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# Clinical Protocol ACCL1333/CV185155

A Phase III Randomized, Open Label, Multi-center Study of the Safety and Efficacy of Apixaban for Venous Thromboembolism Prevention versus No Systemic Anticoagulant Prophylaxis during Induction Chemotherapy in Children with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (T or B cell) Treated with Asparaginase

**Revised Protocol Number: 05**

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

# Document History

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 05 | 03-Sep-2020 | Clarified in the study title that it is for 'Venous' thromboembolism prevention<br>Clarified the type of lymphoma subjects permitted in the study<br>Added Study Director<br>Redistributed the body weight tier of 9 to < 12 kg into two previous weight tiers to make a 6 to < 10.5 kg weight tier and a 10.5 to <18 kg weight tier<br>Clarified language describing treatment duration<br>Indicated that apixaban oral solution is not to be used in children < 5 years of age<br>[redacted]<br>Deleted references to Amendment 3<br>Updated contraception language<br>Added clinically significant bleeding and antiphospholipid syndrome to list of exclusion criteria<br>Clarified that the allowed chemotherapy protocol would be a 'planned' 3-4 drug systemic induction<br>Clarified acceptable bilirubin levels<br>Reinforced the collection of radiographic imaging following discontinuation of the study<br>Indicated that PK/PD sampling could occur on days other than Day 7, 8 or 15<br>Clarified the reference GFR values in Appendix 13<br>Updated the Statistical Consideration Sections to be in alignment with the primary analysis population (intent-to-treat or randomized subjects), as well as the sample size calculation [redacted] |
| Administrative Letter 03 | 03-Nov-2018 | Corrected synopsis to indicate that apixaban can be administered when the platelet count is ≥ 20,000 microL |
| Revised Protocol 04 | 08-Dec-2017 | Incorporates Amendment 04 |
| Amendment 04 | 08-Dec-2017 | Changed design of study to indicate that all forms of asparaginase could be used<br>Changed apixaban dosing scheme from a mg/kg dosing to a fixed-dose, body weight-tiered regimen<br>Introduced the 0.5 mg tablet with dosing instructions and development rationale<br>Clarified that the first dose of apixaban should began no later than 12 hours after the first dose of asparaginase<br>Changed enrollment to include children ≥ 1 and < 18 years of age and ≥ 6 kg of weight<br>Indicated that children ≥ 5 years of age can be administered apixaban solution and tablets while children < 5 years of age can only be administered apixaban tablets |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | Indicated that children weighing between 9 and < 12 kg cannot be enrolled in the study until appropriate apixaban formulation/dose available<br>Increased the window of visits from 3 days to 5 days<br>Removed inclusion criteria of having a platelet count ≥ 20,000/microL to administer apixaban and moved to sections regarding apixaban discontinuation and study restrictions and precautions<br>Indicated that Grade 1-2 chemotherapy induced neutropenia or hospitalization for the possibility of neutropenia do not have to be collected as adverse events<br>Move the sensitivity analysis to assess the impact of various primary endpoint event rates in subjects with missing or non-interpretable assessments from the protocol to the Statistical Analysis Plan |
| Revised Protocol 03 | 14-Dec-2016 | Incorporates Amendment 03 |
| Amendment 03 | 14-Dec-2016 | The study is only enrolling children > 2 years of age until the dose for children 1 year of age is determined from an ongoing pharmacology study<br>Clarified that the secondary endpoint of CVST included both fatal and non-fatal CVST<br>Added to Secondary endpoints apixaban pharmacokinetics and anti-FXa activity<br>[redacted]<br>Increased the window of when the central venous catheter is inserted to Day -7 to Day 4 of when induction chemotherapy is started<br>Clarified that subjects randomized to apixaban should begin apixaban treatment following randomization and before they start PEG<br>Clarified that if the catheter is to be removed due to the subject experiencing an event other than a VTE or other endpoint related events (eg, bleeding), the subject should not have the study mandated ultrasound and echocardiogram until Day 29 and should continue with the study treatment<br>Allowed subjects to be enrolled who will have the administration of more than one dose of PEG-L asparaginase during the induction chemotherapy<br>Allowed subjects to be enrolled who have a mixed-phenotype acute leukemia (MPAL) who will be treated with the COG ALL induction chemotherapy<br>Allowed subjects to be enrolled who have had the central venous catheter inserted prior to obtaining informed consent as long as this is part of the subject's standard of care<br>Clarified that subjects with a total bilirubin ≤ 2XULN can be |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| | | enrolled<br><br>Clarified that subjects with an INR >1.4 can't be enrolled<br><br>Removed as an exclusion criteria the PT, PTT, and prolonged Reptilase Time or a prolonged Thrombin Time (TT) values and replaced with an exclusion criteria of an INR > 1.4 and aPTT > 3 seconds above the upper limit of normal for age<br><br>Clarified that the screening period would be between Day -7 to Day 4 of induction chemotherapy<br><br>Allow screening labs to be performed as part of the standard of care prior to signing the informed consent within 1 week prior to enrollment<br><br>Excluded subjects with a risk of bleeding such as hemophilia and von Willebrand disease, etc<br><br>Clarified that the exclusion criteria extreme hyperleukocytosis, white blood cell (WBC) counts over 200 x 109/L (200,000/microL) is at the time of enrollment and not at the time of diagnosis<br><br>Clarified that the Doppler ultrasound should be performed for both of the ipsilateral and the contralateral sides whenever possible. If there is difficulty in performing the imaging procedure, the Doppler ultrasound from just the ipsilateral side alone is acceptable<br><br>Indicated that a chest X-ray is not mandated by the study but if one was performed as SOC then it should be submitted as part of the adjudication package<br><br>[redacted]<br><br>Clarified that decisions to transfuse platelets > 20,000/uL or to interrupt study medication should platelets fall below 20,000/uL is left to the discretion of the clinician<br><br>Removed surveillance of subject contraception 1 month prior to dosing<br><br>Clarified that apixaban can be given with or without food 12 hours apart and subjects can take a missed dose up to 6 hours after the normal dosing time<br><br>Indicated that SAEs need to be collected up to 30 days after the last dose of study medication<br><br>[redacted] |
| Administrative Letter 02 | 26-Apr-2016 | Specified that labs, exams, and CVD placement as part of standard of care procedures could be used for screening purposes prior to signing the informed consent form |

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Revised Protocol 02 | 14-Aug-2015 | Incorporates Amendment 02 |
| Amendment 02 | 14-Aug-2015 | Dose adjustment [redacted]<br>The age of subjects eligible for enrollment has been expanded to include children 2 to 18 years of age<br>Clarified the study procedures that should be followed if a catheter is lost or replaced and planned replacements of the catheter is allowed<br>Removed exclusion criteria of Central Nervous Status 3 and replaced with LP's > 3 over the course of the treatment period<br>Clarified the exclusion criteria of 'Major Surgery'<br>Clarified the timing of performing the radiographic imaging<br>Aligned the Secondary safety endpoint and other safety endpoints with the Objectives<br>Added to Exclusion Criteria the administration of any investigational drug including multiple doses of PEG-L asparaginase<br>Added to Prohibited Therapies the chronic daily use of nonsteroidal anti-inflammatory drugs more than 7 days<br>Removed Appendix on "CNS Leukemia at Diagnosis" since exclusion criteria of CNS is being replaced by a number of LP's done during the treatment period, and added a list of NSAIDS. |
| Administrative Letter 01 | 04-May-2015 | Clarified that the apixaban dose was BID |
| Revised Protocol 01 | 28-Jan-2015 | Incorporates Amendment 01 |
| Amendment 01 | 28-Jan-2015 | To align the collection of cerebral spinal fluid to obtain red cell blood counts around the standard of care for the subjects.<br>To clearly define the time period around discontinuing apixaban prior to the lumbar punctures.<br>To clearly define the exclusion criteria of uncontrolled severe hypertension at enrollment using the age, height and gender adjusted standard. |
| Original Protocol | 12-Dec-2014 | Not applicable |

## OVERALL RATIONALE FOR REVISED PROTOCOL 05:

The rationale for this amendment was the following:

- Clarified in the study title that it is for 'Venous' thromboembolism prevention
- Clarified the type of lymphoma subjects permitted in the study
- Added Study Director
- Redistributed the body weight tier of 9 to < 12 kg into two previous weight tiers to make a 6 to < 10.5 kg weight tier and a 10.5 to <18 kg weight tier
- Clarified language describing treatment duration
- Indicated that apixaban oral solution is not to be used in children < 5 years of age
- [redacted]
- Deleted references to Amendment 3
- Updated contraception language
- Added clinically significant bleeding and antiphospholipid syndrome to list of exclusion criteria
- Clarified that the allowed chemotherapy protocol would be a 'planned' 3-4 drug systemic induction
- Clarified acceptable bilirubin levels
- Reinforced the collection of radiographic imaging following discontinuation of the study
- Indicated that PK/PD sampling could occur on days other than Day 7, 8 or 15
- Clarified the reference GFR values in Appendix 13
- Updated the Statistical Consideration Sections to be in alignment with the primary analysis population (intent-to-treat or randomized subjects), as well as the sample size calculation [redacted]

The revised protocol is for all patients.

| SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Synopsis: Study Design and Body: Introduction and Study Drugs | Redistributed the body weight tier of 9 to < 12 kg into a 6 to < 10.5 kg weight tier and a 10.5 to <18 kg weight tier | Redistributed and opened this cohort due to practical considerations for clinical dosing which are supported by clinical pharmacology data. |
| Throughout Synopsis and Body | Clarified that the allowed chemotherapy protocol would be a 'planned' 3-4 drug systemic induction | Allowed the addition of other chemotherapy agents during induction |
| Synopsis and Body: Study Drug Table | Indicated that the apixaban solution is not to be used in children < 5 years of age | Reinforced when the apixaban solution can be used in children |

| SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Synopsis and Body: Study Assessments, Day 8 and Day 15 of chemotherapy | Clarified that PK/antiXa sampling could occur on an alternative day other than Day 7, 8, or 15 | Reflected the flexibility in taking the PK/PD samples |
| Synopsis and Body: Statistical Considerations, Sample size | Edited text to read: With a total of approximately 500 randomized subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban (intervention) or no systemic anticoagulant prophylaxis (control) groups, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates of primary endpoint (composite of non-fatal asymptomatic and symptomatic DVT, pulmonary embolism (PE), and CVST, and VTE-related death) are 17% and 8.5% in the control and the apixaban groups, respectively.<br><br>Sample size estimation is based on Pearson's chi-square test.<br><br>Additionally, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates are 20% and 10% in the control and the apixaban groups, respectively with analyses that assume that 20% of the subjects will be excluded from the primary analysis due to either early dropout without end-of-treatment imaging evaluation or non-evaluable end of treatment imaging measurement in the calculation | Aligned the statistical considerations with the primary analysis population (intent-to-treat or randomized subjects) and the sample size calculation [redacted] |
| Synopsis and Body: Populations for Analyses | Modified text to include description of enrolled, randomized/intent-to-treat, modified intent-to-treat, and evaluable populations, and specified randomized/intent-to-treat as population that will be generally used for efficacy and safety analyses. | Clarified that efficacy and safety analyses will be performed using all randomized subjects, [redacted] |

| SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 05 | | |
|---|---|---|
| **Section Number & Title** | **Description of Change** | **Brief Rationale** |
| Synopsis and Body: Dose Selection | Clarified language describing treatment duration. | Clarified language [redacted]. |

# SYNOPSIS

## Clinical Protocol ACCL1333/CV185155

**Protocol Title:** A Phase III Randomized, Open Label, Multi-center Study of the Safety and Efficacy of Apixaban for Venous Thromboembolism Prevention versus No Systemic Anticoagulant Prophylaxis during Induction Chemotherapy in Children with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (T or B cell) treated with asparaginase

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s)**:

Subjects 1 to < 18 years of age will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range as per below Table during approximately 28 days of induction chemotherapy including asparaginase.

| Weight range | Dose |
|---|---|
| ≥ 35 kg | 2.5 mg twice daily |
| <35 to 25 kg | 2 mg twice daily |
| <25 to 18 kg | 1.5 mg twice daily |
| <18 to 10.5 kg | 1 mg twice daily |
| <10.5 to 6 kg | 0.5 mg twice daily |

The previously communicated dosing for the body weight tier of 9 to < 12 kg has been redistributed into a 6 to < 10.5 kg weight tier and a 10.5 to < 18 kg weight tier.

Treatment with apixaban should begin after randomization. Study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of planned 3-4 drug systemic induction chemotherapy, whichever is first and will stop on approximately Day 29 of planned 3-4 drug systemic induction chemotherapy. During the study, the apixaban treatment will be discontinued at least 24 hours prior to any planned lumbar puncture (LP) and resumed no sooner than 18-24 hours after the procedure. In the event of a traumatic lumbar puncture (defined in this protocol as a lumbar puncture with ≥ 10 red blood cells (RBCs)/μL of cerebrospinal fluid (CSF), apixaban should be held for 48 hours after the procedure.

**Study Phase: Phase III**

**Research Hypothesis**: Oral or enteric administration of prophylactic apixaban during induction chemotherapy will reduce the risk of venous thromboembolism (VTE) (symptomatic + asymptomatic), compared to no systemic anticoagulant prophylaxis, during induction chemotherapy in children with newly diagnosed acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (T or B cell) with central venous line treated with asparaginase.

**Study Objectives:**

**Primary Objectives:**

To compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT, including symptomatic and asymptomatic), pulmonary embolism (PE), and cerebral venous sinus thrombosis (CVST); and VTE-related-death.

To assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on adjudicated major bleeding events.

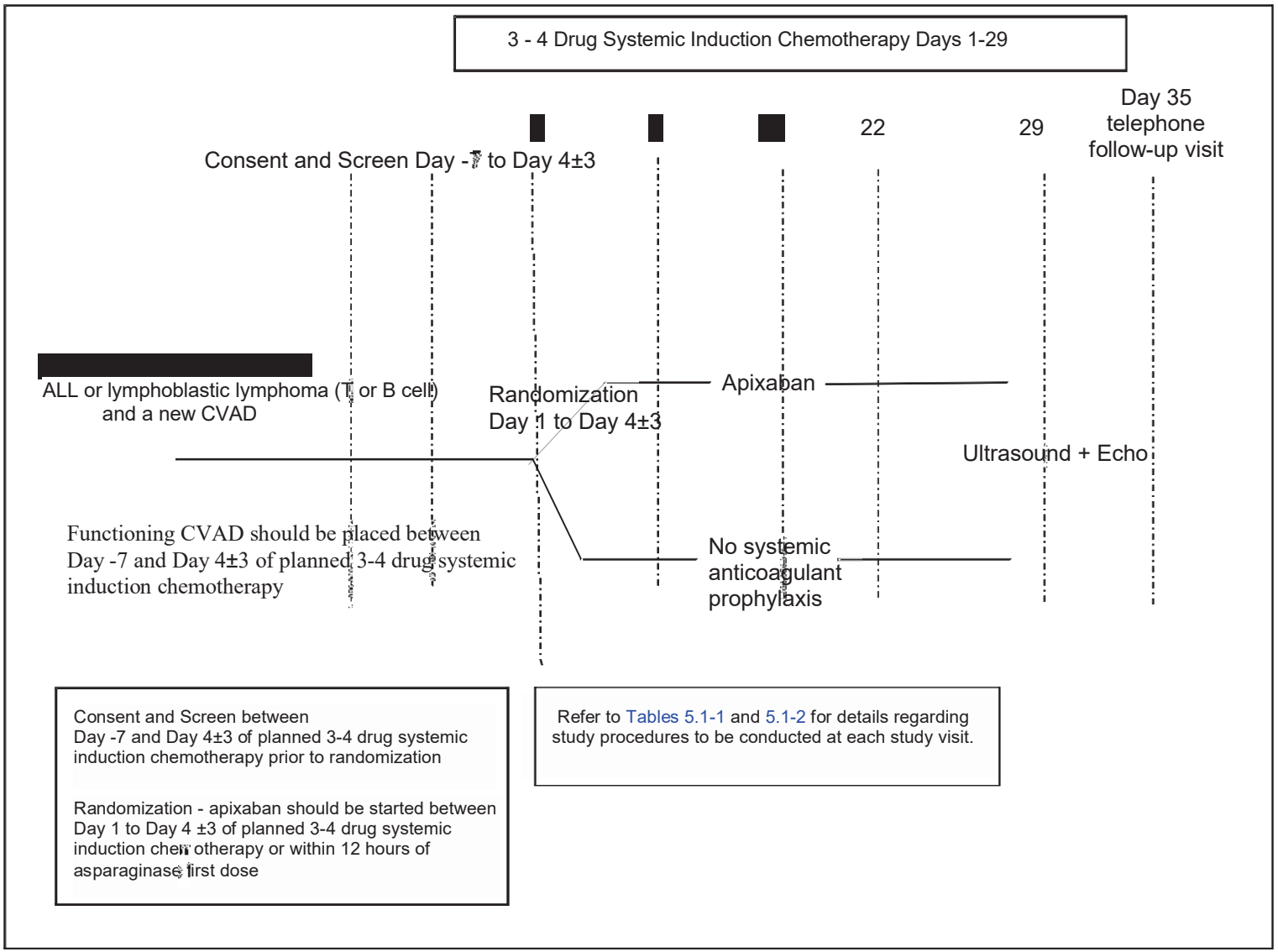
**Secondary Objectives:**

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on single adjudicated endpoints of non-fatal DVT (including symptomatic and asymptomatic), PE, and CVST; and VTE-related-death.

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated major and clinically relevant non-major bleeding (CRNMB) events.

**Study Design:**

**Figure -1: Study Design**



**Study Design:**

Recruitment will start for children of ages 1 to < 18 years of age and weighing equal to or > 6 kg.

The current study is a randomized, open-label, multi-center clinical trial in which pediatric subjects will be randomized 1:1 to prophylactic apixaban for thromboembolism prevention versus no systemic anticoagulant prophylaxis during induction chemotherapy. Subjects randomized to apixaban will receive a prophylactic-dose of apixaban. While subjects ≥ 5 years may be administered either 2.5-mg, 0.5-mg tablets or oral solution apixaban, use of 2.5 mg or 0.5 mg tablets is encouraged. Subjects < 5 years and < 35 kg may be administered 0.5-mg tablets only.

