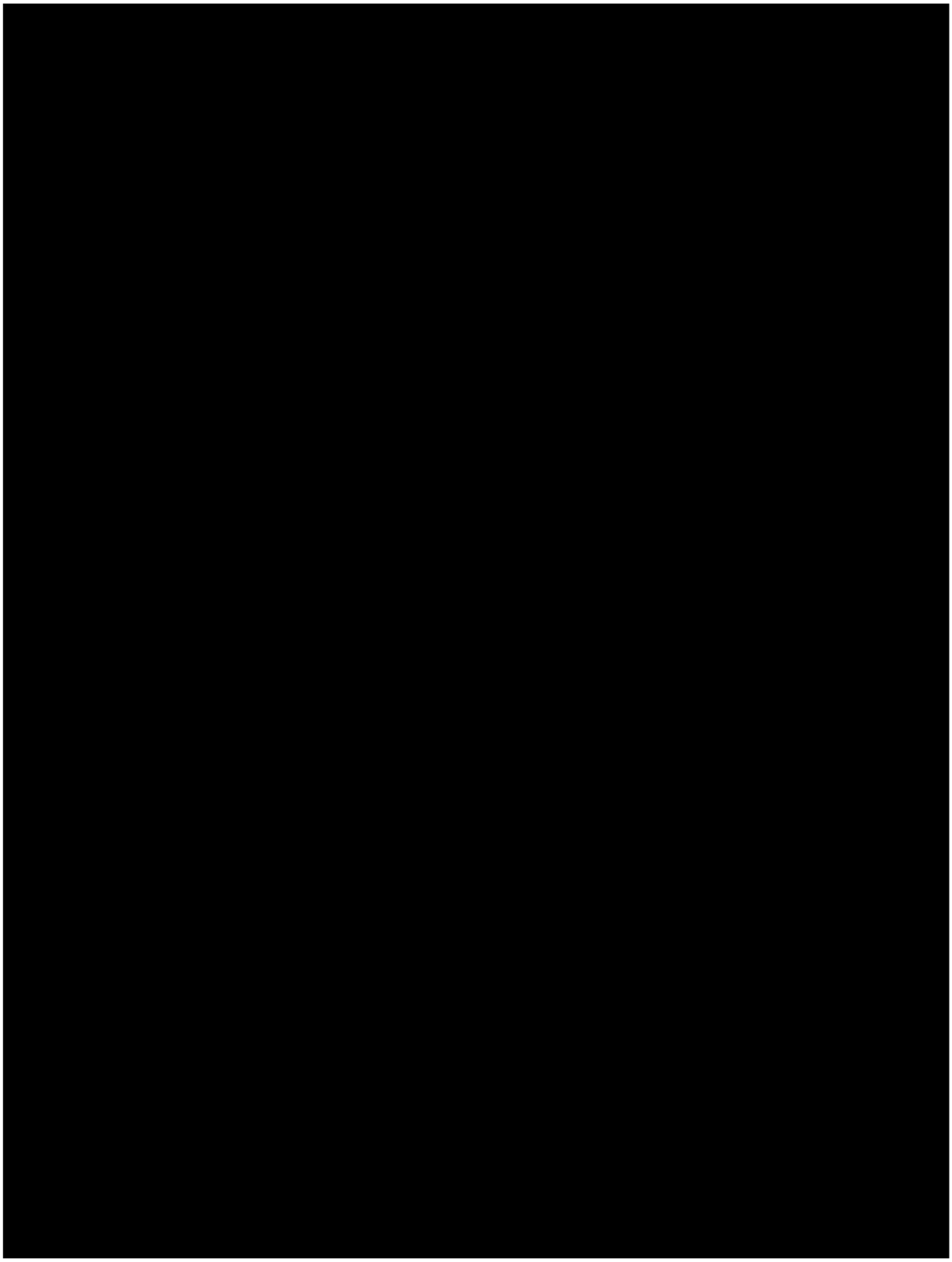
10.14.15 Treatment Preference Survey

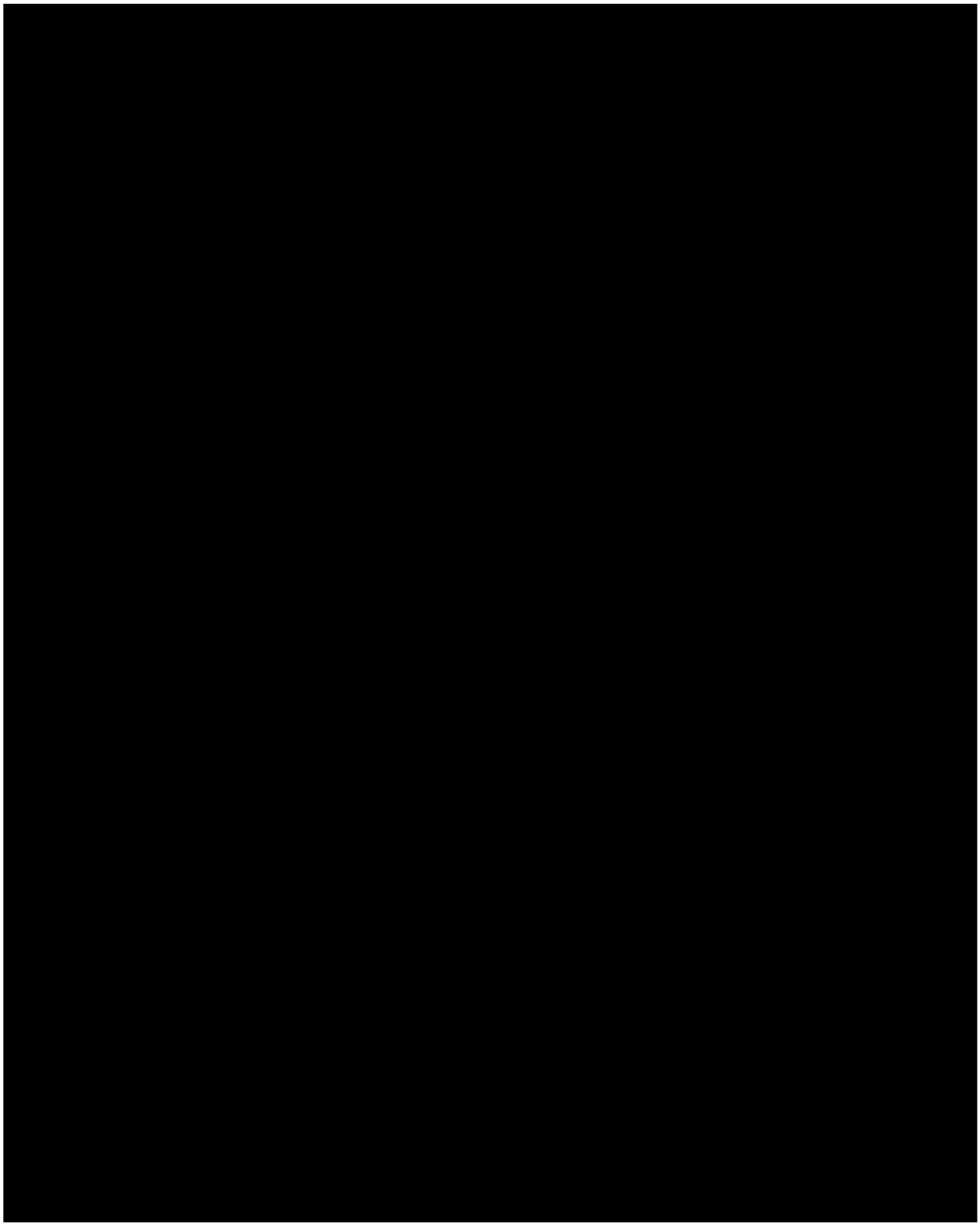
10.14.16 Exit Interview

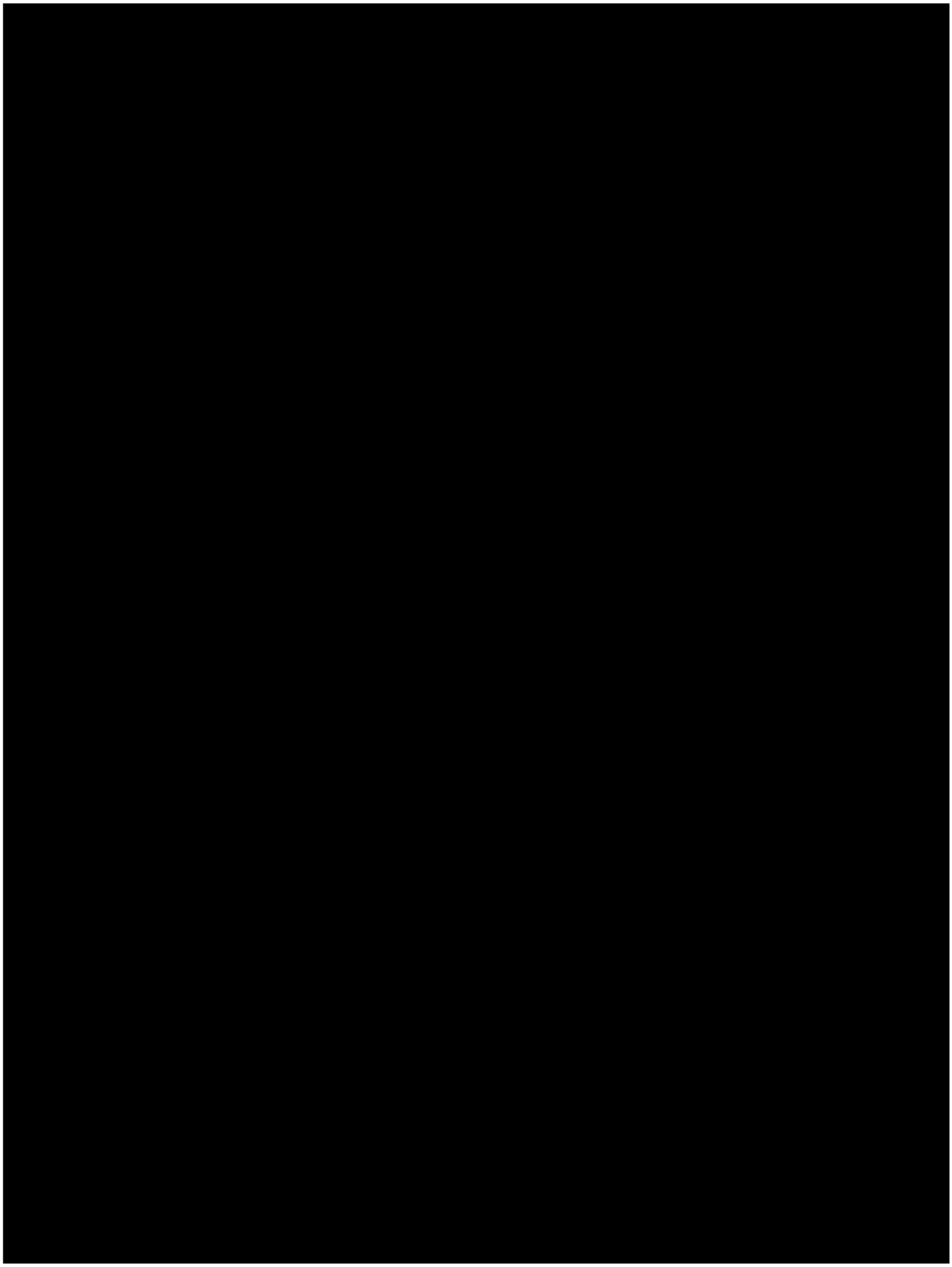


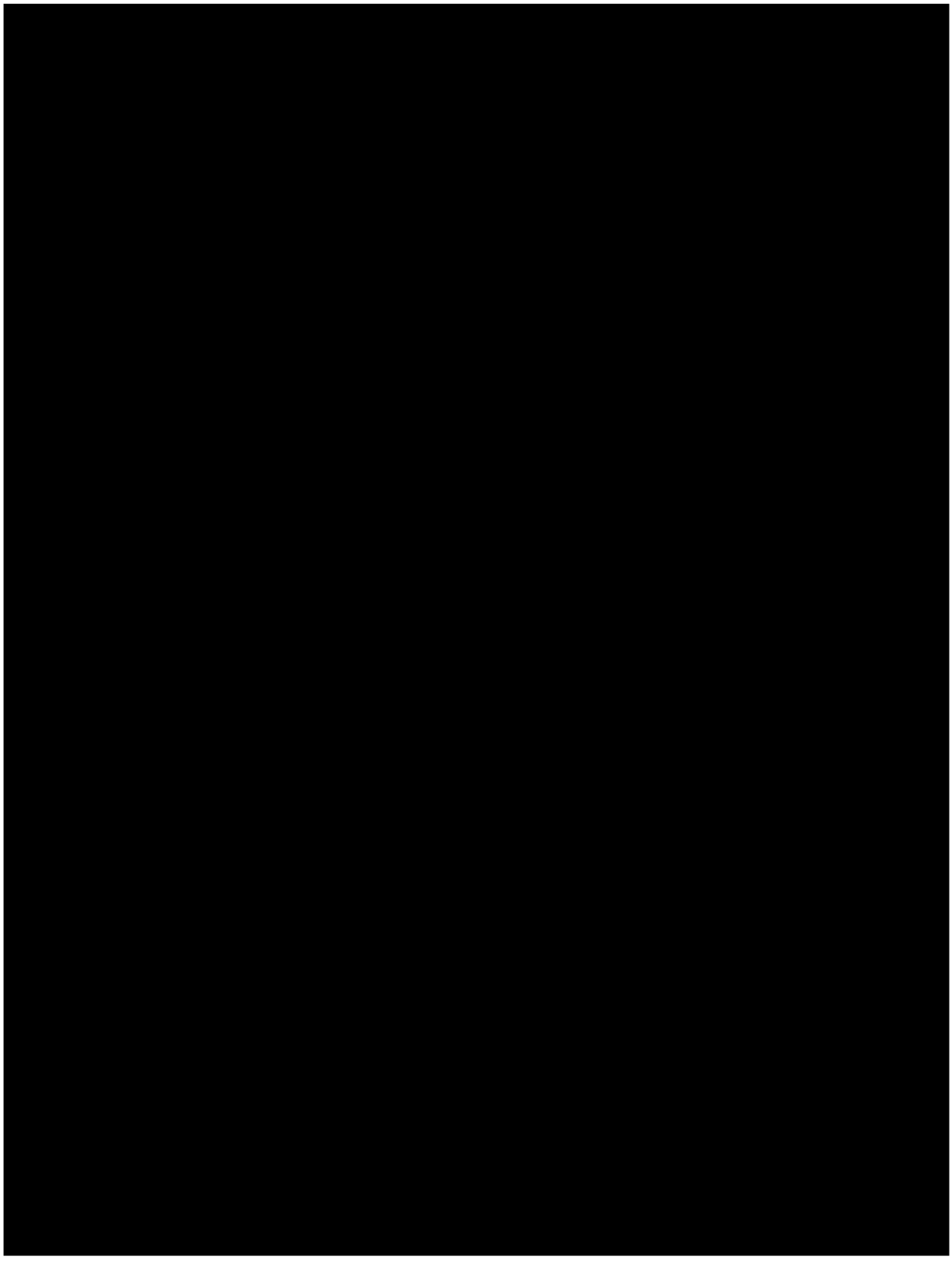


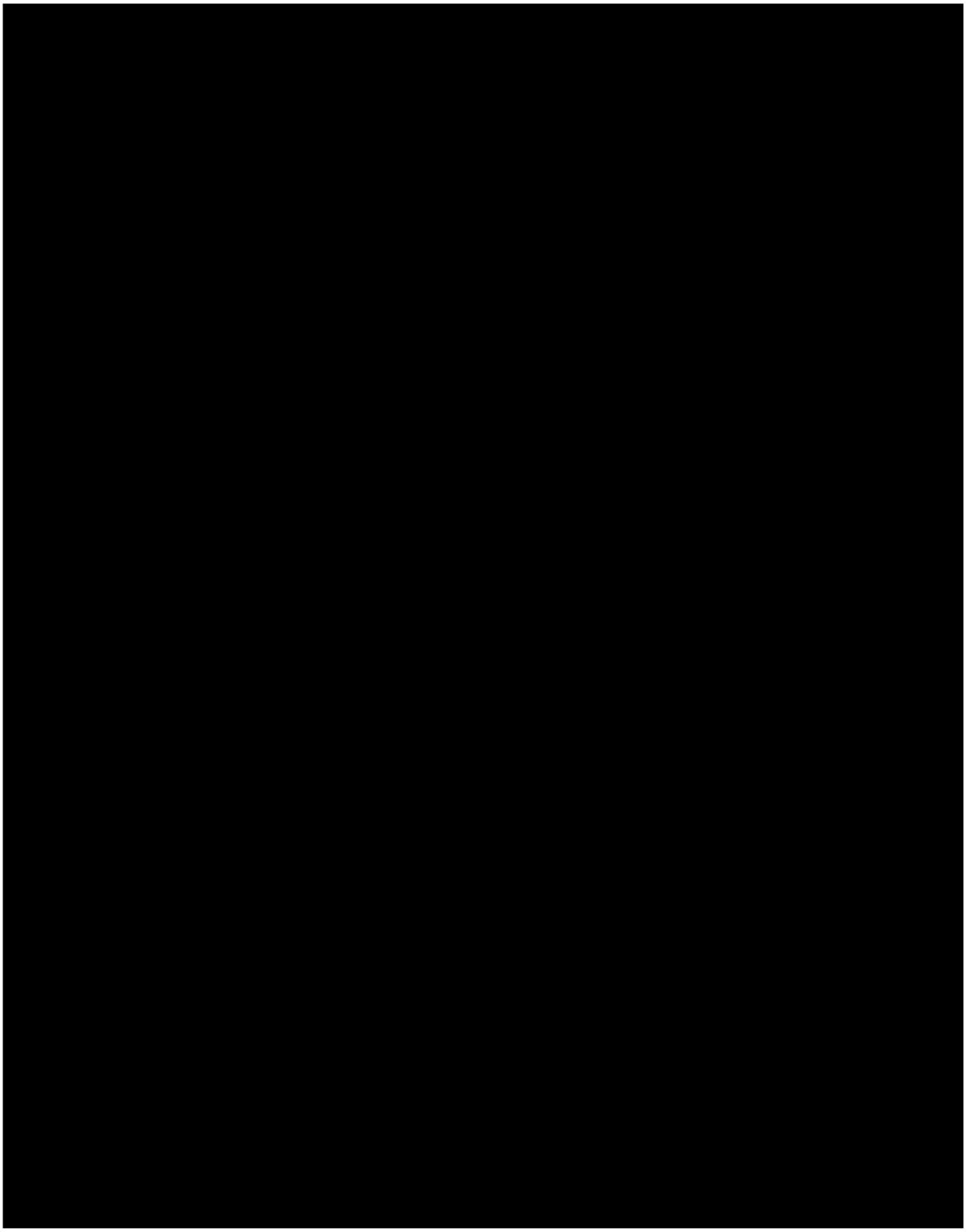


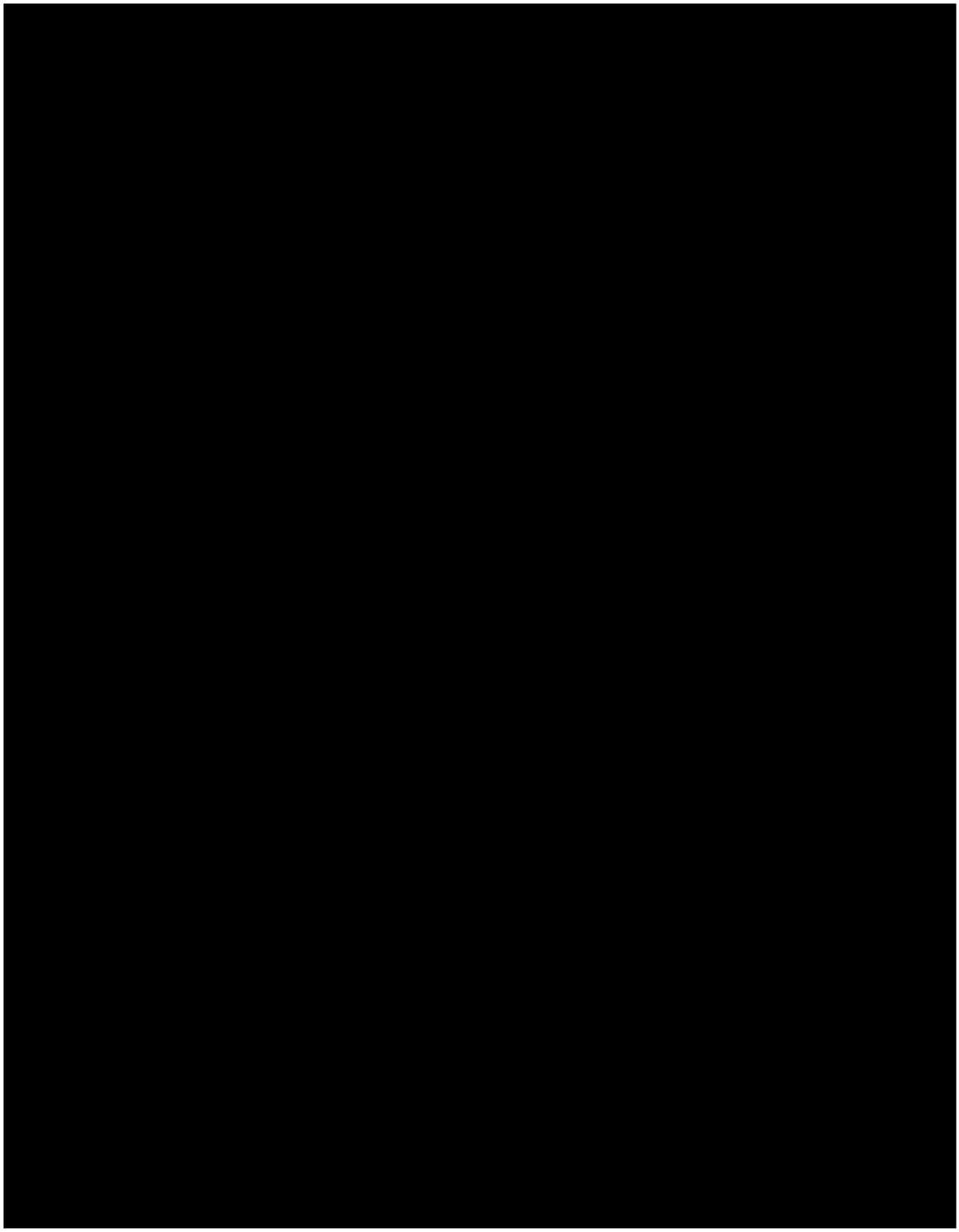


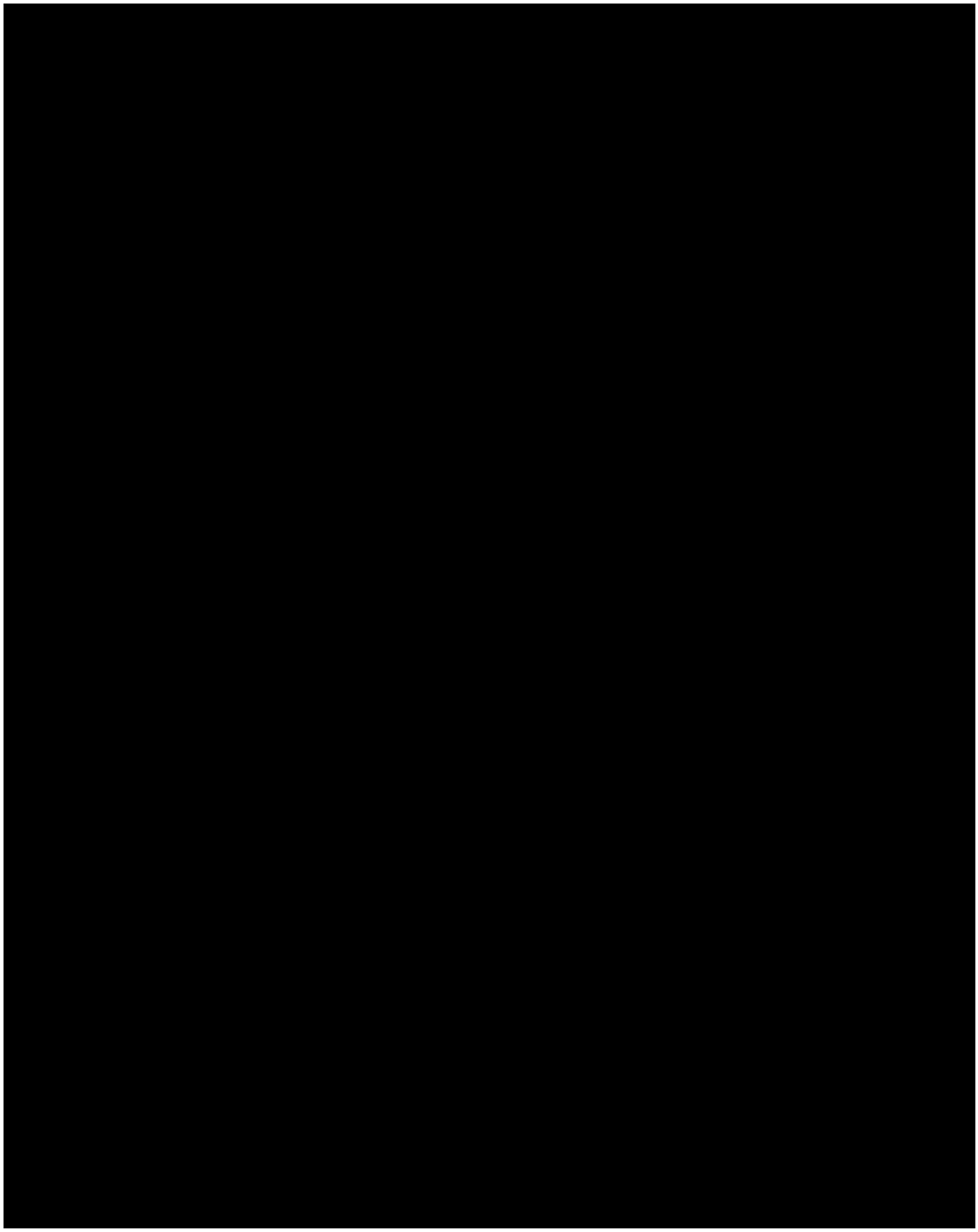


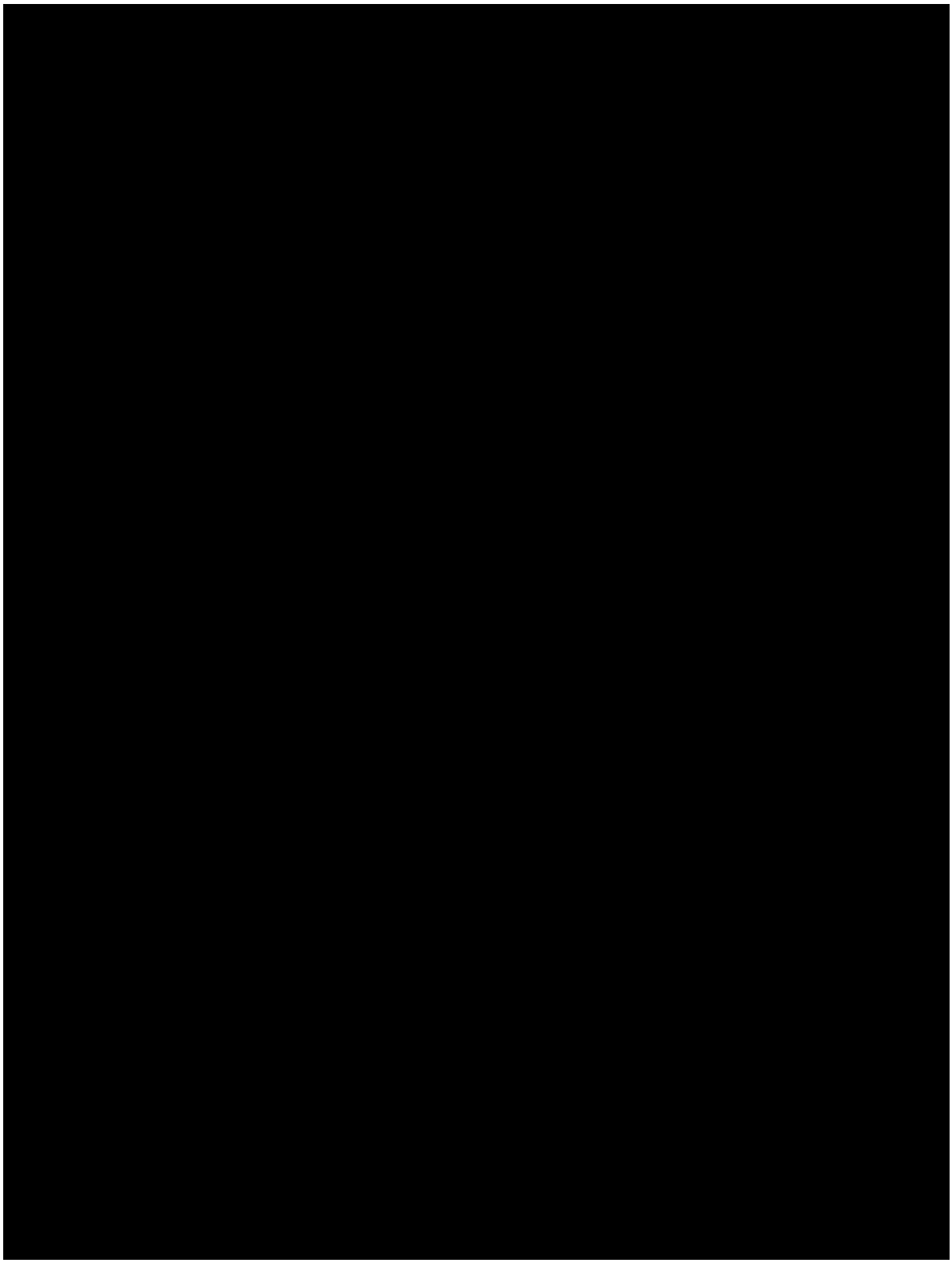


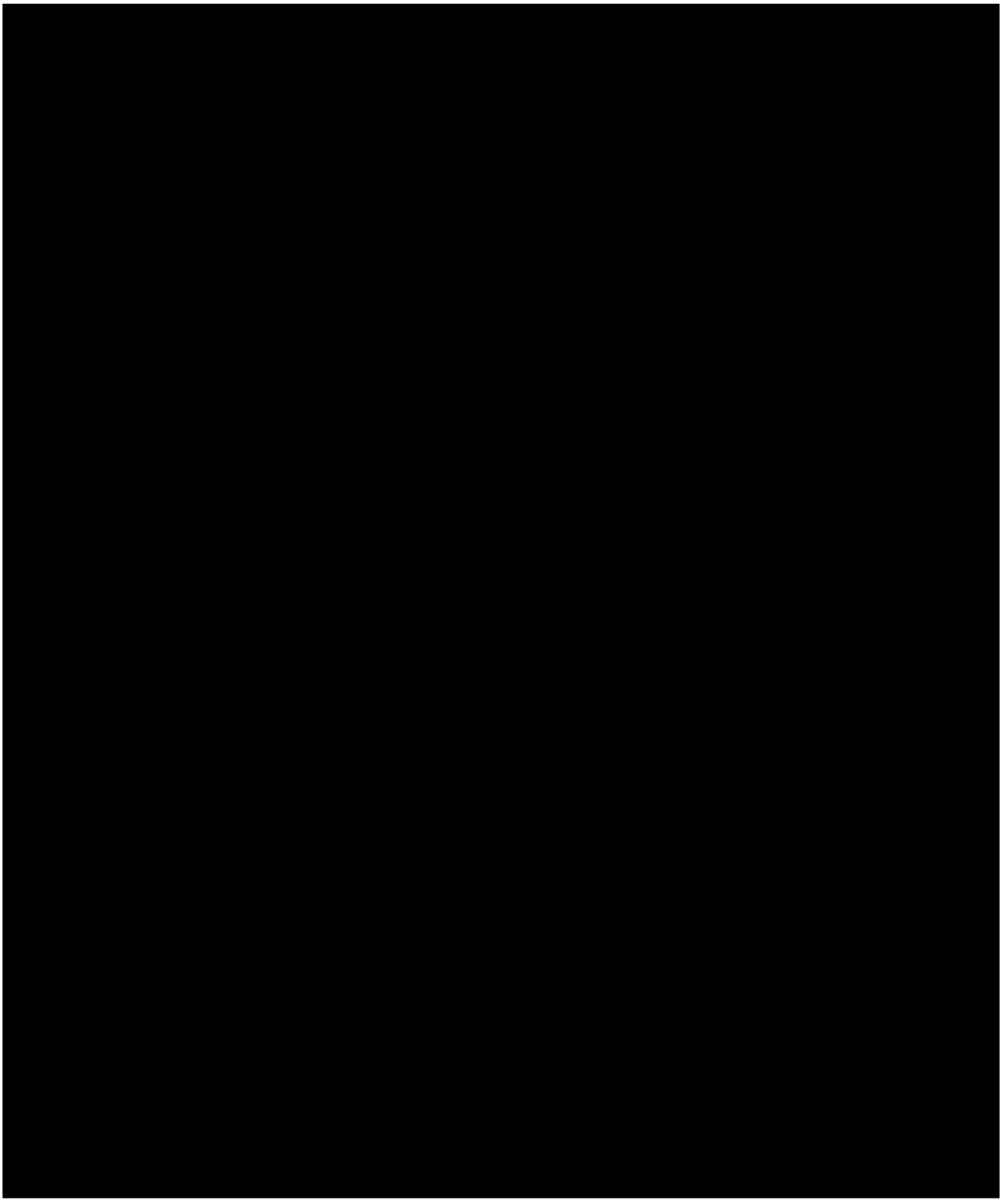


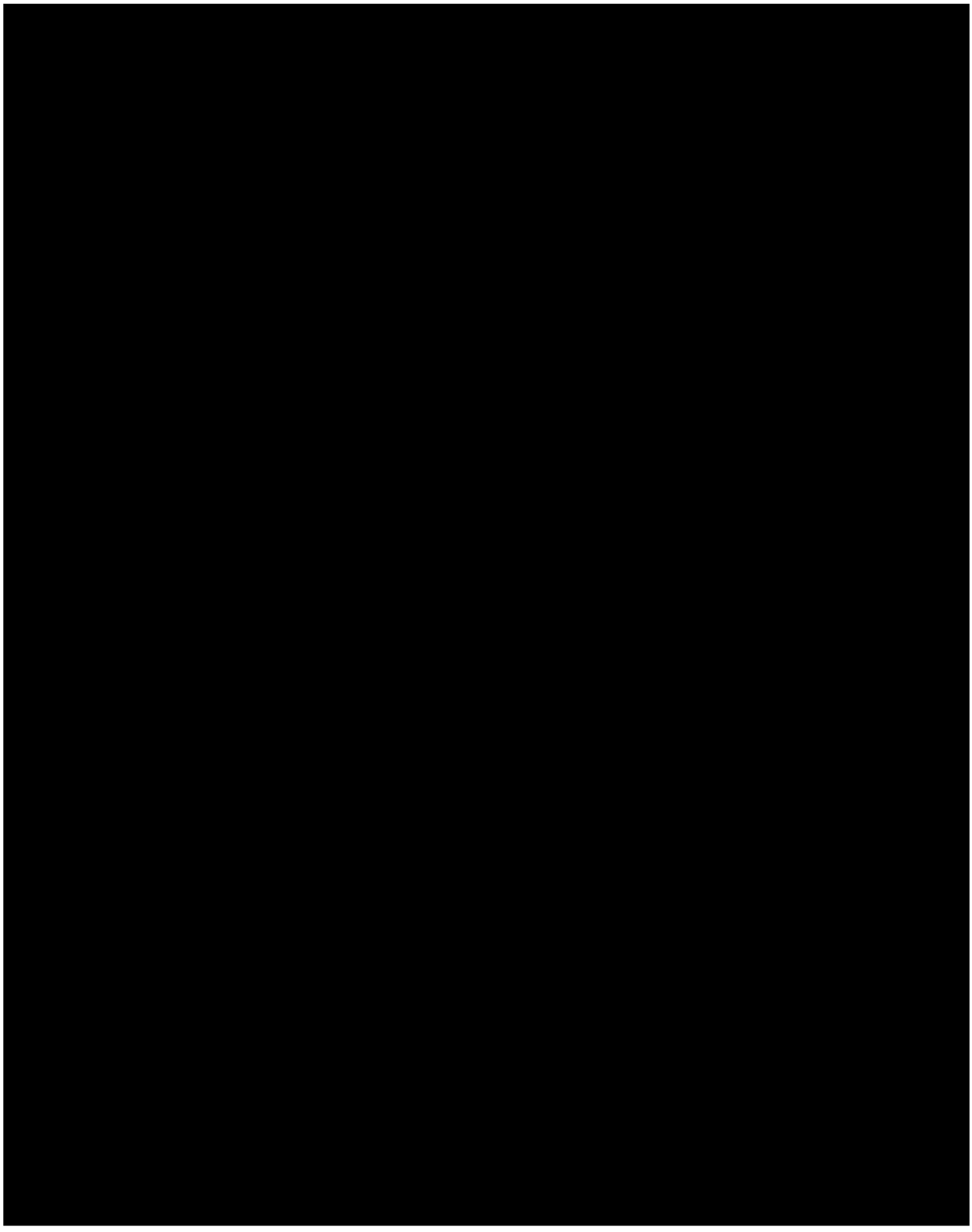


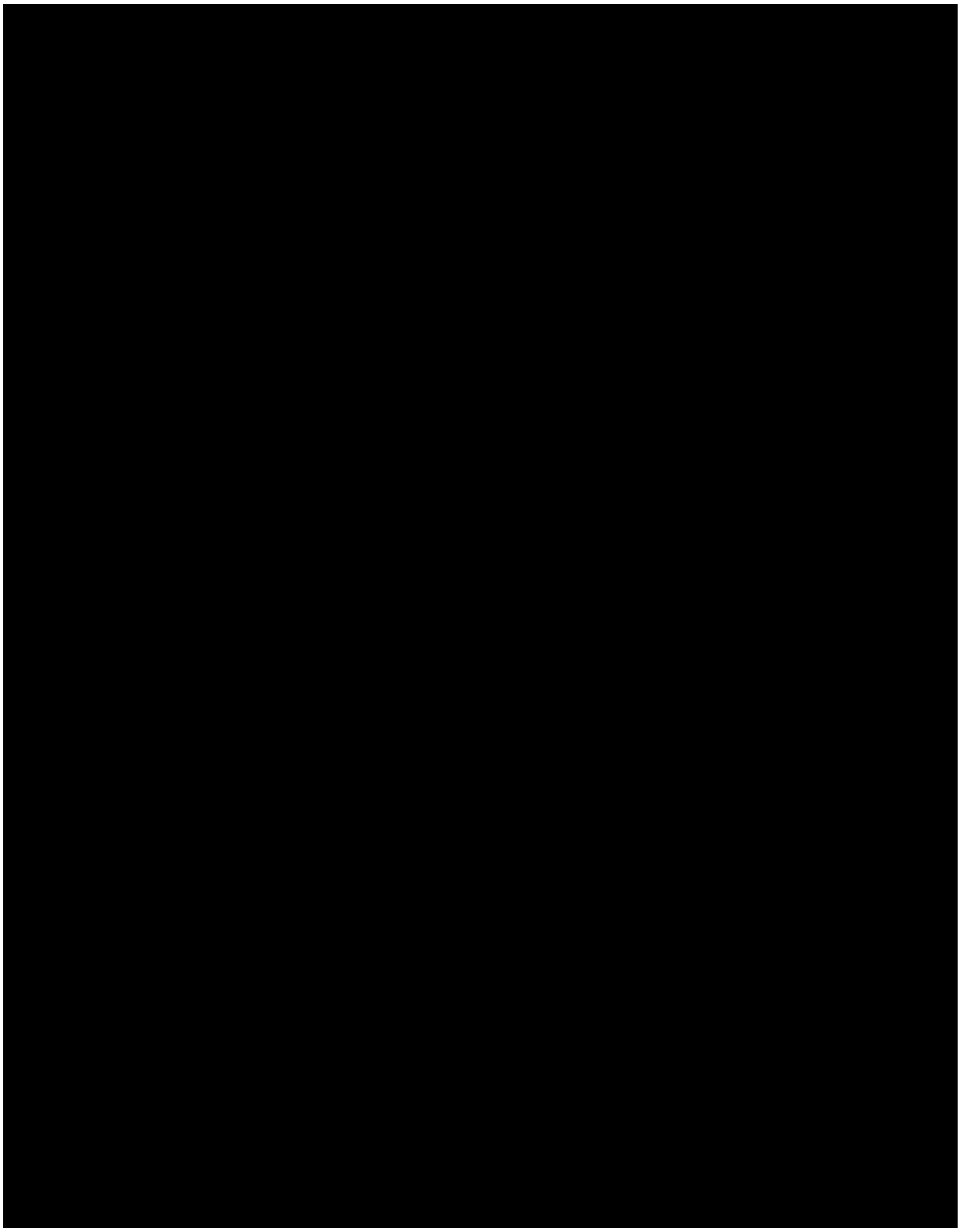












10.14.17 Health Resource Utilization (HRU)

[redacted]

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment 5 is located directly before the Table of Contents (TOC).

Amended protocol 04 (13 May 2020)

This amended protocol 04 is considered to be non-substantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The main reasons for this amendment are the following:

- to modify the requirements for the washout of FVIII products before screening and allow inclusion of patients based on historical FVIII results or documented genotype known to produce severe hemophilia A
- to allow for flexibility in the washout of FVIII products before the Baseline visit in patients participating in the abbreviated PK group
- to allow for faster infusion rate for the BIVV001 injection performed at home
- to clarify that in case of minor surgery the FVIII activity and the BIVV001 dosing at the 24h follow up will be performed only if clinically warranted
- to clarify the reporting of overdoses
- to clarify that 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

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated Sponsor name to - Bioverativ Therapeutics Inc. (a Sanofi Company) Added NCT number - NCT04161495	Administrative change
Section 1.1 Synopsis Overall Design	Added following sentence: The washout period before the Baseline Visit for subjects in abbreviated PK sampling may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor.	Allow for flexibility in the washout before the Baseline visit

Section # and Name	Description of Change	Brief Rationale
Table 1, Table 2, Section 4.1 Overall design - Screening Section 8.5 Pharmacokinetics	Washout prior to the Screening inhibitor test is updated to at least 48 hours (time period to obtain interpretable test results)	Modification of the washout period before the screening visit
	The washout period before the baseline visit or prior to BIVV001 Day 1 dose administration for subjects in abbreviated PK sampling sub-group is updated to be modifiable at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with medical monitor.	Allow for flexibility in the washout before the Baseline visit
Table 1 - Overall schedule of activities from screening to safety follow-up call or visit	Deleted chromogenic assays from FVIII activity assessments at screening visit	Removal of the FVIII chromogenic assay at the screening visit
	Coagulation parameters (aPTT) assessment is added on Baseline, Week 26, and Week 52.	Addition of coagulation parameters at the Baseline visit
	Footnote “c” is updated as described below: Participants should schedule their study visits to be 7 ±1 day after the previous prophylactic dose of BIVV001.	To clarify this is applicable to all patients (not only to the sequential PK arm
	For home BIVV001 injections rate of administration is updated as per Table 7, section 6.1.1.1 Study treatment schedule and administration	To allow for faster injection duration
	Footnote “n” is updated to clarify that for required pregnancy tests after screening, the choice of the pregnancy test (urine or serum) is at the discretion of the Investigator.	Clarification