Subjects will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range as per below Table during approximately 28 days of induction chemotherapy including asparaginase.

| Weight range | Dose |
|---|---|
| ≥ 35 kg | 2.5 mg twice daily |
| <35 to 25 kg | 2 mg twice daily |
| <25 to 18 kg | 1.5 mg twice daily |
| <18 to 10.5 kg | 1 mg twice daily |
| <10.5 to 6 kg | 0.5 mg twice daily |

The previously communicated dosing for the body weight tier of 9 to < 12 kg has been redistributed into a 6 to < 10.5 kg weight tier and a 10.5 to < 18 kg weight tier.

Pediatric subjects randomized to apixaban should begin treatment following randomization (as long as conditions for apixaban administration are met). Study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of planned 3-4 drug systemic induction chemotherapy, whichever is first. Day 1 is the first day of planned 3-4 drug systemic induction ALL chemotherapy.

For a subject who experiences a reaction to asparaginase during the infusion and has to switch to Erwinia asparaginase during the induction chemotherapy, it is recommended that the subject continue the study treatment. The percentage of the original asparaginase dose delivered will be collected in the patient chart and case report form.

A platelet count ≥ 20,000 /μL must be obtained within 24 hours prior to the first dose of apixaban. A subject may be transfused platelets per investigator's clinical judgment but may not be transfused solely to meet entry criteria.

Apixaban should be discontinued at least 24 hours prior to any planned lumbar puncture (LP) and resumed no sooner than 18-24 hours after the procedure. In the event of a traumatic lumbar puncture (defined in this protocol as a lumbar puncture with ≥ 10 red blood cells (RBCs)/μL of cerebrospinal fluid (CSF), apixaban should be held for 48 hours after the procedure.

For example, for a LP scheduled on the morning of Day 8, the Day 7 PM and Day 8 AM and PM doses of apixaban should be held and may be restarted the morning of Day 9. If a subject will receive an LP on Day 29, the last dose will be the AM dose on Day 28.

During the study treatment period, study visits will occur on Day 8 ± 5 days, Day 15 ± 5 days, Day 22 ± 5 days and Day 29 ± 5 days of planned 3-4 drug systemic induction chemotherapy. Windows for study visits after randomization will be ± 5 days. The timing of these study visits will coincide with standard of care visits for pediatric subjects in induction chemotherapy. Visits will consist of reporting adverse events (including bleeding and secondary endpoints as described below), monitoring medication adherence and laboratory testing. On the Day 29 visit, imaging evaluation will occur for all randomized subjects except for those who are discontinued from protocol therapy. For those subjects randomized to apixaban, imaging evaluations will be performed within 3 days but no more than 5 days of discontinuing apixaban. For those subjects randomized to the standard of care arm, it would be preferred that the imaging evaluations be performed within three days but no more than 5 days from Day 29 (Day 24 to Day 34). The evaluation will include a) a bilateral Doppler ultrasound that will include imaging of the venous system in which the CVAD is placed and the similar location for the opposite side; and b) an echocardiogram to assess for right atrial

thrombi according to the protocol guidance in appendices 1 and 2. Subjects will not undergo routine radiologic screening for CVST.

Additional clinical and radiologic evaluations prompted by clinical suspicion of any DVT, PE, CVST, arterial thromboembolic events, bleeding or death will be performed at the discretion of the treating clinician; and information from these visits and imaging findings will be captured for study analysis. A chest X-ray is not mandated by the study. However, if a chest X-ray has been performed as part of the standard of care, the chest X-ray should be submitted as part of the adjudication package.

Every effort must be made to confirm a suspected thromboembolic or bleeding event before discontinuing a subject from protocol therapy. Management of any asymptomatic or symptomatic events will be according to the local standards of practice. If study medication is discontinued for a suspected thromboembolic event, alternative anti-thrombotic therapy may be initiated per the Investigator's discretion and standard of care.

All subjects who discontinue study drug due to an event (eg, thromboembolic or major bleeding event), or due to loss of the catheter prior to Day 29 end-of-study evaluation, should remain in the study and report any adverse events or clinical events and comply with protocol specified follow-up procedures. Every attempt must be made to have the study-related radiographic procedures, Ultrasound and Echocardiogram within 72 hours of the event and the telephone or in-person safety assessment on Day 35 ± 5 days. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

Sparse samples for PK and PD (anti-FXa activity) will be taken in subjects receiving apixaban. Pre-dose and post dose concentrations of apixaban may be measured on the same day if feasible (eg, in-patients). Alternatively samples may be collected on separate days (eg, out-patients), for example, the pre-dose before the Day 8 LP and the post-dose concentrations on Day 15.

PK/PD samples may be drawn through the CVAD. No PK/PD samples will be drawn in subjects who are not randomized to apixaban.

For all subjects, a follow up telephone or in person safety assessment will be scheduled on Day 35 ± 5 days. Subjects will be instructed to report all adverse events, including those symptoms suggestive of thromboembolism and bleeding to the Investigator.

If the catheter is lost or replaced before the Day 29 end-of-study evaluation because of achieving a primary endpoint (eg, VTE, major bleeding), protocol therapy will be discontinued and the ultrasound and echocardiogram should be performed within 72 hours of this event or prior to the catheter being replaced. The subject would discontinue study treatment but be followed until the end of the study. If the catheter is to be removed and replaced within 48 hours due to events other than a primary endpoint event, the subject should not have the study mandated ultrasound and echocardiogram until Day 29±5 and should continue with the study treatment (for temporary apixaban interruptions related to an invasive procedure, see Table 4.5.2-1).

**Study Population:** Subjects eligible for the study include males and females age 1 to < 18 years with newly diagnosed ALL or newly diagnosed lymphoblastic lymphoma (T or B cell) and a new CVAD inserted between Day -7 to Day 4 ± 3 of planned 3-4 drug systemic induction chemotherapy and planned to remain in place until at least Day 29±5 of induction. The CVAD must be inserted prior to the start of study medication. The CVAD can be replaced if it is a planned replacement. Recruitment will start for children ages 1 to < 18 years and weighing equal to or > 6 kg.

**Key Inclusion Criteria:** (a) New diagnosis of de novo ALL, lymphoblastic lymphoma (T or B cell); (b) Planned 3-4 drug systemic induction chemotherapy with a corticosteroid, vincristine, a single dose or multiple doses of asparaginase, with or without daunorubicin; (c) Patients with mixed-phenotype acute leukemia (MPAL) that are treated with ALL-type induction therapy are also eligible; (d) Males and females ≥1 to < 18 years of age and weighing equal to or > 6 kg; (e) Functioning CVAD, defined as no known mechanical problem and including external tunneled CVAD, implantable ports, and peripherally inserted central catheters (PICC) placed in a new location between Day -7 to Day 4 ± 3 of planned 3-4 drug systemic induction chemotherapy and planned to remain in place until at least Day 29±5 of induction. The CVAD must be inserted prior to the start of study medication, and could be inserted prior to obtaining informed consent as part of the standard of care, and can be replaced if it is a planned replacement; (f) Able to tolerate oral medication or have it administered via an enteral tube; and (g) Females of reproductive potential (FRP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening. (h) Females must not be breastfeeding.

**Key Exclusion Criteria:** (a) History of documented VTE in the past 3 months; (b) Known inherited bleeding disorder or coagulopathy with increased bleeding risk (eg, hemophilia, von Willebrand disease, etc.); (c) Uncontrolled severe hypertension at enrollment. Severe hypertension is defined as a systolic or diastolic blood pressure (BP) > 5 mm Hg above the 95th percentile as defined by the National High Blood Pressure Education Program Working Group (NHBPEP) established guidelines for the definition of normal and elevated blood pressures in children. (d) Liver dysfunction manifested by SGPT (ALT) > 5X ULN and/or (SGOT) AST > 5X ULN and/or direct (conjugated) bilirubin > 2X ULN (subjects with total bilirubin ≤ 2XULN can be enrolled); (e) Renal function < 30% of normal for age and size as determined by Schwartz formula:[eGFR (ml/min/1.73m2) = 0.413 * (height (cm) / serum creatinine (mg/dl)]; (f) INR > 1.4, AND aPTT > 3 seconds above the upper limit of normal for age within 1 week prior to enrollment. If needed, confirmation by repeat testing is permissible (Repeat aPTT tests using venous puncture if values are high and heparin contamination is suspected). (g) Extreme hyperleukocytosis, white blood cell (WBC) counts over 200 x 109/L (200,000/microL) at time of enrollment except subjects who have had leukopheresis, these subjects will be excluded regardless of WBC count; (h) Subject scheduled to have > 3 LP's over the course of the study treatment period, ie, Day of Randomization to Day 29 visit; (i) Females with a positive pregnancy test; (j) Major surgery (excluding CVAD replacement and bone marrow aspiration and non-open biopsy) within the last 7 days prior to enrollment that may be associated with an increase in the risk of bleeding. Open biopsy is considered a major surgery; (k) Unable to take oral or enteric medication; (l) In the opinion of the Investigator, it is not possible for the subject to be compliant with the protocol and study procedures; (m) Failure to provide written informed consent

**Prohibited Therapies and/or Medications:** (i) Concurrent prophylactic or therapeutic treatment with LMWH, unfractionated heparin, other oral anticoagulant, or systemic tPA (heparin flushes to maintain CVAD patency and local tPA to restore CVAD patency are permitted); (ii) Any anti-platelet therapy with aspirin or thienopyridines such as clopidogrel, ticagrelor, or prasugrel (iii) Concomitant systemic treatment with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, clarithromycin, ritonavir, voriconazole, indinavir, nelfinavir, saquinavir, and cobicistat. (See Appendix 10); (iv) Concomitant systemic treatment with strong inducers of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as rifampin, carbamazepine, phenytoin and St. John's Wort. (v) Chronic daily use of nonsteroidal anti-inflammatory drugs (NSAIDs, eg, naproxen, ibuprofen, diclofenac, etc.) may increase the risk of bleeding. Therefore, concomitant use of NSAIDS more than 7 days is prohibited. (VI) During the entire study period, no other investigational agents, other than apixaban should be administered to the patient

*Note: Fluconazole, topical azole antifungal agents, trimethoprim-sulfamethoxazole, H2-antagonists and proton pump inhibitors are permitted.*

**Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:**

| **Study Drug: Apixaban** | | |
|---|---|---|
| **Medication** | **Potency** | **IP/Non-IP** |
| BMS-562247-01 Film Coated Tablet, 2.5 mg | 2.5 mg | IP |
| BMS-562247-01 Oral Solution, 0.4 mg/mL<br>(not to be used in children < 5 years of age in CV185155) | 0.4 mg/ml | IP |
| BMS-562247-01 Film Coated Tablet, 0.5 mg | 0.5 mg | IP |

**Study Assessments:**

No study-related procedure may be performed until the subject or their legally acceptable representative has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an informed consent document, and where appropriate assent form, approved by a licensed Institutional Board Review (IRB) or Independent Ethics Committee (IEC). Every attempt should be made to coordinate the study-related visits with the subjects' medical visits.

The **Screening Period** will occur after consent is obtained, and it can occur between Day -7 to Day 4 ±3 of planned 3-4 drug systemic induction chemotherapy. Screening labs done as standard of care prior to signing consent can be used. At the screening visit the IVRS system will be contacted to obtain a unique subject number. A complete medical history and a physical examination including vital signs, height, BP, and body weight, will be obtained. The screening visit laboratory studies will include: CBC with platelets, ALT, AST, WBC and RBC in CSF (LP prior to receiving study treatment), conjugated bilirubin (if total bilirubin is abnormal) and serum creatinine (estimated GFR), PT (if available), aPTT, and INR and serum or urine pregnancy test for females of reproductive potential (FRP).

For all FRP that will be inpatients from consenting to the first dose of apixaban, it is expected that a negative pregnancy test be recorded in the subject's hospital chart at any time point from the time of hospitalization but prior to first treatment.

All FRP that will be treated as outpatients from consenting to the first dose of Apixaban must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

**The Randomization** visit will occur between Day 1 and Day 4 ± 3 of planned 3-4 drug systemic induction chemotherapy. Day 1 is the first day of planned 3-4 drug systemic induction ALL chemotherapy. For pediatric subjects who meet all the inclusion/exclusion criteria, the IVRS system will be contacted and the subjects will be randomized. The subjects randomized to apixaban will receive instructions about the study drug and will start the study drug following randomization as long as conditions for apixaban administration are met (e.g. platelet counts are equal to or > 20,000 / microL). Study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of planned 3-4 drug systemic induction chemotherapy, whichever is first.

The screening and randomization visits can be done on the same day if the subject is eligible by medical history, clinical exam, and has local laboratory results that are within the appropriate inclusive parameters.

**Day 7 ± 5 of chemotherapy:** For all subjects randomized to apixaban who are inpatients on planned 3-4 drug systemic induction chemotherapy, a pre- and post-dose PK and anti-FXa sample may be taken on the same day. For example, the samples may be taken prior to the Day 7 ± 5 AM dose of apixaban, followed by a PK and anti-FXa sample taken 1-4hr post-dose.

Subjects who are not able to provide a pre and post dose sample on the same day (eg, those who are outpatients) will have a PK and anti FXa sample collected on separate occasions, for example once on Day 8 ±5 and once on Day 15 ± 5.

Local CBC with platelets, SGPT (ALT), AST, and direct (conjugated) bilirubin (if total bilirubin is abnormal), RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed.

**Day 8 ± 5 of chemotherapy:** The Day 8 assessment is meant to coincide with those patients unable to attend the Day 7 visit. Local CBC with platelets, SGPT (ALT), AST and direct (conjugated) bilirubin (if total bilirubin is abnormal), RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed unless they were done at Day 7 for subjects that were inpatients.

Subjects who are randomized to apixaban and did not have a pre- and post- dose sample collected on the same day (eg, those who are outpatients), will have a PK and anti-FXa sample collected on separate days, for example, on either Day 8 ± 5 prior to LP procedures and within 24 hours of the subjects last apixaban dose.

**Day 15 ± 5 of chemotherapy:** Local CBC with platelets, SGPT (ALT), AST, and direct (conjugated) bilirubin (if total bilirubin is abnormal), adverse event data collection and concomitant therapy assessment will be performed.

Subjects who are randomized to apixaban and did not have a pre- and post- dose sample collected on the same day (eg, those who are outpatients), will have a PK and anti-FXa sample collected on separate days, for example, on Day 15 ± 5 of chemotherapy, 0.5 to 12 hr after the AM dose of apixaban (and prior to the PM dose on that day).

**Day 22 ± 5 of chemotherapy:** Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin (if total bilirubin is abnormal), adverse event data collection and concomitant therapy assessment will be performed.

**Day 29 ± 5 of chemotherapy:** Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin (if total bilirubin is abnormal), RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed.

On the Day 29 visit, the imaging evaluation will occur for all randomized subjects who remain on protocol therapy. The imaging evaluation will include a Doppler ultrasound and an echocardiogram. The Doppler ultrasound will evaluate the extremity in which the CVAD is placed according to a standardized protocol, or at the location of the insertion if the CVAD is placed in the neck or chest, and the similar location for the opposite side. The Doppler ultrasound should be performed for both the ipsilateral and the contralateral sides whenever possible. If there is difficulty in performing the imaging procedure, Doppler ultrasound from the ipsilateral side alone is acceptable (see Appendix 1 for detailed guidance). The echocardiogram will assess the right atrial thrombi. For those subjects randomized to apixaban, imaging evaluations will be performed preferably within 3 days but no more than 5 days of discontinuing apixaban. For those subjects randomized to the standard of care arm, it would be preferred that the imaging evaluations be performed within 3 days but no more than 5 days from Day 29 (Day 24 to Day 34). Subjects will not undergo routine radiologic screening for CVST.

If the catheter is lost or replaced before the Day 29 end-of-study evaluation because of achieving a primary endpoint (eg, VTE, major bleeding), protocol therapy will be discontinued and the ultrasound and echocardiogram should be performed within 72 hours of this event or prior to the catheter being replaced. The subject would discontinue study treatment but be followed until the end of the study. If the catheter is to be removed and replaced within 48 hours due to events other than a primary endpoint event, the subject should not have the study mandated ultrasound and echocardiogram until Day 29±5 and should continue with the study treatment.

**Day 35 ± 5 of chemotherapy:** Telephone or in person follow up safety assessment will be scheduled on Day 35 ± 5 for all subjects. In this assessment, adverse event data collection and concomitant therapy assessment will be obtained.

**Statistical Considerations:**

**Sample Size Determination:** With a total of approximately 500 randomized subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban (intervention) or no systemic anticoagulant prophylaxis (control) groups, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates of primary endpoint (composite of non-fatal asymptomatic and symptomatic DVT, pulmonary embolism (PE), and CVST; and VTE-related-death) are 17% and 8.5% in the control and the apixaban groups, respectively.

Sample size estimation is based on Pearson's chi-square test.

Additionally, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates are 20% and 10% in the control and the apixaban groups, respectively with analyses that assume that 20% of the subjects will be excluded from the primary analysis due to either early dropout without end-of-treatment imaging evaluation or non-evaluable end-of-treatment imaging measurement in the calculation

Randomization will be stratified by age groups as < 10 years or ≥ 10 to < 18 years, to reflect the major peaks of disease prevalence and risk stratification criteria for acute lymphoblastic leukemia (ALL) in children.

**Primary Endpoints:**

**Efficacy:**

The primary efficacy endpoint is a composite of non-fatal DVT (including asymptomatic and symptomatic), PE, and CVST; and VTE-related-death objectively confirmed by independent adjudication.

All components of the primary efficacy endpoint will be adjudicated by a blinded, independent adjudication committee.

**Safety:**

The primary safety endpoint will be adjudicated major bleeding which is defined as bleeding satisfies one or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (ie, 2 g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS; and/or (iv) bleeding that requires surgical intervention in an operating suite, including interventional radiology. Of note, the major bleeding will not be considered as part of the primary endpoint for the purpose of the European application, but will be assessed as part of the safety profile of apixaban.

Prophylactic transfusions without overt bleeding and without a decrease in hemoglobin of at least 20 g/L (ie, 2 g/dL) in a 24 - hour period are not considered bleeding events.

All bleeding events will be adjudicated by a blinded, independent adjudication committee as major bleeding, CRNM bleeding, or minor bleeding. These endpoints are consistent with those recommended by the International Society on Thrombosis and Haemostasis for pediatric clinical trials in venous thromboembolism.

**Secondary Endpoints:**

**Efficacy:**

1) Non-fatal asymptomatic DVT
2) Non-fatal symptomatic DVT
3) Non-fatal PE
4) CVST
5) VTE-related-death

**Safety:**

a) Composite of major and CRNM bleeding (CRNMB). CRNM bleeding is defined as bleeding that satisfies one or both of the following:
   i. overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition and
   ii. bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room

**Pharmacokinetics and Anti-FXa Activity**

a) Apixaban pharmacokinetics using a population pharmacokinetic (PPK) approach
b) Anti-FXa activity

[redacted]

**Populations for Analyses**

**Enrolled Population:**

The Enrolled Subjects population consists of all subjects who signed informed consent.

**Randomized /Intent-To-Treat (ITT) Population**

The Randomized/Intent-to-Treat (ITT) population consists of all subjects who were randomized to a treatment, regardless of whether they received study drug or not. Except as noted otherwise, the Randomized/ITT Population will be used for the evaluation of efficacy.

**Modified Intent-To-Treat (mITT) Population**

The mITT population includes randomized subjects who have either an adjudicated event making up the primary efficacy endpoint or evaluable end of study imaging evaluations, including ultrasound and echocardiogram.

**Evaluable Population**

The Evaluable population will include the Randomized/ITT population except those subjects with relevant protocol deviations expected to affect the primary efficacy endpoint.

**Safety Population**

The safety population includes all randomized subjects since there is no intervention on top of standard care in the control arm and will be used for the evaluation of safety.

**Pharmacokinetic Measures:**

PK/PD samples will be taken in subjects receiving apixaban. Pre-dose and post dose concentrations of apixaban will either be measured on the same day if feasible (eg, in-patients) or on separate days (eg, out-patients). For example, the pre-dose may be taken on Day 8±5 and the post-dose may be taken on Day 15 ± 5. [redacted]

A PPK model will be developed using plasma concentration versus time data. Model-derived population and individual PK parameters (eg, CL/F, Vc/F, KA) will be used to estimate Cmax, Cmin, and AUC(TAU) in each subject. Modeling results will be reported separately.

**Anti-FXa Activity Measures:**

Observed pre-dose and post-dose anti-FXa activity will either be measured on the same day if feasible (eg, in-patients) or on separate days (eg, out-patients). For example the pre-dose on the Day 8 visit and the post-dose anti-FXa activity on Day 15 visit or another day. [redacted]

A PPK-PD model will be developed using plasma concentration and measured Anti-FXa activity versus time data. Model-derived population and individual parameters (eg, slope of anti-FXa activity vs apixaban concentration relationship) will be used to estimate maximum and minimum Anti-FXa activity in each subject. Modeling results will be reported separately.

**Analyses:** For primary efficacy endpoint and primary safety endpoint, statistics including event rate, 95% confidence interval (CI) for event rate, relative risk, 95% CI for relative risk and p-value will be displayed.

For other endpoints, descriptive statistics including single event rate, 95% confidence interval (CI) for single event rate, relative risk and 95% CI for relative risk will be displayed.

To construct p-values, the Cochran-Mantel-Haenszel test stratified by age groups of $< 10$ and $\geq 10$ years old will be used at the one-sided $\alpha = 0.025$ level.

To construct descriptive statistics:

- The 95% CI for the relative risk will be computed based on the Cochran-Mantel-Haenszel's method stratified by age groups of $< 10$ years and $\geq 10$ years.
- Construction of CIs for event rates will be based on the Agresti Coull's method

The analyses on all the efficacy endpoints will be based on the Randomized/ITT population.

Listings of observed PK and Anti-FXa data will be provided by Visit and age-group as appropriate.

Analyses related to the PK, PK-PD relationship, and exposure-response relationships will be described in a separate analysis plan and the results reported separate from the Clinical Study Report (CSR).

# TABLE OF CONTENTS

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# 1 INTRODUCTION [redacted]

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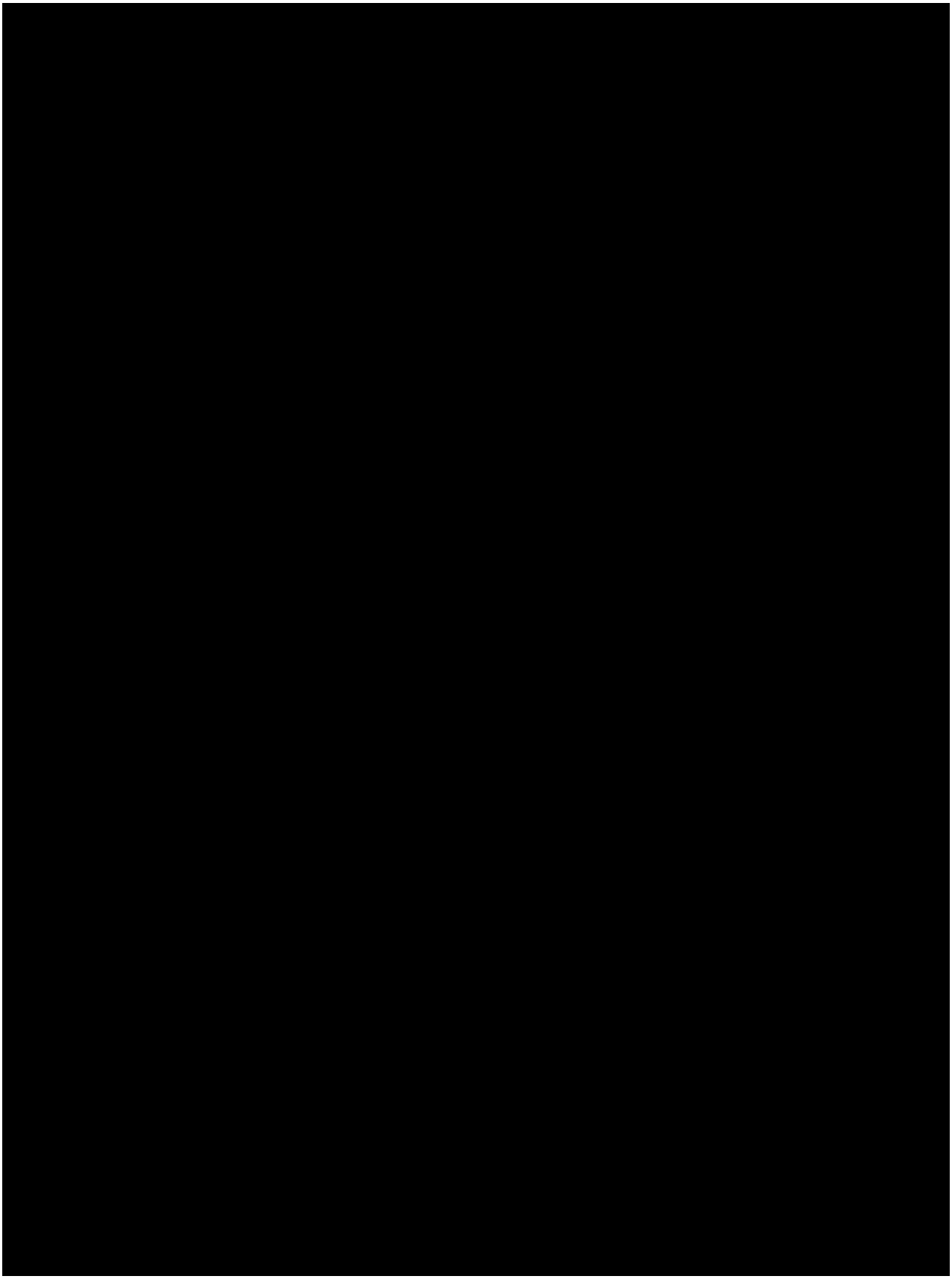
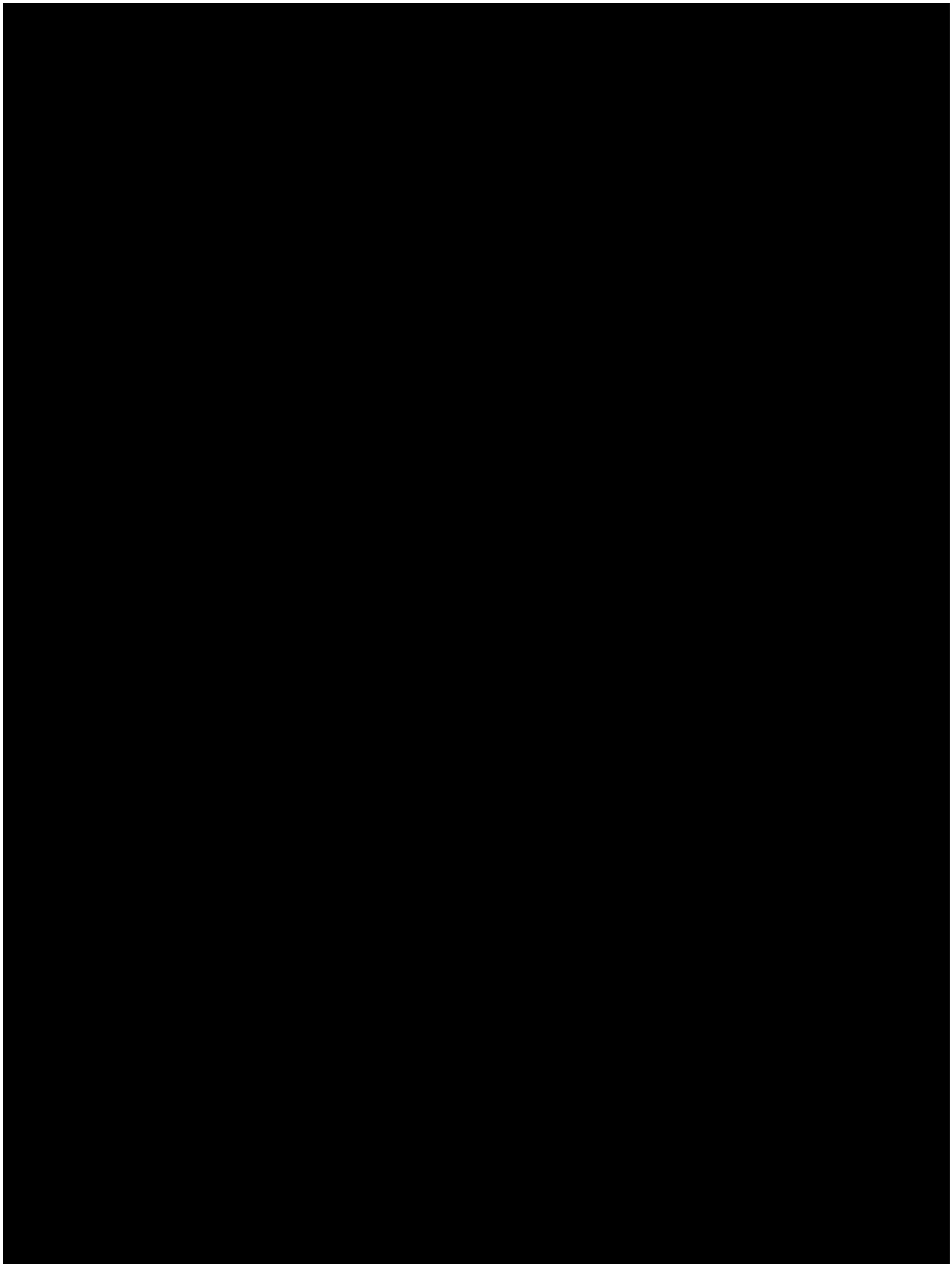
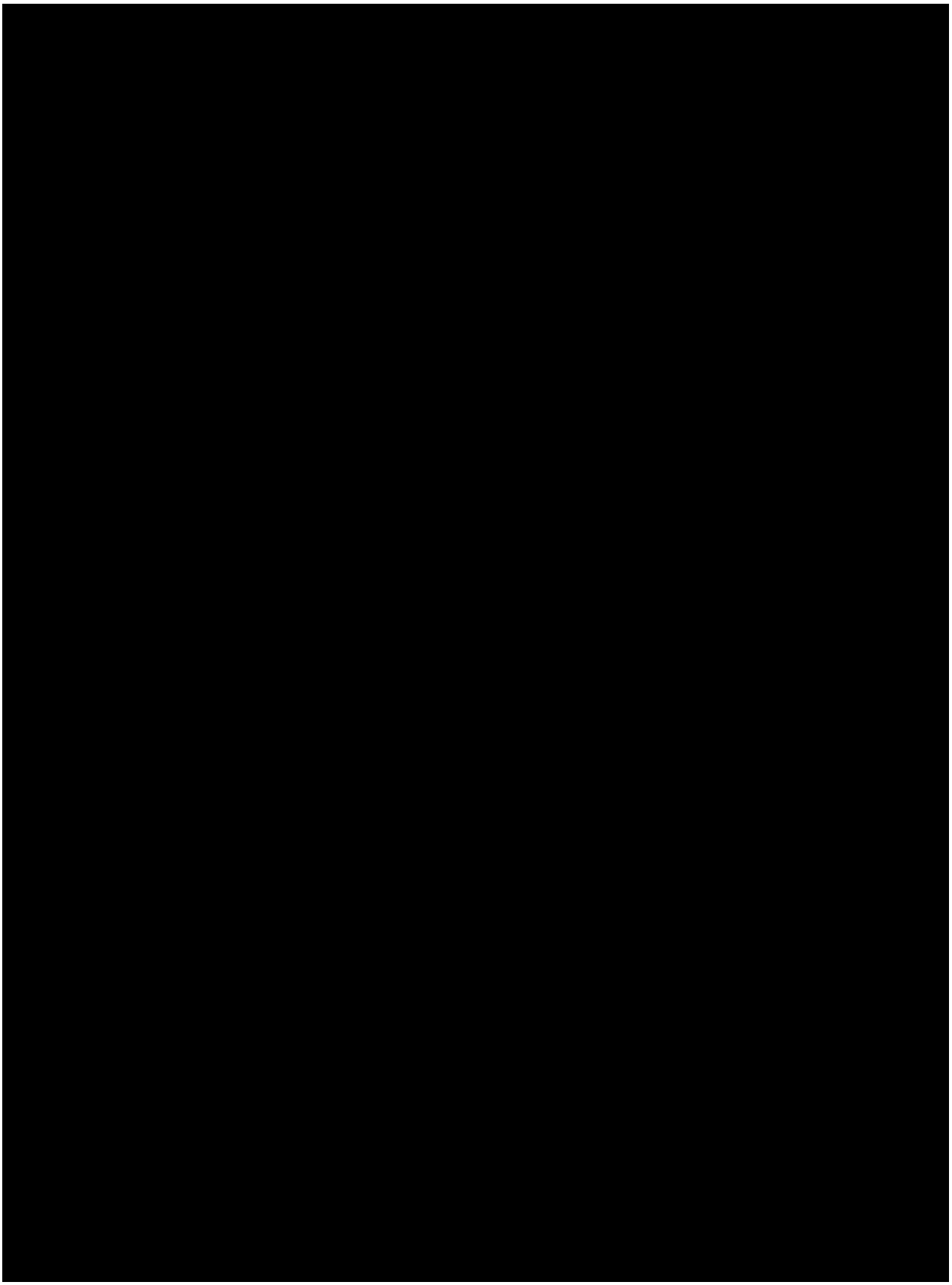






[redacted]

## 1.2 Dose Selection

[redacted]

[redacted] Based on PK simulations performed with this model a dosing scheme has been selected for the age cohort to be enrolled (1 to < 18 years):

[redacted]

**Dose Selection**

With the introduction of 0.5-mg tablets, the dosing paradigm of apixaban changed from mg/kg dosing to a fixed-dose, body weight-tiered regimen, as outlined in Table 1.2-2. The fixed-dose, body weight-tiered regimen will use apixaban doses in increments of 0.5-mg according to the appropriate weight range, regardless of apixaban formulations (i.e. oral solution or 0.5-mg tablets). The modelling and simulation results, support the current dosing recommendation of a fixed-dose body weight-tiered regimen for pediatric subjects aged 3 months to < 18 years. The age range for enrollment in this study will remain age 1 year to < 18 years. Study medication will be administered in accordance with the instructions provided. While subjects ≥ 5 years may be administered either 2.5-mg, 0.5-mg tablets or oral solution apixaban, use of 2.5 mg or 0.5 mg tablets is encouraged.

Subjects < 5 years and <35 kg may be administered 0.5-mg tablets only. Switching formulations during the course of the study is not encouraged but is allowed.

The previously unopened 9 to < 12 kg weight tier will be redistributed into the 2 adjacent weight tiers and dosed as follows: 6 to < 10.5 kg patients will be dosed 0.5 mg and 10.5 to <18 kg patients will be dosed 1 mg. The original proposal was for patients with body weight in the tier of 9 to < 12 kg to receive a 0.75-mg dose. The redistributed regimen provides similar exposures to the 0.75-mg dose originally listed in the protocol.

Subjects 1 to < 18 years of age will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range as per below Table 1.2-2 during approximately 28 days of induction chemotherapy including asparaginase.

**Table 1.2-2: Apixaban Doses for Ages 1-18 Years of Age**

| Weight range | Dose |
|---|---|
| ≥ 35 kg | 2.5 mg twice daily |
| <35 to 25 kg | 2 mg twice daily |
| <25 to 18 kg | 1.5 mg twice daily |
| <18 to 10.5 kg | 1 mg twice daily |
| <10.5 to 6 kg | 0.5 mg twice daily |

The previously communicated dosing for the body weight tier of 9 to < 12 kg has been redistributed into a 6 to < 10.5 kg weight tier and a 10.5 to < 18 kg weight tier.

Apixaban will be administered during approximately 28 days of induction chemotherapy including asparaginase.

## 1.3 Research Hypothesis

Administration of prophylactic apixaban, orally or via a nasogastric or gastric tube (NGT, GT), during induction chemotherapy will reduce the risk of venous thromboembolism (symptomatic + asymptomatic), compared to no systemic anticoagulant prophylaxis, during induction chemotherapy in children with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase.