	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.	Clarification on the type of testing performed
	In prior and concomitant medications, pain medication related to Hemophilia and administered within 2 weeks prior to any visit is to be recorded in CRF.	Clarification
	Ultrasound assessment is updated with flexibility of performance at Baseline visit or up to 2 weeks after the Baseline Visit.	To allow flexibility
	ActiGraph Activity Monitor wearing by patient is updated to 8 consecutive days after the scheduled visits at Screening, Baseline, Weeks 4, 13, 26, 39, and for 8 consecutive days before the Week 52 visit	Clarification
Table 4 - Surgical schedule of activities	Added below text in footnote “g” and “j”, respectively	To clarify the requirement at the 24h follow up in case of minor surgery
	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).	
	The 24h post-operative BIVV001 dosing will be performed only if clinically needed (based on FVIII activity level).	
Section 2.3 Benefit/Risk assessment	The paragraphs pertaining to “Benefits” and “Risks” is updated for clarification.	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	Inclusion criteria I02 is updated as below: I 02. Severe hemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII activity 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	To allow for inclusion based on historical FVIII level or genetic testing
Section 5.1 Inclusion criteria	Inclusion criteria I04 is updated as below: I 04. Current regimen includes one of the following: • Prophylactic treatment regimen with a FVIII product or prophylactic emicizumab therapy for at least 6 months during the previous 12 months. Appropriate washout time needs to be taken into account. • On-demand regimen with a FVIII product with a history of at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment. - On-demand participant is accepting to move to a prophylaxis treatment regimen after 26-week on-demand period.	Removal of the word "marketed" for clarification
Section 5.1 Inclusion criteria	The contraceptive use condition by female participants in Inclusion criteria I08 is updated as below: - A WOCBP must have a negative highly sensitive pregnancy test before the first dose of study intervention as described in Section 10.2. A serum pregnancy test should be performed at screening. For all other time points, the choice of the pregnancy test (urine or serum) is at the discretion of the Investigator.	To clarify that for required pregnancy tests after screening, the choice of the pregnancy test (urine or serum) is at the discretion of the Investigator
Section 5.3 Exclusion criteria	Exclusion criteria E11 is updated as below: Treatment with acetylsalicylic acid (ASA) or non-NSAID anti-platelet therapies within 2 weeks prior to screening Exclusion criteria E23 is removed.	To add non NSAIDs antiplatelet agent to the exclusion criteria
Section 6.1.1.1 Study treatment schedule and administration	Following paragraph is added: During Scheduled study visit BIVV001 will be delivered via a slow push IV injection of 8 ±2 minutes, at a rate of administration determined by the participant's comfort level. For all BIVV001 injections performed at home BIVV001 will be delivered via a slow push IV injection at a rate of administration determined by the participant's comfort level according to the vial injection rate recommendations (Table 7). Following table is added:	To allow shorter duration of the BIV001 infusion administered at home