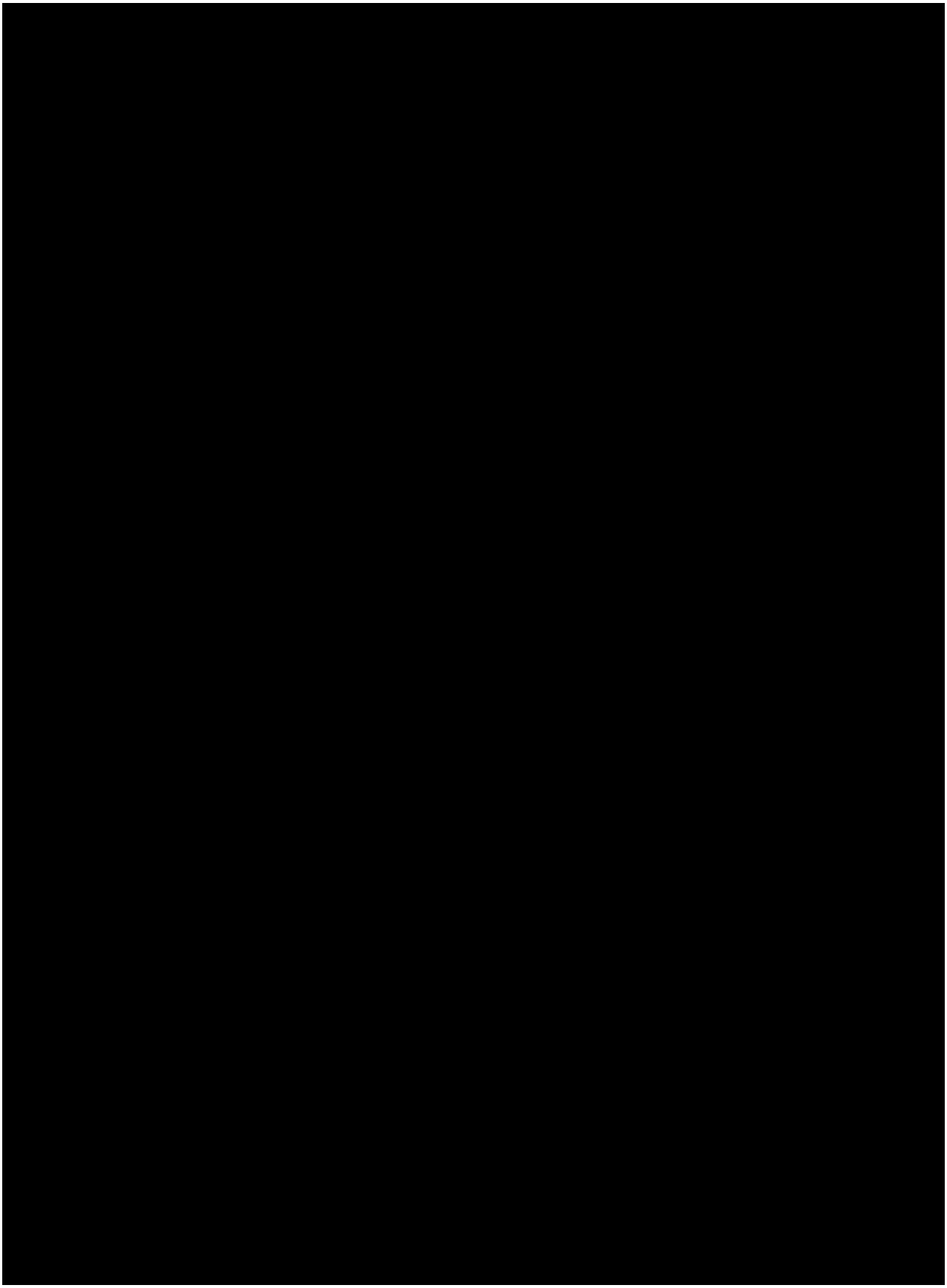
## 1.4 Objectives(s)

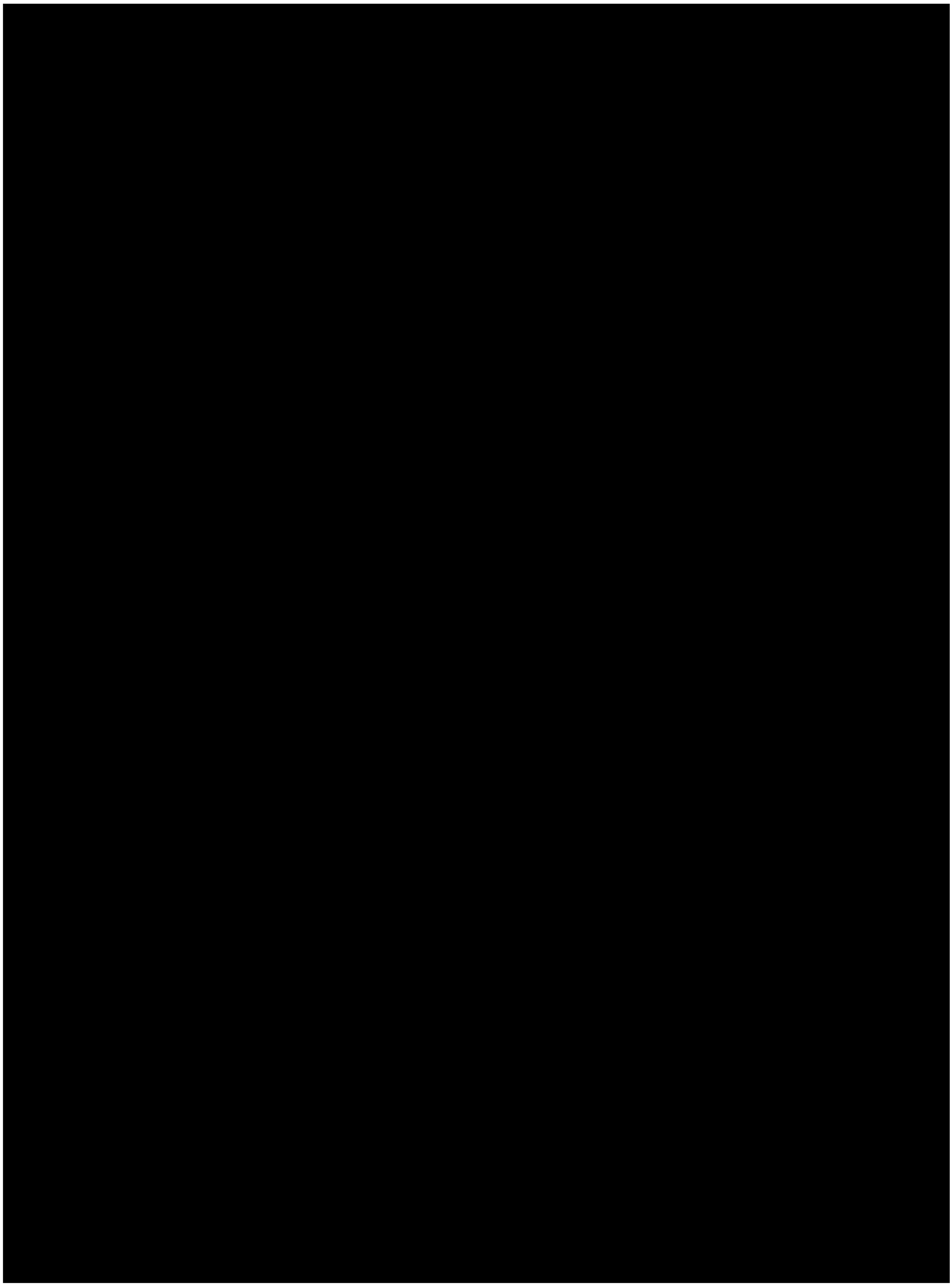
### *1.4.1 Primary Objectives*

- To compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT, including symptomatic and asymptomatic), pulmonary embolism (PE), and CVST; and VTE-related-death.
- To assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on adjudicated major bleeding events.

### *1.4.2 Secondary Objectives*

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on single adjudicated endpoints of non-fatal DVT (including symptomatic and asymptomatic), PE, and CVST; and VTE-related-death.
- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated major and clinically relevant non-major bleeding (CRNMB) events.





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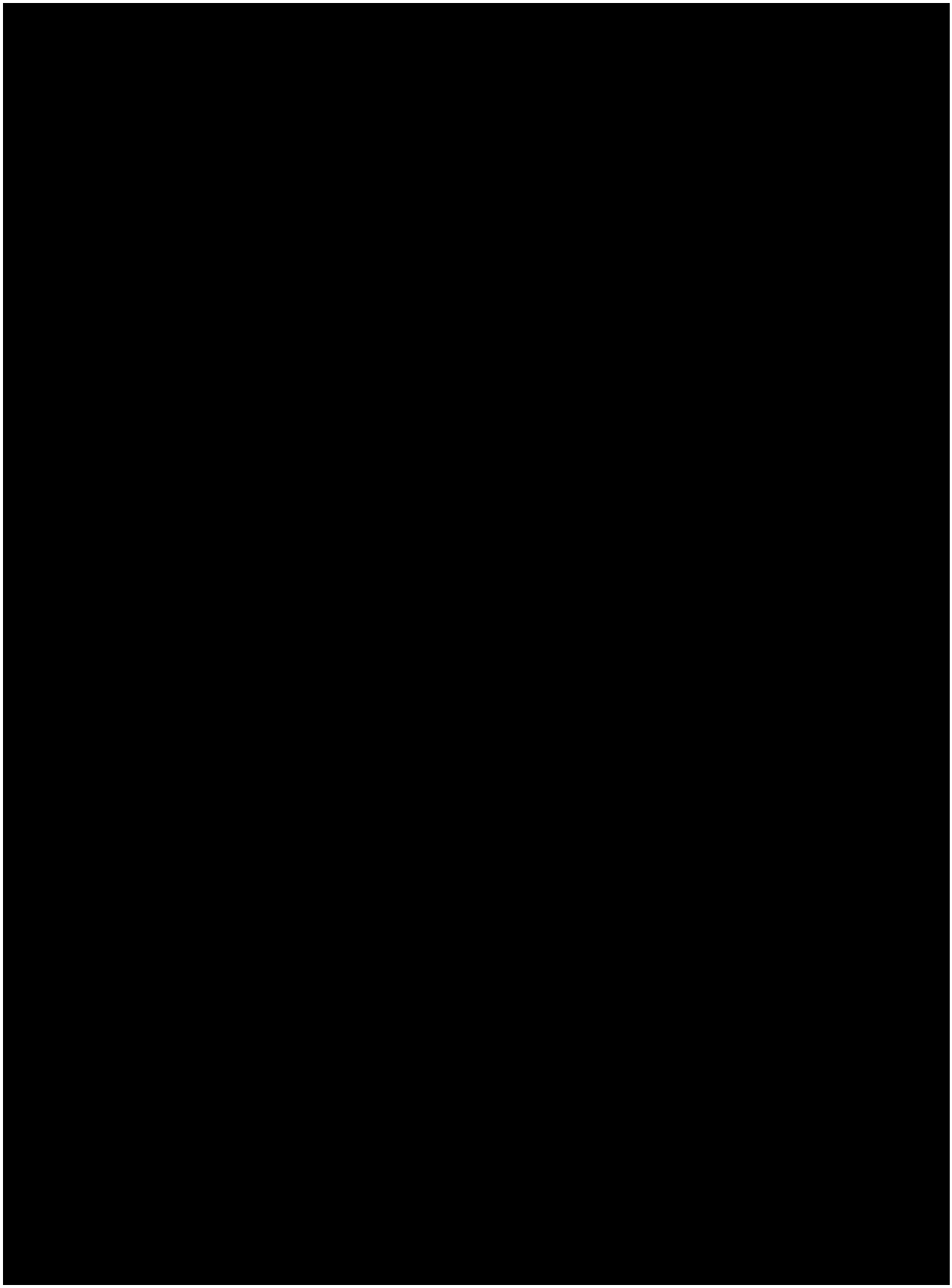

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# 2 ETHICAL CONSIDERATIONS

## 2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal

Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study. All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

## 2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials

(eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates. The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

## 2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC’s written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject’s legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the

US, the subjects' signed HIPAA Authorization. The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason as determined by local requirement should also give their assent. The assent should be documented based on local requirements.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

# 3 INVESTIGATIONAL PLAN

## 3.1 Study Design and Duration

Children and adolescents with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase will be eligible for this randomized, open-label, study. The subjects on the apixaban arm will receive study drug during approximately 28 days of induction chemotherapy including asparaginase. The study sample size is approximately 500 randomized patients.

**Design**

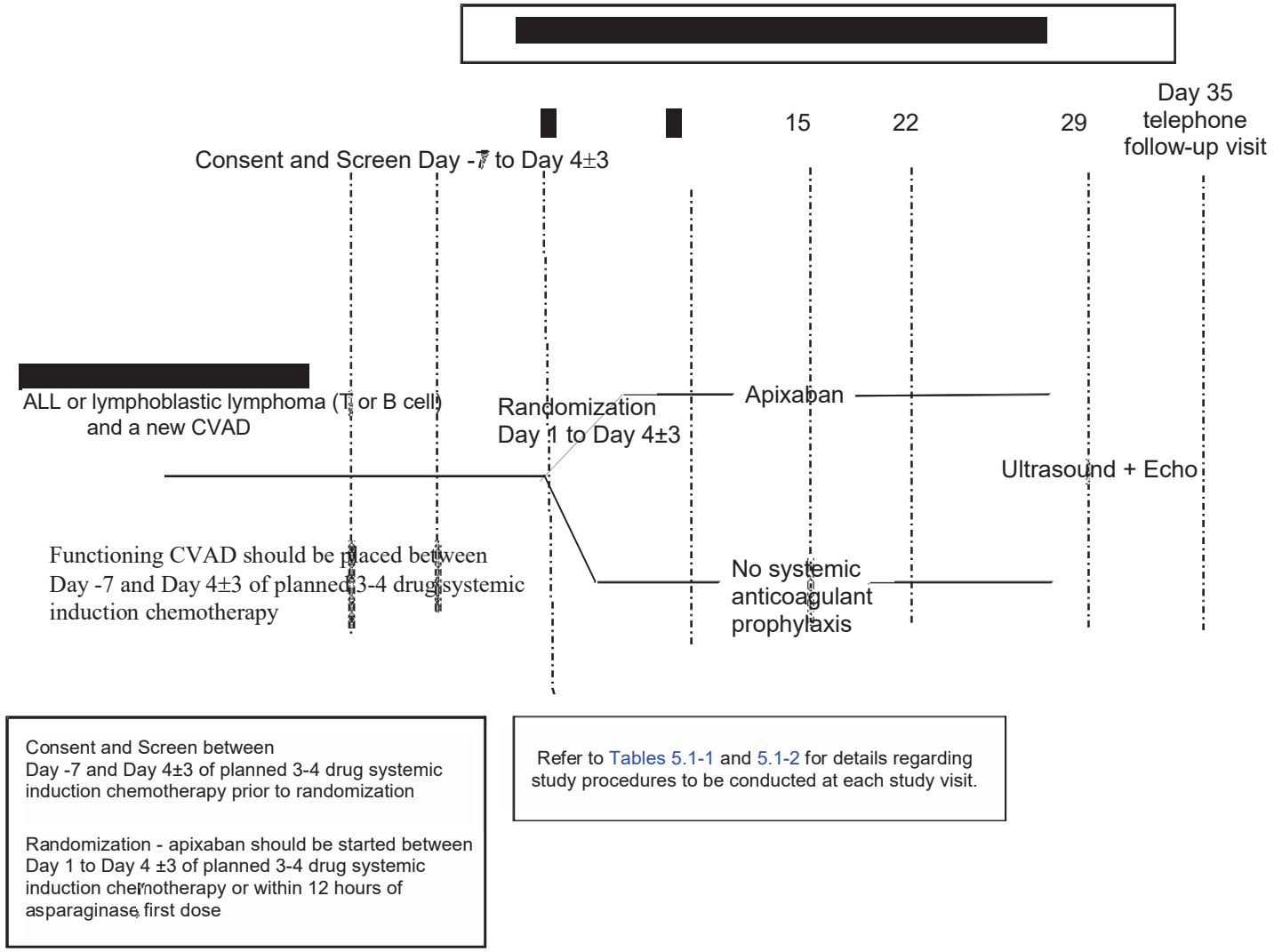
The study is designed to compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during approximately 28 days of induction chemotherapy on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT, including symptomatic and asymptomatic), pulmonary embolism (PE), and CVST; and VTE-related-death in subjects (1 to < 18 years) with newly diagnosed ALL or lymphoblastic lymphomas (T or B cell), a functioning CVAD and receiving asparaginase during planned 3-4 drug systemic chemotherapy induction.

There are four study periods extending up to a maximum total of approximately five weeks in duration:

- a screening period between Day -7 to Day 4 ±3 days of planned 3-4 drug systemic induction chemotherapy prior to randomization
- Note: Screening labs done as part of standard of care prior to signing the informed consent can be used to determine eligibility as long as they were obtained within 1 week prior to enrollment
- Day 1 is defined as the first day of planned 3-4 drug systemic induction chemotherapy
- a randomization period occurring between Days 1 to 4±3 of planned 3-4 drug systemic induction chemotherapy
- a treatment period, starting with the day of randomization, and extending through Day 29 ± 5 days of planned 3-4 drug systemic induction chemotherapy. Subjects ≥ 5 years will be administered either 2.5 mg, 0.5 mg tablets or oral solution as per Table 1.2-2. Subjects < 5 years and < 35 kg will be administered 0.5 mg tablets as per Figure 3.1-1.
- a follow-up period starting the day after the Day 29 ± 5 days visit.

The study design schematic is presented in the figure below (Figure 3.1-1).

**Figure 3.1-1: Study Design**



**Definition of Last Visit** – the last visit is the follow-up assessment (telephone or office visit) that occurs on Day 35 ± 5 days.

**Definition of End of Study -** the date of the last subject visit of the last subject to complete the study OR the date at which the last data point from the last subject, which was required for statistical analysis (ie, key safety and efficacy results for decision making), was received, whichever is the later date.

**Duration**

The total duration of the trial will be approximately 6 years and includes an estimated recruitment period and the follow-up at Day 35 ± 5.

[redacted] recruitment will include children of ages 1 to < 18.

## 3.2 Post Study Access to Therapy

At the end of the treatment period, the sponsor will not continue to supply study drug to subjects/investigators unless the sponsor chooses to extend the study. If the investigator considers that the subject should receive continuous VTE prevention after the Day 29 visit, the investigator should ensure that the subject receives appropriate standard of care to provide VTE prevention.

## 3.3 Study Population

Subjects eligible for the study include both males and females, age 1 to < 18 years with newly diagnosed ALL or newly diagnosed lymphoblastic lymphomas (T or B cell) and a new CVAD inserted between Day -7 and Day 4 ±3 of planned 3-4 drug systemic induction chemotherapy.

The study will be conducted at approximately 100 sites in selected countries globally. A total of approximately 500 patients are expected to be randomized into the study. For entry into the study, all of the following criteria MUST be met.

### *3.3.1 Inclusion Criteria*

1. **Signed Written Informed Consent**
   a. Signed written informed consent obtained from subject's legally acceptable representative (parents or guardians) according to local regulations and if mentally capable, assent from subject if required locally
2. **Target Population**
   a. New diagnosis of de novo ALL, or lymphoblastic lymphomas (T or B cell)
   b. Planned 3-4 drug systemic induction chemotherapy with a corticosteroid, vincristine and a single dose or multiple doses of asparaginase, with or without daunorubicin
   c. Patients with mixed-phenotype acute leukemia (MPAL) who will be treated with ALL induction chemotherapy as described above (Inclusion 2b) are also eligible
   d. Functioning CVAD, defined as no known mechanical problem and including external tunneled CVAD, implantable ports, and peripherally inserted central catheters (PICC) placed in a new location between Day -7 and Day 4±3 of induction chemotherapy and planned to remain in place until at least Day 29±5 days of induction. The CVAD must be

inserted prior to the start of study medication and could be inserted prior to signing informed consent as part of standard of care.

Note: The CVAD can be replaced if it is a planned replacement (eg, it is allowed to have a PICC at the time of enrollment that will be changed to a more permanent line later in induction); and it is allowed if a CVAD is not in place at the time of enrollment as long as it is in place before apixaban starts.

e. Not applicable per protocol amendment 04

f. Able to tolerate oral medication or have it administered via an NGT or GT tube.

g. Subject Re-enrollment: This study permits re-enrollment of a subject that has previously failed screening but currently meets entry criteria. If re-enrolled, the subject must be re-consented and receive a new patient identification number.

**3. Age and Reproductive Status**

a. Males and females, age ≥ 1 year (365 days) to < 18 (17 years and 364 days) years at the time of consent.

Females of reproductive potential (FRP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening.

For all FRP that will be inpatients from consenting to the first dose of apixaban, a negative pregnancy test must be recorded in the subject's hospital chart prior to receiving the first dose of apixaban.

All FRP that will be treated as outpatients from consenting to the first dose of apixaban, must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

b. Women must not be breastfeeding

c. FRP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (approximately 28 days), plus 30 days (duration of ovulatory cycle) for a total of 30 days post-treatment completion. (As outlined in Appendix 15)

i. Abstinence will be considered an acceptable form of birth control.

Men who are sexually active with FRP must agree to follow instructions for method(s) of contraception as outlined in Appendix 15.

Investigators shall counsel FRP on the importance of pregnancy prevention with highly effective forms of contraception and the implications of an unexpected pregnancy. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Contraceptive counseling should be provided at the time of assent or consent.

- At a minimum, subjects must agree to the use one method of highly effective contraception as listed in Appendix 15.

Local laws and regulations may require use of alternative and/or additional contraception methods.

### 3.3.2 Exclusion Criteria

**1. Target Disease Exceptions**

a. Not applicable per protocol Amendment 02

b. Subject scheduled to have > 3 LP's over the course of the study treatment period, ie. Day of Randomization to Day 29 visit

**1. Medical History and Concurrent Diseases**

a. Prior history of documented DVT or PE in the past 3 months

b. Known inherited bleeding disorder or coagulopathy with increased bleeding risk (eg, hemophilia, von Willebrand disease, etc.)

c. Major surgery (excluding CVAD replacement and bone marrow aspiration and non-open biopsy) within the last 7 days prior to enrollment that may be associated with an increase in the risk of bleeding. Open biopsy is considered a major surgery.

d. Active clinically significant bleeding

e. Known inherited or acquired antiphospholipid syndrome [APS]

**2. Physical and Laboratory Test Findings**

a. Uncontrolled severe hypertension at enrollment. Severe hypertension is defined as a systolic or diastolic blood pressure (BP) > 5 mm Hg above the 95th percentile as defined by the National High Blood Pressure Education Program Working Group (NHBPEP) established guidelines for the definition of normal and elevated blood pressures in children. See Appendix 14 for references.[57]

Note: Subjects with a blood pressure (BP) > 95th percentile for age, height, and gender which is not life-threatening can be enrolled, provided their hypertension is treated as deemed appropriate by the investigator per standard of care.

b. Extreme hyperleukocytosis, white blood cell (WBC) counts over 200 x 109/L (200,000/microL) at the time of enrollment.

Note: Subjects with WBC counts over 200 x $10^9$/L (200,000/microL) at the time of diagnosis can be enrolled if their WBC counts decreased to 200 x $10^9$/L or below at the time of enrollment, except subjects who have had leukopheresis, these subjects will be excluded regardless of WBC count.

c. Liver dysfunction manifested by SGPT (ALT) > 5X ULN and/or AST > 5X ULN and/or direct (conjugated) bilirubin > 2X ULN (subjects with a total bilirubin value ≤ 2XULN can be enrolled if the direct bilirubin values are not available)

d. Renal function < 30% of normal for age and size as determined by the Schwartz formula: [eGFR (ml/min/1.73 m2) = 0.413 * (height (cm) / serum creatinine (mg/dl)] (See Appendix 13).

Note: Liver and renal function tests obtained within 1 week prior to enrollment are acceptable.

e. INR > 1.4, AND aPTT > 3 seconds above the upper limit of normal for age within 1 week prior to enrollment. If needed, confirmation by repeat testing is permissible.

Repeat aPTT tests using venous puncture if the values are high and heparin contamination is suspected.

f. Positive pregnancy test

**3. Allergies and Adverse Drug Reaction**

a. History of allergy hypersensitivity or anaphylaxis to apixaban or its excipients or Factor Xa inhibitors

b. History of significant adverse reaction or major bleeding related adverse reaction to other anticoagulant or antiplatelet agents

c. History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

**4. Sex and Reproductive Status**

a. Positive pregnancy test

**5. Other Exclusion Criteria**

a. Unable to take oral or enteric medication

b. In the opinion of the Investigator, it is not possible for the subject to be compliant with the protocol and study procedures

c. Failure to provide written informed consent

d. Any investigational drug being administered during the study

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

### *3.3.3 Females of Reproductive Potential*

See Appendix 15

## 3.4 Concomitant Treatments

Medications taken after signing the informed consent form must be recorded on the appropriate case report form (CRF) page.

### *3.4.1 Prohibited and/or Restricted Treatments*

1) Concurrent prophylactic or therapeutic treatment with LMWH, unfractionated heparin, other oral anticoagulant, or systemic tPA (heparin flushes to maintain CVAD patency and local tPA to restore CVAD patency are permitted)
2) Any anti-platelet therapy with aspirin or thienopyridines such as clopidogrel, ticagrelor, or prasugrel.
3) Concomitant systemic treatment with strong inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, telithromycin, clarithromycin, indinavir, nelfinavir, saquinavir, cobicistat, and ritonavir.
4) Concomitant systemic treatment with strong inducers of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp), such as rifampin, carbamazepine, phenytoin and St. John's Wort.

5) Chronic daily use of nonsteroidal anti-inflammatory drugs (NSAIDs, eg, naproxen, ibuprofen, diclofenac) may increase the risk of bleeding. Therefore, concomitant use of NSAIDS more than 7 days is prohibited.

During the entire study period, no other investigational agents, other than apixaban should be administered to the patient.

**Note:** Fluconazole, topical azole antifungal agents, trimethoprim-sulfamethoxazole, H2-antagonists and proton pump inhibitors are permitted.

### *3.4.2 Other Restrictions and Precautions*

Based on pre-clinical and clinical data, apixaban might increase the likelihood of bleeding. Hence, subjects with platelet counts < 20,000 /microL, undergoing a lumbar puncture, or having surgical procedures, including a bone marrow aspirate and dental procedures should be instructed to inform their doctors about these procedures, and proper cautions should be taken by the investigator to reduce potential risk of bleeding (see Section 4.5.2 for instruction).

Apixaban should not be administered if the platelet count is < 20,000/ microL. A subject may be transfused platelets per investigator's clinical judgement but may not be transfused solely to meet entry criteria.

### *3.4.3 Supportive Care Guidelines*

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as medically indicated.

## 3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's or guardian's decision to withdraw for any reason).
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS) / Pfizer
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- CVAD is lost before the Day 29 ± 5 end-of-study evaluation due to endpoint related events (eg, VTE, serious bleeding)
- Major bleeding event
- Thromboembolic event such as DVT, PE, CVST or arterial thromboembolic event.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug (ie, are off protocol therapy), including discontinuation due to thromboembolic or major bleeding event, or loss of catheter before the Day 29 ± 5 end-of-study evaluation because of achieving a primary endpoint, should comply with protocol specified follow-up procedures as outlined in Section 5. Every attempt should be made to have the study-related radiographic procedures, Ultrasound and Echocardiogram performed within 72 hours of the event regardless of receiving apixaban or not, and the telephone or in-person safety assessment completed on Day 35 ± 5 Days.

If the catheter is to be removed and replaced within 48 hours due to events other than a primary endpoint event (eg, VTE or major bleeding), the subject should not have the study mandated ultrasound and echocardiogram until Day 29 visit and should continue with the study treatment (for temporary apixaban interruptions related to an invasive procedure, see Table 4.5.2-1).

Once any study-specified thromboembolic or any major bleeding event endpoint occurs, every effort must be made to confirm a suspected thromboembolic or bleeding event before removing a subject from protocol therapy. This applies to all subjects regardless of receiving apixaban or not. Management of any asymptomatic or symptomatic events will be according to the local standards of practice. If study medication is discontinued for a suspected thromboembolic event, alternative anti-thrombotic therapy may be initiated per the Investigator's discretion and standard of care.

The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

***Emergency procedures***

If a subject requires an emergency procedure or surgery that requires immediate knowledge of the subject's hemostatic status, the study medication should be discontinued. The treating physician should be informed about the specifics of apixaban administration such as timing and dosage. It is also important to let the treating doctor know that routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of anticoagulant effect and are unsuitable for monitoring the anticoagulant effect of apixaban. No specific antidote with an approved pediatric indication exists for apixaban reversal and apixaban is not substantially removed from systemic circulation by dialysis. In the event of apixaban-related hemorrhage, the use of prothrombin complex concentrate (PCC), activated prothrombin complex concentrate, or recombinant factor VIIa may be considered. The use of activated oral charcoal may be considered if ingestion occurred within

2 - 6 hours of presentation. Protamine sulfate and vitamin K will not affect the anticoagulant activity of apixaban.

Temporary treatment interruptions are addressed in Section 4.5.2.

## 3.6 Post Treatment Study Follow up

In this study, the presence or absence of thromboembolism at Day 29 is a key endpoint of the study. Post treatment study follow-up on Day 35 ± 5 days of chemotherapy is important and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of serious adverse event follow-up data as required and in line with Section 5 until death or resolution of the event.

### *3.6.1 Withdrawal of Consent*

Subjects who request to discontinue protocol treatment will remain on study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### *3.6.2 Lost to Follow-Up*

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

# 4 STUDY DRUGS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

## 4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this study, investigational product is apixaban (ie, BMS-562247) in tablets and oral solution.

Apixaban will be provided by Bristol-Myers Squibb and is described in Table 4.1-1.

**Table 4.1-1: Product Description - Treatment Period**

| Product Description and Dosage Form | Potency | Label Type | Packaging/ Appearance | Storage Conditions (per label) |
|---|---|---|---|---|
| BMS-562247-01 Film Coated Tablet | 2.5 mg | Open label | Bottle | Refer to the label on container |
| BMS-562247-01 Oral Solution (not to be used in children < 5 years of age in CV185155) | 0.4 mg/mL | Open label | Bottle | Refer to the label on container |
| BMS-562247-01 Film Coated Tablet | 0.5 mg | Open label | Bottles in kit | Refer to the label on container |

Specific information regarding study drug preparation and administration will be provided to the site.

## 4.2 Non-investigational Product

Other medications used in the study for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, are considered non-investigational products and will not be supplied by the sponsor.

## 4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and BMS should be contacted immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

## 4.4 Method of Assigning Subject Identification

At enrollment, each subject will be assigned a unique sequential number by the Interactive Voice Response System (IVRS). The IVRS will be available 24 hours per day, seven days a week. The subject number will consist of a unique 5 digit number which is assigned sequentially within a study (starting with 00001) by the IVRS. This number will be used for identification throughout the study and will not be used for any other subject.

Patients will be randomized to apixaban or usual care (no systemic anticoagulant) in a 1:1 ratio by the IVRS. Randomization schedules will be generated and kept by Bristol-Myers Squibb. Randomization will be stratified by age groups as < 10 years or ≥ 10 to < 18 years, to reflect the major peaks of disease prevalence and risk stratification criteria for acute lymphoblastic leukemia (ALL) in children.[40,58,59].

## 4.5 Selection and Timing of Dose for Each Subject

A phased recruitment for this study has been done, based on the informed dose selection from the single dose PK/PD study. Recruitment began for children of ages 2 to < 18 years. Subsequently, enrollment for children 1 to < 2 years has started given that the dose selection by the sponsor [redacted] has been completed and endorsed by the DMC. This protocol update includes dosing for children > or equal to 1 year of age.

Subjects 1 to <18 years of age will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range as per below Table 1.2-2 during approximately 28 days of induction chemotherapy including asparaginase.

**Table 4.5-1: Apixaban Doses for Ages 1- <18 Years of Age Under Protocol Amendment 5**

| Weight range | Dose |
|---|---|
| ≥ 35 kg | 2.5 mg twice daily |
| <35 to 25 kg | 2 mg twice daily |
| <25 to 18 kg | 1.5 mg twice daily |
| <18 to 10.5 kg | 1 mg twice daily |
| <10.5 to 6 kg | 0.5 mg twice daily |

The previously communicated dosing for the body weight tier of 9 to < 12 kg has been redistributed into a 6 to < 10.5 kg weight tier and a 10.5 to < 18 kg weight tier.

Note: Study medication will be administered in accordance with the instructions provided. Subjects ≥ 5 years may be administered either 2.5 mg, 0.5 mg tablets or oral solution apixaban while subjects < 5 years and < 35 kg may be administered 0.5 mg tablets only.

Apixaban can be administered by mouth (PO) or via a NGT or GT followed with or without food approximately 12 hours apart. The oral solution should be administered with the appropriate dosing syringe provided by the Sponsor. The apixaban 2.5 mg tablet can be crushed and suspended in water or 5% dextrose in water (D5W) or apple juice or can be mixed with applesauce and promptly administered orally. Alternatively, apixaban 2.5 mg tablets can be crushed and suspended in 60 mL of water or D5W and promptly delivered through a NGT. The apixaban 0.5 mg tablets can be mixed with applesauce or can be suspended in water, apple juice, or formula and promptly administered orally.

Study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of planned 3-4 drug systemic induction chemotherapy, whichever is first. Dose modifications of study medication are not permitted. Patients may start their study medication at the same time each day.

**Missed dose**: If a dose is missed the subject should take the study medication immediately and then continue with twice daily administration as before. A double dose should not be taken to make up for a missed dose. Subjects may take a missed dose up to 6 hours after the normal dosing time. If it is greater than 6 hours from the normal dosing time, the dose should not be taken. Instead, the next scheduled dose should be taken at the normal dosing time.

**Vomiting/regurgitation**: If a subject vomits or regurgitates within 30 minutes of ingestion of the study drug, re-dosing is allowed and the study drug can be given again one time. If the subject vomits/regurgitates more than 30 minutes after study drug ingestion, no additional study drug should be taken and the subject should resume study drug ingestion according to the usual schedule.

[redacted]

### 4.5.2 Temporary Treatment Interruptions

During the course of the study, situations might occur in which the investigator considers a temporary interruption of study drug treatment necessary. For example, a lumbar puncture, a planned catheter replacement, a scheduled surgical procedure, occurrence of thrombocytopenia or elevated liver function tests. The treating physician should be informed about timing and dosage of apixaban administration at such circumstances. It is important to let the treating physician know that routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of activity and therefore may be unsuitable for monitoring. Dose interruptions for selected events are described in the table below (Table 4.5.2-1). For treatment interruptions ≥ 48 consecutive hours, the period of interruption should be noted and the investigator should document on the CRF the time and date of discontinuation and restart of therapy, as well as the reason for discontinuation and measures taken to correct the event, excluding protocol mandated interruptions. An AE/SAE should be reported if applicable. For an individual subject, dose interruptions and treatment discontinuation may be more or less conservative than indicated below in Table 4.5.2-1 based on the clinical judgment of the investigator. Note that discontinuation of subjects from treatment is addressed in Section 3.5

Apixaban should not be administered if the platelet count is < 20,000/ microL. A subject may be transfused platelets per investigator's clinical judgement but may not be transfused solely to meet entry criteria.

Note: Once enrolled in the study, decisions to transfuse to maintain platelet counts ≥ 20,000/ microL or to interrupt study medications should platelet counts fall < 20,000 microL is left to the discretion of the clinician as to what is best available care for patients.