Section # and Name	Description of Change	Brief Rationale
	Table 7 – Home Injection: BIVV001 weight-based vial injection rate recommendations Participant Weight: Minimum Injection Duration Per Vial <=55 kg: 2 minutes per vial >55 kg: 1 minute per vial Following sentence is deleted: BIVV001 will be delivered via a slow push IV injection of 8 ±2 minutes at a rate of administration determined by the participant's comfort level.	
Section 6.1.1.4 Surgical dosing	Added text for sending a portion of the samples to the central laboratory for analysis.	Clarification
Section 6.2 Preparation/ Handling/ Storage/ Accountability	Added option for drug delivery from clinical sites directly to patient's home, in exceptional circumstances.	For crisis management
Section 6.2.4 Study drug administration	The following sentence is added: 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.	To clarify PK sampling procedures during study visits
Section 6.5 Concomitant Therapy	Non-NSAID anti-platelet therapies is added in prohibited concomitant therapy during the study	Addition of non-NSAID anti-platelet therapy to prohibited medication
Section 6.7 Intervention after the end of the Study	Paragraph regarding long-term trial participation is updated as below: 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.	Clarification
Section 8.1.1.6 Surgery	Sentence describing end of surgical/rehabilitation period is updated. Paragraph describing requirement for minor surgeries is updated.	To clarify the requirement at the 24h follow up in case of minor surgery
Section: 8.1.3 Physical activity monitoring	The paragraph regarding physical activity is updated.	To clarify the period when the device is worn by the patient
Section 8.1.4 Ultrasound measures (if applicable)	The section regarding ultrasound measures is updated for clarification	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.3.1.1 Other compound specific AESI(s)	Definitions of Grade 3, 4 and 5 allergic reactions are added	Clarification
Section 8.3.2 Time period and frequency for collecting AE and SAE information	The sentence regarding SAE causality is updated as below: 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.	Clarification
Section 8.3.4 Follow-up of AEs and SAEs	The sentence for SAE and AESI follow ups is updated as below: At the pre-specified study end-date, all SAEs, and AESIs [and non-serious AEs of special interest (as defined in Section 8.3), will be followed until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3).	Clarification
Section 9.4.3 Pharmacokinetics	Deleted below text: Non-compartmental PK analyses will be described fully in the statistical analysis plan finalized before database lock.	Clarification
Section 10.2 Appendix 2: Clinical Laboratory Tests	Table 14 - Protocol-required laboratory assessments updated for consistency along with Table 1	For consistency with table 1
Section 10.5 Appendix 5: Overdose	Added new appendix for information on reporting of Overdoses	To add information on reporting of overdoses
Section 10.9 Appendix 9: Washout and Blood Sampling Summary	Appendix 9 is updated for consistency along with Table 1 and PK chart	For consistency

Amended protocol 03 (06 Apr 2020)

This amended protocol 03 is considered to be non-substantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

Based on the request from Italy Competent Authority (AIFA) the protocol is amended to update an exclusion criterion related to renal function, as well as to add additional assessments for height and physical examination.

Protocol amendment summary of changes

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Added note on E07 with reference to Appendix 10.10.2 Italy	Appendix for Italy-specific requirements added as per AIFA request
Section 1.3 Schedule of Activities (SOA)	Added footnote with reference to Appendix 10.10.2 Italy	Appendix for Italy-specific requirements added as per AIFA request
Appendix 10.10 Country-specific requirement: Appendix 10.10.2 Italy	Added this appendix for country-specific requirement for Italy with changes as below: Modified Exclusion criterion E07 from: Abnormal renal function, defined as serum creatinine >2.0 mg/dL taken at Screening to: E07 Impaired renal function, defined as creatinine clearance by Cockcroft-Gault formula <60 mL/min (for ≥18 years) or glomerular filtration rate by Bedside Schwartz formula <60 mL/min/1.73m2 (for <18 years) And Addition of height measurement at Day 1, Week 26, and Week 52 visits for participants 12-17 years of age And Addition of physical exam at Week 13 and Week 39.	Added as per AIFA request

Amended protocol 02 (06 Feb 2020)

This amended protocol 02 is considered to be nonsubstantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it does not significantly impact the scientific value of the study].

OVERALL RATIONALE FOR THE AMENDMENT

Based on the scientific advice from French Health Authority (ANSM), the protocol is amended to add a new exclusion criterion, add a pregnancy testing control at the safety follow-up visit, and provide clarity that the patient has the option at the end of the study to join a planned long-term study. Based on comments from the French Ethics Committee exclusion criterion E23 has been removed.

Protocol amendment summary of changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (Table 1)	The following sentence was added in footnote "f": For France-specific pregnancy testing at the safety follow-up visit refer to Section 10.10.1.	Added per French Health Authority request
Section 4.4 End of Study Definition Section 4.5 Study Stopping Rules	The following sentence was added: "For France-specific clarification on end of study refer to Section 10.10.1.	Added per French Health Authority request
Section 5.2 Exclusion Criteria	The following sentence added to exclusion criterion E23: For France-specific E23 requirements refer to Section 10.10.1. The following sentence was added: For additional France-specific exclusion criteria refer to Section 10.10.1.	Based on comments from the French Ethics Committee exclusion criterion E23 has been removed Added per French Health Authority request
Appendix 10.10 Country-specific requirement: Appendix 10.10.1 France	The following France-specific protocol revisions are provided in this appendix • A pregnancy assessment was added to the schedule of activities at the safety follow-up visit • Footnote "f" in the schedule of activities was revised to specify that for female participants in France, a visit must be conducted for purposes of pregnancy testing • Footnote "ii" was added to the schedule of activities to specify that pregnancy testing at the safety follow-up visit will be for France only • A statement was added in Section 4.4 (End of Study Definition) and Section 4.5 (Study Stopping Rules) to clarify that at the end of study eligible patients will have the option to participate in a planned long-term extension study • The exclusion criterion E23 "Any specific situation during study implementation/course that may raise ethical considerations" was removed from Section 5.2. • A new exclusion criterion E25 was added in Section 5.2 as follows: History of an unprovoked venous thromboembolism, myocardial infarction within 12 months prior to screening, or occlusive cerebral vascular	Added per French Health Authority request or based on comments from the French Ethics Committee

Section # and Name	Description of Change	Brief Rationale
	accident within 12 months prior to screening. Patients who have experienced thrombosis associated with indwelling venous access may be enrolled.	

Amended protocol 01 (28 August 2019)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union [because it significantly impacts the scientific value of the study].

OVERALL RATIONALE FOR THE AMENDMENT

Based on the final results of the repeat dose study and in alignment with scientific advice from Health Authorities, the protocol is amended to modify the dose regimen, efficacy endpoint analysis pertaining to an intra-patient comparison, and the safety endpoint of "the occurrence of vascular thrombotic events".