**Table 4.5.2-1: Temporary Dose Interruptions for Apixaban**

| Event | Apixaban |
|---|---|
| Lumbar punctures (LPs) | Apixaban should be discontinued at least 24 hours prior to any planned lumbar puncture (LP) ie, there should be at least 24 hours between the last dose of apixaban and the planned LP. Apixaban should be resumed no sooner than 18 - 24 hours after the procedure. In the event of a traumatic lumbar puncture (defined in this protocol as a lumbar puncture with ≥ 10 red blood cells (RBCs)/μL of cerebrospinal fluid (CSF)[60], apixaban should be held for 48 hours after the procedure.<br>For example: for a LP scheduled on the morning of Day 8 :<br>1. Discontinue apixaban for at least 24 hours prior to the Day 8 Lumbar Puncture (hold apixaban the night before and the morning of the procedure, the Day 7 PM and Day 8 AM and PM doses of apixaban).<br>2. Resume apixaban 18-24 hours after the Day 8 AM Lumbar Puncture (resume apixaban with the AM dose on the day after the procedure, Day 9).<br>Recommend participating institutions follow local standards of care regarding minimum platelet thresholds prior to lumbar punctures.<br>In the event of a traumatic lumbar puncture (defined in this protocol as a lumbar puncture with ≥ 10 red blood cells (RBCs)/μL of cerebrospinal fluid (CSF), apixaban should be held for 48 hours after the procedure.<br>The last dose of apixaban will be on Day 29±5 of induction chemotherapy.<br>Lumbar punctures for study subjects should only be performed by trained personnel. |
| Scheduled surgical procedures | If a subject participating in the study requires an elective procedure or surgery, the following considerations should be taken into account: The effective half-life of apixaban when administered twice daily is approximately 12 hours and it is expected that most of the anticoagulation effect will be gone within 24 hours after the last dose of the drug. Apixaban must be stopped for a sufficient period of time (eg, at least 24 hours if low risk of bleeding and at least 48 hours for moderate or high risk of bleeding) prior to the procedure to minimize the risk of anticoagulant-related bleeding. The treating physician should be made aware of the time and dosage of apixaban administration and be informed that routine coagulation tests such as INR/PT and aPTT are relatively insensitive measures of anticoagulation activity and are unsuitable for monitoring the anticoagulation effect of apixaban. The subject will re-start study medication once hemostasis is secure and when, in the opinion of the investigator, it is safe to do so. |
| Thrombocytopenia.<br>An AE/SAE should be reported if applicable | A platelet count should be ≥ $20 \times 10^9$ per L within 24 hours of starting apixaban. There are no evidence-based guidelines for anticoagulation therapy in relation to platelet counts. In absence of any other coagulopathy, following guidelines are recommended during the course of the study period:<br>• Full-dose apixaban therapy for patients with platelet count ≥ $20 \times 10^9$ per L.<br>• Withhold apixaban for platelet count < $20 \times 10^9$ per L. Platelet transfusions can be given per the investigator's clinical judgement.<br>It is important to maximize thromboprophylaxis therapy. In some circumstances, physicians may choose to give platelet transfusions prior to anticoagulation to maximize anticoagulation exposure in patients with thrombocytopenia. Close monitoring of platelet count and careful watching for signs of bleeding are necessary. Depending on anticipated drop in platelet count, the platelet counts should be checked at least twice a week and |

**Table 4.5.2-1: Temporary Dose Interruptions for Apixaban**

| Event | Apixaban |
|---|---|
| | apixaban should be re-started only after platelets are ≥ 20 × $10^9$ per L OR after a platelet transfusion that is predicted to increase the platelet count to this threshold according to clinical judgment. |
| Elevated liver function tests.<br>An AE/SAE should be reported if applicable | If at any time during the treatment period a subject's liver function test (LFT) results show:<br>An isolated elevation of either SGPT (ALT)/SGOT (AST) ≥ 10 x ULN **AND/OR** a direct (conjugated) bilirubin > 3 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, CK as soon as possible (ie, within 3 days).<br>If the repeat tests indicate:<br>1) ALT/AST < 10 x ULN and conjugated bilirubin ≤ 3 x ULN, study medication may **continue.**<br>2) If the repeat ALT/AST ≥ 10 x ULN **AND/OR** the conjugated bilirubin is > 3 x ULN, the study medication must be **discontinued**.<br>The study medication must be **discontinued** if:<br>Clinical jaundice is present for a subject at any time<br>OR<br>If ALT/AST ≥ 10 x ULN on any two consecutive occasions<br>OR<br>Conjugated bilirubin > 3 x ULN on any two consecutive occasions.<br>All subjects with an ALT/AST ≥ 10 x ULN or direct bilirubin > 3 x ULN will be followed weekly until ALT/AST returns to < 3 x ULN *or to baseline*, and the conjugated bilirubin returns to ≤ 1.5 x ULN *or to baseline.*<br>If study medication is **discontinued** due to elevated ALT/AST OR BILIRUBIN, as defined above, inform the medical Monitor and Study Director and perform the following:<br>-PT, aPTT, fibrinogen to assess liver synthetic function<br>-Abdominal ultrasound, including liver and hepatobiliary system<br>-Hepatitis screen (anti-HAV, HBsAg, anti-HBc, anti-HBs and anti-HCV.<br>Obtain relevant specialist consultation. |

[redacted]

## 4.7 Treatment Compliance

Each time study medication is dispensed, compliance will be reinforced.

For inpatients, apixaban will be administered in the clinical facility under the supervision of clinical staff. The date, time and volume or dosage of administered drug will be recorded at the clinical site by clinical personnel in the patient's diary and eCRF. If an infant or a young child regurgitates a portion of or the entire drug product during or after administration, this should be recorded in the eCRF.

At each study visit, the patient/parents should bring the study medication and compliance will be assessed based upon subject's/parents interview and a count of the tablets or volume of solution returned. Compliance should be between ≥ 80% and ≤ 120% of that prescribed, excluding the protocol defined dose interruption period. The investigator (or designee) will record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, must be recorded on the eCRF. If a subject is not ≥ 80% compliant after exclusion of the protocol defined dose interruption period, then the period of noncompliance should be noted as a protocol deviation and the sponsor should be notified. The subject should be re-educated regarding recording these values.

## 4.8 Destruction and Return of Study Drug

### *4.8.1 Destruction of Study Drug*

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site. Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

### *4.8.2 Return of Study Drug*

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor. It is the investigator's responsibility

to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

[redacted]

# 5 STUDY ASSESSMENTS AND PROCEDURES

## 5.1 Flow Chart/Time and Events Schedule

**Table 5.1-1: Screening Procedural Outline ACCL1333 / CV185155**

| Procedure | Consent/Screening Visit[a] Day -7 to 4±3 | Randomization Visit[a], Day 1 to 4±3 | Notes |
|---|---|---|---|
| **Eligibility Assessments** | | | |
| Informed Consent/Assent | X | | Informed consent/assent must be signed prior to initiating any study procedures. |
| Inclusion/Exclusion Criteria | X | X | |
| Medical History | X | | |
| Physical Measurements | X | | Height, Body Weight, and calculated Body Mass Index |
| Catheter History | X | | |
| Concomitant Medication Assessment | X | X | Medications taken at the time of signing the informed consent and after signing the informed consent must be recorded on the appropriate CRF page |
| **Safety Assessments** | | | |
| Full Physical Examination | X | | Includes assessment of signs of venous thromboembolism or bleeding. |
| Vital Signs | X | | Heart rate, BP, respiratory rate and temperature |
| Adverse Events Assessment | | X | Collection of SAEs begins after signed consent; Collection of non-serious AE begins after randomization |

| **Table 5.1-1: Screening Procedural Outline ACCL1333 / CV185155** | | | |
|---|---|---|---|
| **Procedure** | **Consent/Screening Visit[a]** Day -7 to 4±3 | **Randomization Visit[a,] Day 1 to 4±3** | **Notes** |
| Laboratory Tests | X | | CBC with platelets, ALT, AST, conjugated bilirubin, serum creatinine, PT (if available), aPTT and INR<br>(Total bilirubin is acceptable if it is normal. Conjugated bilirubin should be obtained if total bilirubin is high).<br>Renal function must be > 30% of normal for age and size.<br>A platelet count ≥ 20 x $10^9$ per L must be obtained within 24 hours prior to starting apixaban.<br>Screening labs as part of the standard of care obtained within 1 week prior to signing the informed consent can be used |
| Laboratory Tests during LP<br>WBC and RBC in CSF | X | X | WBC and RBC in CSF required only once |
| [redacted] | | | |
| Pregnancy Test FRP only | X | | Negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) for FRP. |
| **Clinical Drug Supplies** | | | |
| Dispense Study Drug | | X | Study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of induction chemotherapy , whichever is first |
| Enroll via IVRS | X | | |
| Randomize via IVRS | | X | Randomization occurs between Day 1 and 4±3 of planned 3-4 drug systemic induction chemotherapy. Subjects can be enrolled and randomized during the same visit. |

[a] Screening visit can occur up to 14 days prior to randomization. It can also occur at the treatment visit (Day 1 - 4±3) as long as the subject is eligible by medical history, clinical exam, and has the laboratory results back to confirm the inclusive parameters.

| **Table 5.1-2: Study Procedural Outline ACCL1333 / CV185155** | | | | | |
|---|---|---|---|---|---|
| **Procedure** | **During Treatment Days 7 ± 5 For in-patients only** | **During Treatment Days 8 ± 5, 15 ± 5, 22 ± 5** | **End of Treatment Day 29 ± 5 or early drug discontinuationa** | **Follow-up Visit Day 35 ± 5** | **Notes** |
| Concomitant Medication Assessment | X | X | X | X | If done on Day 7 do not need to repeat on Day 8 |
| **Safety Assessments** | | | | | |
| Targeted Physical Examination | X | X | X | | Includes organ systems pertinent to the subject's signs, symptoms, or adverse events, eg, assessment of signs of VTE or bleeding.<br>If done on Day 7 do not need to repeat on Day 8 |
| Vital Signs | X | X | X | | Heart rate, BP, respiratory rate and temperature<br>If done on Day 7 do not need to repeat on Day 8 |
| Adverse Events Assessment | X | X | X | X | Collection of SAEs begins after signed consent<br>Collection of non-serious AE begins after randomization |
| Laboratory Tests: CBC with Platelets, ALT, AST, and direct (conjugated) bilirubin | X | X | X | | If done on Day 7 do not need to repeat on Day 8 |
| Laboratory Tests during the LP<br>RBC in the CSF | | X | X | | RBC in the CSF only taken at investigator defined LPs |

| **Table 5.1-2: Study Procedural Outline ACCL1333 / CV185155** | | | | | |
|---|---|---|---|---|---|
| **Procedure** | **During Treatment Days 7 ± 5 For in-patients only** | **During Treatment Days 8 ± 5, 15 ± 5, 22 ± 5** | **End of Treatment Day 29 ± 5 or early drug discontinuationa** | **Follow-up Visit Day 35 ± 5** | **Notes** |
| In-patient Pharmacokinetic (PK) and anti-Xa sample collection. See Section 5.5 | X | | | | For subjects receiving apixaban only. For inpatient, a pre-dose PK and anti-FXa sample may be taken 1 day prior to LP (prior to the day 7 AM dose if LP on day 8) followed by a PK and anti-FXa sample taken 1-4 hr post dose. If the subject is outpatient, follow alternate sample collection procedures. |
| [redacted] | | | | | |
| Alternate PK sample and anti-Xa collection. See Section 5.5 | | X | | | For outpatients, random PK and anti-FXa samples may be obtained prior to LP procedures for example during the Day 8 ± 5 visit and during Day 15 ± 5 visits. |
| **Efficacy Assessments** | | | | | |
| Doppler ultrasound | | | X | | The Doppler ultrasound should be performed for both of the ipsilateral (extremity in which the CVAD was placed) and the contralateral sides whenever possible. If there is a difficulty in performing the imaging procedure, Doppler ultrasound from the ipsilateral side alone is acceptable (see Appendix 1 for detailed guidance). **It should be performed within 3 days (not exceed 5 days) after termination of the study medication**. |

| **Table 5.1-2: Study Procedural Outline ACCL1333 / CV185155** | | | | | |
|---|---|---|---|---|---|
| **Procedure** | **During Treatment Days 7 ± 5 For in-patients only** | **During Treatment Days 8 ± 5, 15 ± 5, 22 ± 5** | **End of Treatment Day 29 ± 5 or early drug discontinuationa** | **Follow-up Visit Day 35 ± 5** | **Notes** |
| Echocardiogram | | | X | | Echocardiogram should be performed within 3 days (not exceed 5 days) after termination of the study medication. |
| **Clinical Drug Supplies** | | | | | |
| End taking Study Drug | | | X | | Apixaban will start between Day 1 and Day 4±3 of planned 3-4 drug systemic chemotherapy induction and is stopped on Day 29±5. Based on the quantity of the study drug returned by subjects, dosing compliance will be calculated. |

a Subjects who discontinue before the end of treatment need to complete all end of study procedures including ultrasound and echo imaging

No study-related procedure may be performed until the subject or their legally acceptable representative has been completely informed of the study, has freely consented to take part in the study, and has signed and dated an informed consent document, and where appropriate assent form, approved by a licensed Institutional Board Review (IRB) or Independent Ethics Committee (IEC). Every attempt should be made to coordinate the study-related visits with the subjects' medical visits.

The **Screening Period** will occur after consent is obtained between Day -7 to Day 4±3 of planned 3-4 drug systemic induction chemotherapy, and will begin with a screening visit. Screening labs as part of the standard of care can be used prior to signing the informed consent. At the screening visit the IVRS system will be contacted to obtain a unique subject number. A complete medical history and a physical examination including vital signs, height, BP, and body weight, will be obtained. The screening visit laboratory studies will include: CBC with platelets, ALT, AST, conjugated bilirubin, WBC and RBC in CSF (LP prior to receiving study medication), and serum creatinine (estimated GFR), PT (if available), aPTT, and INR and serum or urine pregnancy test for FRP.

For all FRP that will be inpatients from consenting to the first dose of apixaban, it is expected that a negative pregnancy test be recorded in the subject's hospital chart at any time point from the time of hospitalization but prior to first treatment.

All FRP that will be treated as outpatients from consenting to the first dose of apixaban, must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

Day 1 is defined as the first day of planned 3-4 drug systemic induction chemotherapy.

**The Randomization** visit will occur between Day 1 and Day 4±3 of planned 3-4 drug systemic induction chemotherapy. For pediatric subjects who meet all the inclusion/exclusion criteria, the IVRS system will be contacted and the subjects will be randomized.

Pediatric subjects randomized to apixaban will receive instructions about the study drug. If conditions for apixaban administration are met, study medication must be initiated prior to or within 12 hours of the first dose of asparaginase or by Day 4±3 of planned 3-4 drug systemic induction chemotherapy whichever is first. Day 1 is the first day of planned 3-4 drug systemic induction ALL chemotherapy.

For a subject who experiences a reaction to asparaginase during the infusion and has to switch to Erwinia Asparaginase during the induction chemotherapy, it is recommended that the subject continue the study treatment. The percentage of the original Asparaginase dose delivered will be recorded in the patient charter.

The screening and randomization visits can be done on the same day if the subject is eligible by medical history, clinical exam, and has local laboratory results that are within the appropriate inclusive parameters.

**Day 7 ± 5 of chemotherapy visit:** For all consenting subjects randomized to apixaban who are inpatients on Day 7 ± 5 of planned 3-4 drug systemic induction chemotherapy, a pre- and post-dose PK and anti-FXa sample may be taken on the same day, for example, prior to the Day 7 ± 5 AM dose of apixaban, followed by a PK and anti-FXa sample taken 1 - 4h after the AM dose of apixaban.

Subjects who are not able to provide a pre and post dose sample on the same day (eg, those who are outpatients) will have a PK and anti FXa sample collected on separate occasions, for example once on Day 8 ± 5 and once on Day 15 ± 5. Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin, RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed.

**Day 8 ± 5 of chemotherapy visit:** The Day 8 visit is required only if the Day 7 visit can't be completed. Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin, RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed unless they were performed on day 7 for inpatients.

Subjects who are randomized to apixaban and did not have a pre- and post- dose sample collected on the same day (eg, those who are outpatients), will have a PK and anti-FXa sample collected on separate days, for example, on either Day 8 ± 5 prior to LP procedures and within 24 hours of the subjects last apixaban dose.

**Day 15 ± 5 of chemotherapy visit:** Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin, adverse event data collection and concomitant therapy assessment will be performed.

Subjects who are randomized to apixaban and did not have a pre- and post- dose sample collected on the same day (eg, those who are outpatients), will have a PK and anti-FXa sample collected on separate days, for example, on Day 15 ± 5 of chemotherapy, 0.5 to 12 hr after the AM dose of apixaban (and prior to the PM dose on that day).

**Day 22 ± 5 of chemotherapy visit:** Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin, adverse event data collection and concomitant therapy assessment will be performed.

**Day 29 ± 5 of chemotherapy visit:** Local CBC with platelets, ALT, AST, and direct (conjugated) bilirubin, RBC in CSF, adverse event data collection and concomitant therapy assessment will be performed.

On the Day 29 visit, the imaging evaluation will occur for all randomized subjects who remain on protocol therapy. For those subjects randomized to apixaban, imaging evaluations will be performed preferably within 3 days but no more than 5 days of discontinuing apixaban. For those subjects randomized to the standard of care arm, imaging evaluations will be performed within 3 days but no more than 5 days from Day 29 (Day 24 to Day 34). The evaluation will include a bilateral Doppler ultrasound that will include imaging of the venous system in which the CVAD is placed and an echocardiogram to assess for right atrial thrombi according to the protocol guidance in appendices 1 and 2. Subjects will not undergo routine radiologic screening for CVST. (see Section 5.4.1)

**Evaluations to be performed at clinical suspicion of VTE or other off protocol therapy criteria including catheter loss:** All subjects who discontinue investigational product due to events such as thromboembolic or major bleeding event, or catheter loss before the Day 29 ± 5 end-of-study evaluation should remain on study. Every effort must be made to confirm a suspected thromboembolic or bleeding event prior to removal from protocol therapy.

Additional clinical and radiologic evaluations prompted by clinical suspicion of any DVT, PE, CVST, arterial thromboembolic events, bleeding or death will be performed at the discretion of the treating clinician; and information from these visits and imaging findings will be captured for study analysis. Management of any asymptomatic or symptomatic events will be according to the local standards of practice. If study medication is discontinued for a suspected VTE event, alternative anti-thrombotic therapy may be initiated per the Investigator's discretion and standard of care.

***It is critical for all patients (SOC and apixaban) that every attempt should be made to have the study-related radiographic procedures, Ultrasound and Echocardiogram, performed within 72 hours of the event and the follow-up safety assessment completed on Day 35 ± 5.***

If the catheter is to be removed, it is preferred that the diagnostic imaging procedures be performed prior to the catheter removal.

**Day 35 ± 5 of chemotherapy visit:** Telephone or in person follow up safety assessment will be scheduled on Day 35 ± 3 for all subjects. In this assessment, adverse event data collection and concomitant therapy assessment will be obtained.

### *5.1.1 Retesting During Screening*

Retesting of laboratory parameters and/or other assessments during the Screening period will not be permitted, except PT, aPTT and INR (this does not include parameters that require a confirmatory result).

Any new result will override the previous result (ie, the most current result prior to randomization) and is the value by which study inclusion will be assessed, as it represents the subject's, most current clinical state.

## 5.2 Study Materials

BMS will supply the sites with the following materials:

- Electronic case report forms (CRFs)
- BMS SAE electronic CRF Form
- BMS Pregnancy Surveillance Form
- Adjudication binder and worksheets
- Mandatory Patient diary for study medication, date and time of doses completed daily by patient/ parent or study staff.
- Laboratory manual

## 5.3 Safety Assessments

Informed consent must be obtained prior to any study screening procedures that would not have been performed as part of normal subject care. Screening activities should be conducted within 14 days prior to randomization to either thromboprophylaxis with apixaban or no thromboprophylaxis.

A platelet count should be performed within 24 hours prior to the start of apixaban therapy.

End of treatment visit must be completed on Day 29 ± 5 days of induction chemotherapy and will be performed after:

- Completion of approximately 28 days of induction chemotherapy in subjects.
- Subject withdrawal from the study as per any of the reasons listed in Section 3.5.

Any additional medical testing and procedures, whether more frequent or in addition to those described, should be performed as medically indicated.

Any safety events occurring after consent and up to Day 35 ± 5 should be sent for adjudication.

### *5.3.1 Bleeding Assessment*

**Major bleeding** is defined as bleeding satisfies one or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2 g/dL) in a 24 - h period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; and (iv) bleeding that requires surgical intervention in an operating suite (including interventional radiology).

**Clinically relevant non-major bleeding** is defined as bleeding satisfies one or both of the following: (i) overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition and (ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating suite.

**Minor bleeding:** is defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding.

Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

All bleeding events and their supporting documentation **MUST** be sent for adjudication.

### *5.3.2 Treatment guidelines for Bleeding / Suspected Bleeding*

Patients with bleeding or suspected bleeding should undergo confirmatory laboratory or other testing as indicated clinically (eg, compression Ultrasound (US), Computer Tomography (CT), Magnetic Resonance Imaging (MRI). The date and time of the onset of the bleeding event will be recorded on the CRF. The following routine measures may be considered:

**Table 5.3.2-1: Treatment Guidelines for Bleeding / Suspected Bleeding**

| | |
|---|---|
| Minor Bleeding | Apixaban may or may not be held based on an individualized benefit-risk assessment |
| Clinically Significant Bleeding | Apixaban should be held if subject meets criteria outlined in section 3.5.<br>• Identify of the source and institute local measures to stop the bleeding.<br>• Perform laboratory test monitoring (eg, hemoglobin, INR, aPTT, platelet count, anti-Factor Xa activity).<br>• Apixaban may be best monitored using an anti-Factor Xa assay rather than the more standard coagulation tests (eg, INR, aPTT) which are less sensitive to apixaban.<br>• If bleeding occurs up to 6 hours after apixaban administration consider administration of activated charcoal oral solution to reduce apixaban plasma exposure.<br>• Consider appropriate symptomatic treatment (eg, mechanical compression, surgical intervention, fluid replacement and hemodynamic support, blood product or component transfusion)<br>• For bleeding that does not respond to local measures, consider administration of fresh frozen plasma (FFP) as a supportive measure, recognizing that FFP does not reverse the anticoagulant effects of apixaban |
| Life Threatening Bleeding | Apixaban should be held for all life threatening bleeding or if subject meets criteria outlined in section 3.5.<br>• Administration of recombinant Factor VIIa may be considered, however, there is no experience with this agent in apixaban-treated patients. Its effectiveness for counteracting the effects of apixaban is not known.<br>• Activated prothrombin complex concentrate (aPCC) or prothrombin complex concentrate (PCC, also referred to as factor IX concentrate) are other procoagulants that may be considered, but considering the variety of formulations available and the complexity of dosing, the decision to employ aPCC or PCC should be made by an experienced clinician with careful evaluation of the risks and benefits.<br>• If bleeding occurs up to 6 hours after apixaban administration activated charcoal oral solution administration may be considered in order to reduce apixaban plasma exposure. |

- Delay the next dose of study drug or discontinue study medication if indicated
- Fluid resuscitation and blood transfusion as indicated
- Fresh frozen plasma or general hemostatic measures as indicated
- There is no specific reversal agent for apixaban approved in the pediatric population

Table 5.3.2-1 provides information for the treatment of bleeding or suspected bleeding. The specific treatment for bleeding is left to the discretion of the investigator and/or the attending physician based on the medical status of the subject and/or institutional policies.

[redacted]

### 5.3.3 Laboratory Assessments

Blood samples will be obtained on selected visits of clinical laboratory evaluations as outlined in Section 5.1 (Table 5.1-1 and Table 5.1-2- Flow chart/ Time and Events Schedule). A local laboratory should perform the analyses and will provide reference ranges for these tests. The following laboratory tests are required for this study, and should be analyzed by the local laboratory: CBC with platelets, serum creatinine, ALT, AST, and Conjugated Bilirubin, WBC and RBC in CSF (WBC at Day 1 Screen only), PT (if available), aPTT, INR (or thrombin time or Reptilase) and pregnancy test when applicable. The PK and PD assessment will be analyzed by a third party laboratory. For these laboratory assessments, materials and detailed instructions for specimen collection, processing, storage and shipment will be provided in special kits and will be described in a separate laboratory manual.

### 5.3.4 Pregnancy tests

For females of reproductive potential (FRP), a serum or urine pregnancy test should have a minimum sensitivity of 25 IU/L or equivalent units of βHCG. All on-study pregnancy testing should follow the schedule detailed in Table 5.1-1.

### 5.3.5 Creatinine Clearance

Based on the results of the enrollment visit clinical laboratory tests, eGFR will be estimated based on the Schwartz formula (See Table 5.1-1 for timing of assessments and Appendix 13 for eGFR assessment).

Inadequate Renal Function < 30% of normal for age and size as determined by the Schwartz formula[68] [eGFR (ml/min/1.73m2) = 0.413 * (height (cms) / serum creatinine (mg/dl). If serum creatinine concentration is measured in SI units (umoles/L), divide this number by the conversion

factor of 88.4 to get the SI units (mg/dl) before inserting into the Schwartz formula to calculate eGFR]. Subjects are required to have an eGFR > 30% of normal for age and size to be enrolled in the study.

### *5.3.6 Physical Examination*

A full physical examination should include general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, lungs, abdomen, lymph nodes, extremities, neurological, skin, musculoskeletal, vital signs (heart rate, respiratory rate, blood pressure), height and weight, as well as assessment of central nervous system status (CNS 1, CNS2, CNS 3).

A targeted physical examination should include any organ systems pertinent to the subject's signs, symptoms, or adverse events, such as assessment of signs of venous thromboembolism or bleeding**.**

**Only Investigators licensed to conduct physical examinations and who are listed on the Delegation of Authority Form are approved to perform physical examinations.**

### *5.3.7 Treatment Guidelines for Thrombocytopenia*

The platelet count should be ≥ 20 x $10^9$ per L within 24 hours of starting apixaban. There are no evidence-based guidelines for anticoagulation therapy in relation to platelet counts. In the absence of any other coagulopathy, the following guidelines are recommended during the course of the study period:

- Full-dose apixaban therapy for patients with platelet count ≥ 20 x $10^9$ per L.
- Hold apixaban for platelet count < 20 x $10^9$ per L and restart when platelet count ≥ 20 x $10^9$ per L or presumed to be above this threshold following a platelet transfusion.

It is important to maximize the thromboprophylaxis therapy. In some circumstances, physicians may choose to give platelet transfusions prior to anticoagulation to maximize the anticoagulation in patients with thrombocytopenia. If at all possible, it is preferred to have as much uninterrupted anticoagulation as possible during the treatment period. A close monitoring of platelet count and careful watching for signs of bleeding are necessary. For subjects with a platelet count < 20 x $10^9$ per L or with platelet counts anticipated to drop to below 20 x $10^9$ per L, the platelet counts should be checked at least twice a week and apixaban should be re-started only after platelets are ≥ 20×$10^9$ per L OR after a platelet transfusion that is predicted to increase the platelet count beyond this threshold.

## 5.4 Efficacy Assessments

The primary efficacy assessment of the study is a composite of non-fatal asymptomatic and symptomatic DVT, PE, and CVST; and VTE-related-death objectively confirmed by independent adjudication. All components of the primary efficacy endpoint will be adjudicated by a blinded, independent adjudication committee.

Any suspected efficacy clinical events occurring after consent and up to Day 35 ± 5 should be sent for adjudication.

Details for the assessment of the components of the primary efficacy endpoint are provided in Appendices 3, 4 and 5.

### 5.4.1 Imaging assessment for the study

On Day 29 ± 3 days, the imaging evaluation will occur **for all** randomized subjects who remain on protocol therapy. **For subjects in the apixaban treatment arm, Doppler ultrasound and echocardiogram should be performed within 3 days (not exceed 5 days) after termination of the study medication including early discontinuation. For those subjects randomized to the standard of care arm, imaging evaluations will be performed within 3 days but no more than 5 days from the Day 29 visit or early discontinuation from the study**.

The evaluation will include a bilateral Doppler ultrasound that will include imaging of the venous system in which the CVAD is placed and an echocardiogram to assess for right atrial thrombi according to the protocol guidance in appendices 1 and 2. The Doppler ultrasound should be performed for both the ipsilateral (extremity in which the CVAD was placed) and the contralateral sides whenever possible. If there is a difficulty in performing the imaging procedure, Doppler ultrasound from the ipsilateral side alone is acceptable (see Appendix 1 for detailed guidance). Subjects will not undergo routine radiologic screening for CVST.

A chest X-ray is not mandated by the study. However, if a chest X-ray has been performed as part of the standard of care, the chest X-ray should be submitted as part of the adjudication package.

[redacted]

## 5.5 Pharmacokinetic and Anti-Xa Assessments

PK and anti-Xa assessments will only be performed for patients randomized to the apixaban arm. Table 5.5-1 summarizes the sampling collection schedule to be followed for these assessments.

Sparse samples for PK and PD (anti-FXa activity) will be taken in subjects receiving apixaban. Pre-dose and post dose samples of apixaban may be taken on the same day if feasible (eg, in-patients). Alternatively samples may be collected on separate days (eg, out-patients), for example, subjects may have the pre-dose sample taken before the LP procedures and the post-dose sample taken on an alternate visit.

The date and time of apixaban administration must be recorded for the dose immediately before PK/anti-FXa sample collection. Whenever possible PK/PD samples should be collected at the same time as the clinical laboratory assessments and may be drawn through the CVAD. Further sample collection and processing instructions will be provided separately.

**Table 5.5-1: PK and Anti-Xa Sample Collections Schedule[a]**

| Patient status | Day of blood sample | Time (Relative to Dosing) Hour[a] | PK and anti-Xa Blood Samples |
|---|---|---|---|
| In patient | 1 day prior to LP (eg, day 7 if day 8 LP ) | 0 (predose)<br>1 - 4h (post-dose) | X |
| Out patient | The day of LP (any day an LP will be performed)[b] | Random sample collected prior to LP procedures | X |
| Out patient | 15 or another day (any visit at which an LP will not be performed)[b] | Random sample collected 0.5 to 12 h after the AM dose of apixaban and prior to the PM dose | X |

[a] The date and time of apixaban administration must be recorded for the dose immediately preceding PK/anti-FXa sample collection.

[b] [redacted]
The date and time of apixaban administration for the dose immediately preceding PK/anti-FXa sample and the time of PK/Anti-FXa sample collection must be recorded.

[redacted]

# 6 ADVERSE EVENTS

***Importance of Adverse Event Reporting***

Timely and complete reporting of safety information assists BMS in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study patients; (2) a greater understanding of the overall safety profile of the investigational product; (3) recognition of dose-related investigational product toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the

use of investigational product, whether or not considered related to the investigational product. Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

For all adverse events, including those that are serious, if the diagnosis of the underlying illness or disorder is known; this diagnosis should be recorded, rather than its individual symptoms.

All adverse events will be graded according to the NCI CTCAE version 4.0.

In this study, expected chemotherapy-related CTCAE Grade 1 or Grade 2 AEs of nausea, vomiting, anorexia, fatigue, headache, fever, neutropenia, or an institution SOC practice to extend a hospitalization for the possibility of chemotherapy induced neutropenia will **not** be collected on the non-serious AE case report form. However, any extended hospitalization due to a confirmed neutropenia or Grade 3 or higher AE/SAE of nausea, vomiting, anorexia, fatigue, fever, neutropenia, or headache **will** be collected, whether considered related to chemotherapy or not.

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used for all BMS clinical study AEs:

- Related - There is a reasonable causal relationship to study drug administration and the AE.
- Not Related - There is not a reasonable causal relationship to study drug administration and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (eg, evidence such as de-challenge/re-challenge) or other arguments to suggest a positive causal relationship.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious. This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study; such patients should receive post-treatment follow-up as appropriate. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

## 6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject 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)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

**NOTE:**

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- planned chemotherapy
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

### *6.1.1 Serious Adverse Event Collection and Reporting*

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting.

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and up to 30 days after the last apixaban administration or last induction chemotherapy drug.

Following study completion, any SAE thought to be related to study drug or clinical trial procedures should also be reported to the Sponsor.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** See Contact Information list.

**SAE Facsimile Number:** See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

**SAE Telephone Contact** (required for SAE and pregnancy reporting): See Contact Information list. If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

## 6.2 Non-serious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

### *6.2.1 Nonserious Adverse Event Collection and Reporting*

The collection of nonserious AE information should begin at randomization for all patients, including the patients randomized to the usual care arm.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## 6.3 Laboratory Test Result Abnormalities

In order for BMS to collect additional information about clinically important laboratory abnormalities, at a minimum, the following laboratory test results abnormalities should be captured on the non-serious or serious AE report pages of the CRF (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy such as platelet transfusions in order to keep platelets≥ $20x10^9$ per L or to treat bleeding episodes. Blood transfusion to correct anemia secondary to bleeding. Plasma infusions to correct bleeding complications.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

## 6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject. Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. Pregnancy and the accompanying forms must be followed up to 30 days following the discontinuation of apixaban.

## 6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose, if excessive and medically important, must be reported as an SAE (see Section 6.1.1 for reporting details).

## 6.6 Potential Drug Induced Liver Injury (DILI)

The following guidelines are intended to identify and manage subjects with LFT abnormalities. Specific laboratory test criteria and instructions for further follow up are provided.

If at any time during the treatment period a subject's liver function test (LFT) results show:

An isolated elevation of either ALT/AST ≥ 10 x ULN AND/OR a direct (conjugated) bilirubin > 3 x ULN, obtain the following laboratories: ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, GGT, CK as soon as possible (ie, within 3 days).

If the repeat tests indicate:

1) ALT/AST < 10 x ULN and conjugated bilirubin ≤ 3 x ULN, study medication may continue.
2) If the repeat ALT/AST ≥ 10 x ULN AND/OR the conjugated bilirubin is > 3 x ULN, the study medication must be discontinued.

The study medication must be discontinued if:

Clinical jaundice is present for a subject at any time

OR

If ALT/AST ≥ 10 x ULN on any two consecutive occasions

OR

Conjugated bilirubin > 3 x ULN on any two consecutive occasions.

All subjects with an ALT/AST ≥ 10 x ULN or direct bilirubin > 3 x ULN will be followed weekly until ALT/AST returns to < 3 x ULN or to baseline, and the conjugated bilirubin returns to ≤ 1.5 x ULN or to baseline.

If study medication is discontinued due to elevated ALT OR BILIRUBIN, as defined above, inform the medical Monitor and Study Director and perform the following:

- PT, aPTT, fibrinogen to assess liver synthetic function
- Abdominal ultrasound, including liver and hepatobiliary system
- Hepatitis screen (anti-HAV, HBsAg, anti-HBc, anti-HBs and anti-HCV.
- Obtain relevant specialist consultation.

## 6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

# 7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

## 7.1 Steering Committee

An academic Steering Committee, participated in the development of the protocol, will provide ongoing scientific and operational oversight to the study. The Steering Committee will monitor all aspects of the study, make recommendations to the sponsor based on the DMC recommendations, and oversee the presentation of the trial results and any publications.

## 7.2 Event Adjudication Committee

The Event Adjudication Committee (EAC), as described in the EAC charter, is an independent committee constituted by experienced clinicians independent of the Investigators and the Sponsor. The responsibilities of the EAC are to validate all study endpoints that are central to the accuracy of results and conclusions of the trial. Specifically, the EAC will classify endpoints according to documentation provided by Investigators. Adjudicated results will be the basis for the final primary analyses.

## 7.3 Data Monitoring Committee

This study will be conducted under the monitoring of an independent Data Monitoring Committee (DMC), whose activities will be described in a DMC charter. Stopping rules for this study will be developed a priori in collaboration with the DMC. In addition, the DMC will use their clinical and statistical judgment to recommend that the study proceed or be terminated early. This committee is constituted to oversee this apixaban pediatric study.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Sample Size Determination

With a total of approximately 500 randomized subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban or no systemic anticoagulant prophylaxis (control) group, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates of primary endpoint (composite of non-fatal asymptomatic and symptomatic DVT, pulmonary embolism (PE), and CVST; and VTE-related-death) are 17% and 8.5% in the control and the apixaban groups, respectively. Sample size estimation is based on Pearson's chi-square test.

Additionally, there is more than 80% power to demonstrate superiority at a one-sided 0.025 level, assuming the true event rates are 20% and 10% in the control and the apixaban groups, respectively with analyses that assume that 20% of the subjects will be excluded from the primary analysis due to either early dropout without end-of-treatment imaging evaluation or non-evaluable end-of-treatment imaging measurement in the calculation.

Randomization will be stratified by age groups as < 10 years or ≥ 10 to < 18 years, to reflect the major peaks of disease prevalence and risk stratification criteria for acute lymphoblastic leukemia (ALL) in children.[40, 69, 70]

## 8.2 Populations for Analyses

- The Randomized/Intent-To-Treat (ITT) population consists of all subjects who were randomized to a treatment, regardless of whether they received study drug or not. Except as noted otherwise, Randomized/ITT Population will be used for the evaluation of efficacy.
- The Modified Intent-To-Treat (mITT) population includes randomized subjects who have either an adjudicated event making up the primary efficacy endpoint or evaluable end of study imaging evaluations, including ultrasound and echocardiogram.
- The Evaluable population will include the Randomized/ITT population except those subjects with relevant protocol deviations expected to affect the primary efficacy endpoint.
- The safety population includes all randomized subjects since there is no intervention on top of standard care in the control arm and will be used for the evaluation of safety.
- The analysis population for pharmacokinetic assessments will include subjects who have received at least one dose of apixaban and have a pharmacokinetic sample collected.
- The analysis population for anti-FXa assessments will include subjects who have received at least one dose of apixaban and have anti-FXa samples collected.

## 8.3 Endpoints

### *8.3.1 Primary Endpoint(s)*

**Efficacy:**

The primary efficacy endpoint is a composite of adjudicated non-fatal DVT (including asymptomatic and symptomatic), PE, and CVST and VTE-related-death objectively confirmed by independent adjudication. All components of the primary efficacy endpoint will be adjudicated by a blinded, independent adjudication committee.