- The prophylactic dosing regimen was amended from 65 IU/kg to 50 IU/kg once weekly (QW). For consistency and in accordance with the weekly prophylaxis dose, the treatment of a bleeding episode and the pre-operative loading dose has also been adapted to 50 IU/kg. The treatment of a bleeding episode will also consist of a single injection of 50 IU/kg. If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. The surgical treatment regimen will consist of a pre-operative loading dose of 50 IU/kg, with additional doses of 30 or 50 IU/kg every 2 to 3 days depending on the desired FVIII activity levels and the severity of the procedure.
- A key secondary efficacy endpoint analysis has been added to the study protocol. For participants in Arm A who previously participated in the observational Study 242HA201/OBS16221 and had at least 6 months of data collection on prophylaxis treatment, an intra-patient comparison of ABR during BIVV001 weekly prophylaxis and historical prophylaxis will be performed in a non-inferiority analysis. If non-inferiority is achieved, superiority will be evaluated.
- The scope of the safety endpoint of "the occurrence of vascular thrombotic events," has been revised to "the occurrence of embolic and thrombotic events." Clarifying text has also been added to confirm that the Standard MedDRA Query of Embolic and Thrombotic events will be included as part of the endpoint analysis.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
All sections of the protocol describing the dose regimen	Dose regimen is changed from 65 IU/kg to 50 IU/kg	Based on the final results of the repeat dose study and in alignment with scientific advice from Health Authorities.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 3 - Table 5 objectives and endpoints	The secondary efficacy endpoint related to intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A has been designated as “key secondary efficacy endpoint”. Updated one of the safety endpoints from “vascular thrombotic events” to “embolic and thrombotic events”.	In alignment with scientific advice from Health Authorities.
Section 1.1 Synopsis Section 3 - Table 5 objectives and endpoints	Clarified the ISTH 4-point response scale related endpoint.	Added for clarity and in alignment with scientific advice from Health Authorities.
Section 1.1 Synopsis (number of participants) Section 4.1 Overall Study Design	Added that at least 75 participants of Arm A will have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline.	To support non-inferiority analysis in alignment with scientific advice from Health Authorities.
Section 1.1 Synopsis (Statistical Consideration) Section 9.2 Sample Size Determination	Added sample size justification to enroll 75 participants of Arm A who will have at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline for the assessment of key secondary efficacy endpoint.	To support non-inferiority analysis in alignment with scientific advice from Health Authorities.
Section 1.1 Synopsis (Statistical Consideration) Section 9.4 Statistical Analyses	Added statistical analysis methods for the key secondary efficacy endpoint. Clarified safety analysis and the definition of embolic and thrombotic events.	In alignment with scientific advice from Health Authorities and to support the analysis of the safety endpoints.
Section 1.3 - Table 1 Overall schedule of activities from screening to safety follow-up call or visit	Clarified that monthly telephone call will start from Week 4. Clarified that Investigator will assess participant’s response to treatment of bleeding episodes treated at the study site. Clarified that the participants will complete ePD including at-home dosing, bleeding episodes, and assessment of response to treatment of bleeding episodes. In footnote “f”, call or visit occurrence changed from 2 to 3 weeks to 14 (+7) days after the last dose of BIVV001. In footnote “h”, cross reference to Section 4.5 has been updated to Section 10.1.4. In footnote “j”, it was clarified that genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate informed consent.	Clarification.
Table 4 Surgical schedule of activities	Clarified that the participants will assess response to treatment of bleeding episodes. Clarified that investigators will assess response to a bleeding episode treated at the study site. In footnote “k”, it was clarified that the participant should record the assessment of response to treatment of bleeding episode in the ePD. In footnote “l”, it was clarified that Investigators or Surgeons will assess participant’s hemostatic response to BIVV001 treatment on the ISTH 4 point response for surgical procedures scale”.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 2.2 Background	Section updated to include the data of completed Study 242HA101.	To provide updated information based on final results of the repeat dose study.
Section 2.3 Benefit/Risk Assessment	Modified from "BIVV001 has the potential to achieve and maintain substantially higher factor activity levels than currently available therapies…" to "BIVV001 has the potential to achieve and maintain higher factor activity levels than currently available therapies…"	Clarification.
Section 4.1 Overall Study Design	Clarified that the refresher ePD training should be provided at any point during the study.	Clarification.
Section 4.2 Scientific Rationale for Study Design	Added a rationale for the key secondary efficacy endpoint.	In alignment with scientific advice from Health Authorities.
Section 4.3 Justification for Dose	Modified the section to provide justification for choosing dose of 50 IU/kg.	Based on the final results of the repeat dose study.
Section 4.4 End of Study Definition	The criterion specifying that at least 63 participants in Arm A should have at least 6 months of participation in this study and at least 6 months of participation in Study 242HA201/OBS16221 prior to baseline was added to define the End of Study.	To ensure sufficient sample size for adequate statistical powering for the analysis of the key secondary endpoint.
Section 5.2 Exclusion Criteria	Removed criteria related to previous exposure to BIVV001.	Previous exposure to BIVV001 was not considered to be an exclusion criterion. Clarification.
Section 5.2 Exclusion Criteria	Clarified the criteria related to re-screen.	Clarification based on the change in washout requirements in Section 10.8 Appendix 8.
Section 6.1.1.1 Study treatment schedule and administration	Clarified that BIVV001 will be delivered via a slow push IV injection of 8 ±2 minutes at a rate of administration determined by the participant's comfort level.	Clarification.
Section 6.1.1.2 Treatment of bleeding episodes during Prophylactic Treatment Regimen	Clarified that if the participant was treated with an initial dose of 30 IU/kg or 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.	Clarification.
Section 6.1.1.4 Surgical dosing	Clarified that continuous infusion will not be allowed in this study. Added that due to the long half-life of BIVV001, the frequency of dosing in the post-surgical period may be extended after the first week post-surgery. In Table 7, for bleeding episodes, it was clarified that for minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose may also be used.	Clarification.
Section 6.3 Measures to minimize bias: Randomization and blinding	Description of measures to prevent bias has been added as well as clarification on the analysis for primary and secondary efficacy endpoints.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Participation Discontinuation/Withdrawal from the study	Clarified that participant withdrawal either by Investigator or Sponsor at any time during the study.	Clarification.
Section 8.1.1.5 Target joint resolution	Clarified that the investigator will assess target joints at Baseline.	Clarification.
Section 8.1.1.6 Surgery	Clarified that continuous infusion will not be allowed in this study. Clarified that any doses administered outside of the clinic prior to returning to the pre-surgical treatment regimen will be captured in the ePD.	Clarification.
Section 8.1.4 Ultrasound measures (if applicable)	Clarified that participants at designated and MSKUS-experienced sites who are in Arm A (prophylactic treatment), meet enrollment criteria and are >17 years of age at enrollment will have the option to participate in the JADE and/or HEAD-US protocol.	Clarification.
Section 8.3.1.1 Other compound specific AESI(s)	Modified “vascular thrombotic event” to “embolic or thrombotic event”.	In alignment with scientific advice from Health Authorities.
Section 9.1 Statistical Hypotheses	Modified the statistical hypotheses inline with the modified key secondary efficacy endpoint.	In alignment with scientific advice from Health Authorities.
Section 9.2 Sample Size Determination	Added a definition for exposure days.	Clarification.
Section 10.1.4 Data protection	Added that the race and ethnicity of participants will be collected in this study and these data may be used in the analysis of the safety and/or PK profile of the study treatment. Added justification for the same.	Clarification.
Section 10.2 - Table 13 Protocol-required laboratory assessments	Updated the footnote “a” related to clinical chemistry.	Clarification.
Section 10.8 Appendix 8 Washout and Blood sampling summary	Updated the criteria to consider additional attempts after consultation with medical monitor, if the second attempt at washout fails.	Clarification for the washout requirements.
Section 10.13.9 Hemophilia Activities List	Updated the questionnaire	To provide the most current questionnaire version.
Throughout the protocol	Minor editorial changes Update in reference numbers due to addition of new references and deletion of duplicate references.	Clarification.

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