**Safety:**

The primary safety endpoint will be adjudicated major bleeding which is defined as bleeding satisfies one or more of the following criteria: (i) fatal bleeding; (ii) clinically overt bleeding associated with a decrease in hemoglobin of at least 20g/L (ie, 2g/dL) in a 24-hour period; (iii) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS; and/or (iv) bleeding that requires surgical intervention in an operating suite, including interventional radiology. Of note, the major bleeding will not be considered as part of the primary endpoint for the purpose of the European application, but will be assessed as part of the safety profile of apixaban.

Prophylactic transfusions without overt bleeding and without a decrease in hemoglobin of at least 20 g/l (ie, 2 g/dl) in a 24-hour period are not considered bleeding events.

All bleeding events will be adjudicated by a blinded, independent adjudication committee as major bleeding, CRNM bleeding, or minor bleeding. These endpoints are consistent with those recommended by the International Society on Thrombosis and Haemostasis for pediatric clinical trials in venous thromboembolism.[71]

### *8.3.2 Secondary Endpoint(s)*

**Efficacy**:

a) Non-fatal asymptomatic DVT
b) Non-fatal symptomatic DVT
c) Non-fatal PE
d) CVST
e) VTE-related-death

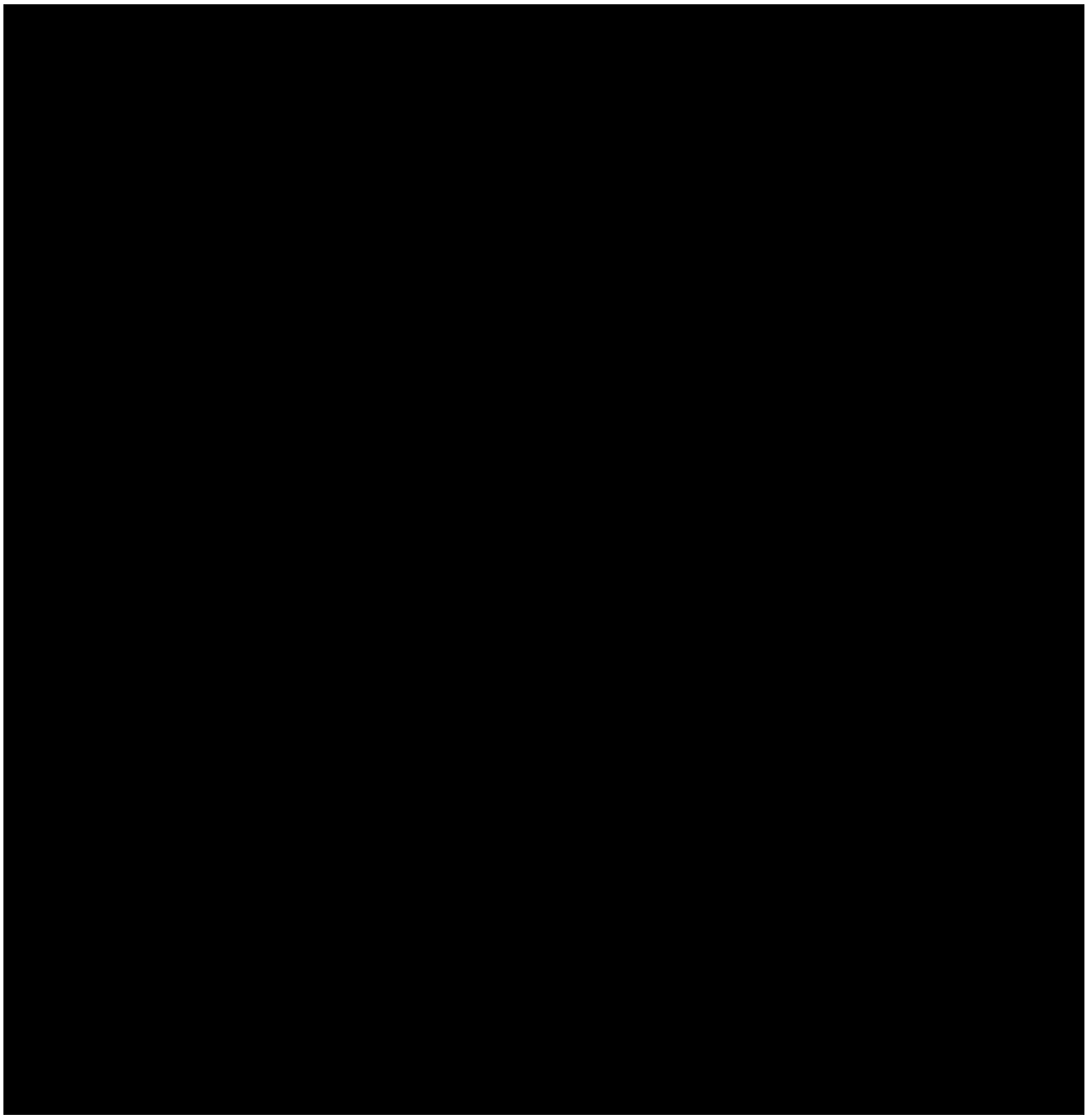
**Safety**

a) Composite of major and CRNM bleeding (CRNMB). CRNM bleeding is defined as bleeding that satisfies one or both of the following:
   i) overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition and
   ii) bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room

**Pharmacokinetics and Anti-FXa Activity**

a) Apixaban pharmacokinetics using a population pharmacokinetic (PPK) approach
b) Anti-FXa activity

[redacted]



## 8.4 Analyses

### *8.4.1 Demographics and Baseline Characteristics*

Frequency distribution and summary statistics for demographic and baseline variables will be presented by treatment group and for all subjects combined. Key demographic and baseline variables to be summarized include: geographic region, age, gender, race, height, weight, body mass index, vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) and medical history.

### 8.4.2 Efficacy Analyses

For the primary efficacy endpoint, statistics including event rate, 95% CI for event rate, relative risk, 95% CI for relative risk and p-value will be displayed. For other endpoints, descriptive statistics including single event rate, 95% CI for single event rate, relative risk and 95% CI for relative risk will be displayed.

To construct p-values, the Cochran-Mantel-Haenszel test stratified by age groups of < 10 years and ≥ 10 years old will be used at the one-sided $\alpha = 0.025$ level.

To construct descriptive statistics:

- The 95% CI for the relative risk will be computed based on Cochran-Mantel-Haenszel method stratified by age group.
- Construction of CIs for single event rates will be based on the Agresti-Coull's method

The above analyses on all the efficacy endpoints will be based on the Randomized/ITT population.

Following additional sensitivity analyses will also be performed for the primary endpoint.

- An analysis will be performed using the mITT Population.
- An analysis will be performed for all randomized subjects with missing primary endpoint or non-evaluable imaging data to be assessed via multiple imputation using 1000 repetitions, with imputation of events for patients with missing data in both treatment groups based on the event rate observed from the corresponding stratum in the standard-of-care arm
- If results from the primary efficacy analysis show a significant difference between treatment groups, then a "tipping point" analysis will be performed with a non-stratified analysis. In each analysis, subjects with missing data in the standard-of-care arm will be assumed to be event-free, while progressively more subjects with missing data in the apixaban arm will be assigned with an event, up to the limit of the number of subjects with missing data in the apixaban arm. The number of subjects in the apixaban arm imputed with event that would change the result from significant to non-significant would be noted.
- An analysis will be performed based on the Evaluable Population, if at least 10% of subjects have a relevant protocol deviation.

### 8.4.3 Safety Analyses

For the primary safety endpoint, statistics including event rate, 95% CI for event rate, relative risk, 95% CI for relative risk and nominal p-value will be displayed. To construct nominal p-values and 95% CI for relative risk, the Cochran-Mantel-Haenszel test stratified by age groups of < 10 years and ≥ 10 years old will be used at the one-sided $\alpha = 0.025$ level. Construction of CIs for event rates will be based on the Agresti Coull method.

### *8.4.4 Pharmacokinetic and Pharmacodynamic Analyses*

**Pharmacokinetic Measures:**

Samples collected as described in Section 5.5 will be analyzed by LC-MSMS to determine apixaban plasma concentration. Individual data will be listed. Interim analyses of PK will be performed to better understand apixaban PK and to inform apixaban dose selection.

A PPK model will be developed using plasma concentration versus time data. Model-derived population and individual PK parameters (eg, CL/F, Vc/F, KA) will be used to estimate Cmax, Cmin, and AUC(TAU) in each subject. Modeling results will be reported separately.

**Anti-FXa Activity:**

Samples collected as described in Section 5.5 will be analyzed by a one-step chromogenic anti-FXa assay. Individual data will be listed. [redacted]

A PPK-PD model will be developed using both apixaban plasma concentration and measured anti-FXa activity versus time data. Model-derived population and individual parameters (eg, slope of anti-FXa activity vs apixaban concentration relationship) will be used to estimate maximum and minimum anti-FXa activity in each subject. Modeling results will be reported separately.

[redacted]

# 9 STUDY MANAGEMENT

## 9.1 Compliance

### *9.1.1 Compliance with the Protocol and Protocol Revisions*

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion

- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS. If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment. If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

### *9.1.2 Monitoring*

Representatives of BMS must be allowed access to all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential. The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

#### *9.1.2.1 Source Documentation*

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

### *9.1.3 Investigational Site Training*

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of FRP.

## 9.2 Records

### *9.2.1 Records Retention*

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study. BMS will notify the investigator when the study records are no longer needed. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

### *9.2.2 Study Drug Records*

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### *9.2.3 Case Report Forms*

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study. For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and

Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs. The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections. Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

## 9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- Study Steering Committee chair or their designee
- Involvement in trial design
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

# 10 GLOSSARY OF TERMS

| Term | Definition |
|---|---|
| Adverse Reaction | An adverse event that is considered by either the investigator or BMS as related to the investigational product |
| Unexpected Adverse Reaction | An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for unapproved investigational product) |
| Serious Adverse Event | Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject 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), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events. |

## 11 LIST OF ABBREVIATIONS

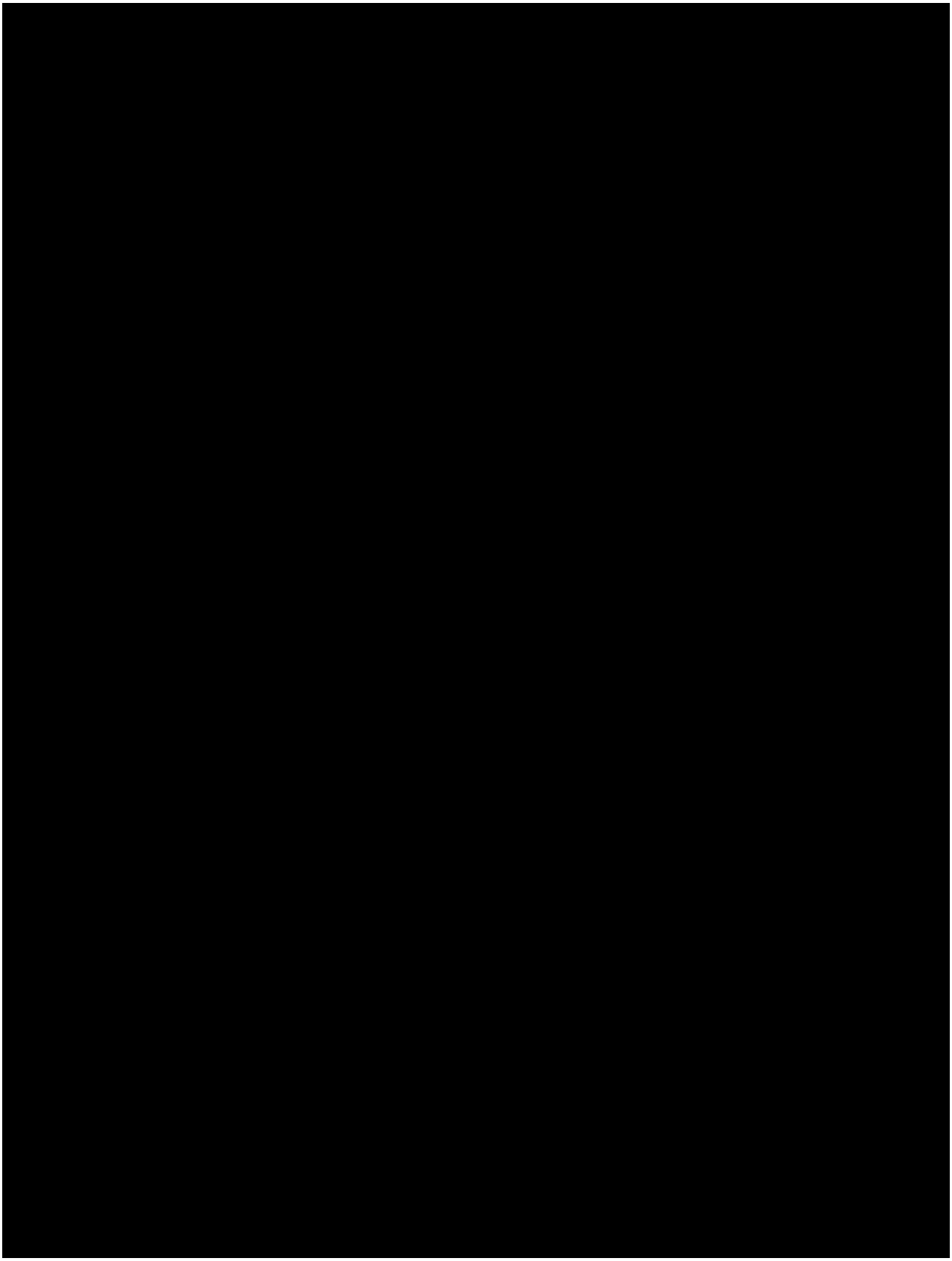
| Term | Definition |
|---|---|
| AE | adverse event |
| [redacted] | |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| [redacted] | |
| AUC(TAU) | area under the concentration-time curve in one dosing interval |
| [redacted] | |
| BID, bid | bis in die, twice daily |
| [redacted] | |
| BMI | body mass index |
| BMS | Bristol-Myers Squibb |
| BP | blood pressure |
| [redacted] | |
| CBC | complete blood count |
| [redacted] | |
| CI | confidence interval |
| [redacted] | |

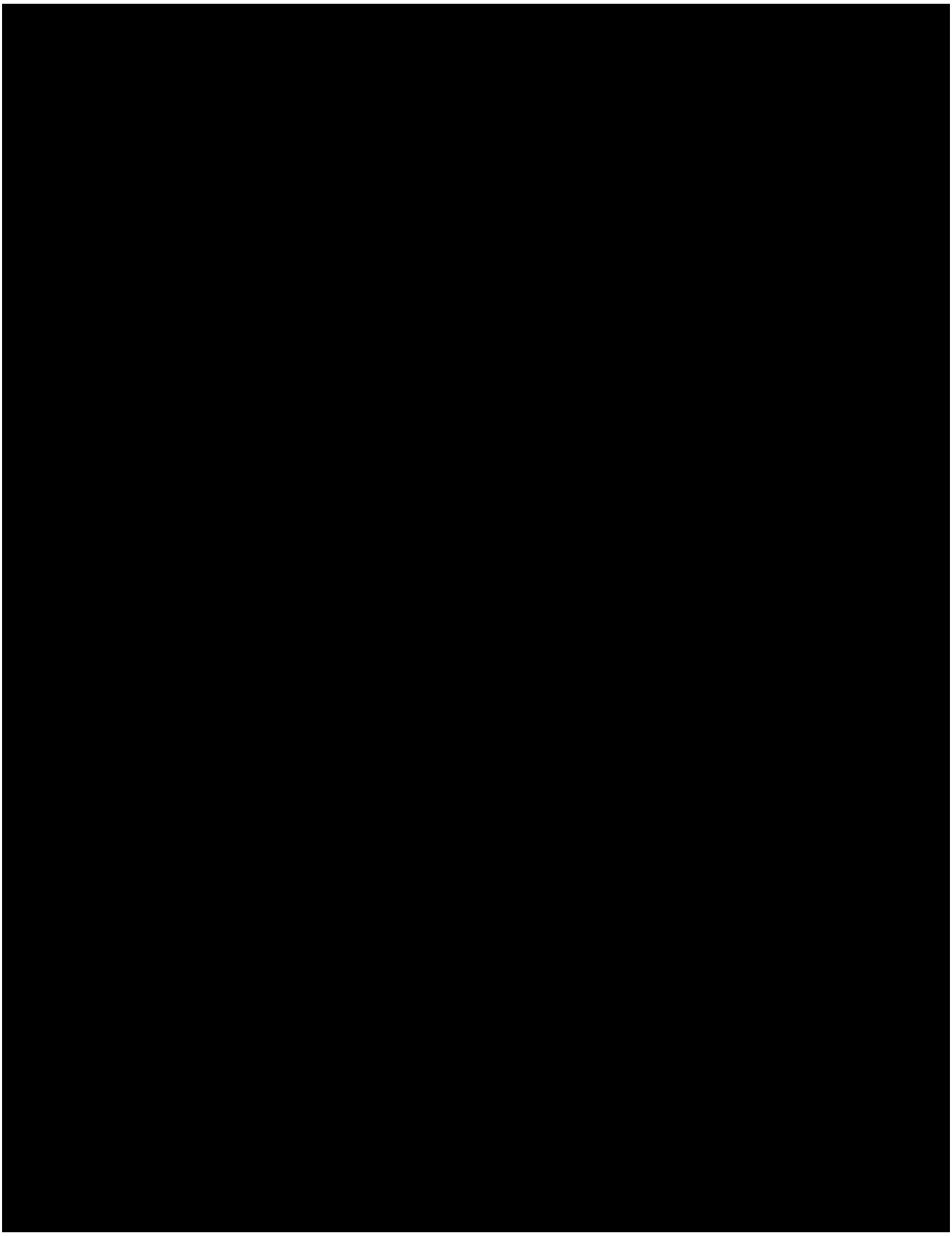
| Term | Definition |
|---|---|
| [redacted] | |
| Cm | centimeter |
| Cmax, CMAX | maximum observed concentration |
| Cmin, CMIN | trough observed concentration |
| CNS | Central nervous system |
| [redacted] | |
| CRF | Case Report Form, paper or electronic |
| CRNM | Clinically Relevant Non-Major |
| CSF | Cerebral spinal fluid |
| CVAD | Central Venous Access Device |
| CYP | cytochrome p-450 |
| [redacted] | |
| dL | deciliter |
| [redacted] | |
| ECG | electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| [redacted] | |
| Eg | exempli gratia (for example) |
| [redacted] | |
| FRP | Females of Reproductive Potential |
| FSH | follicle stimulating hormone |
| [redacted] | |
| G | gram |

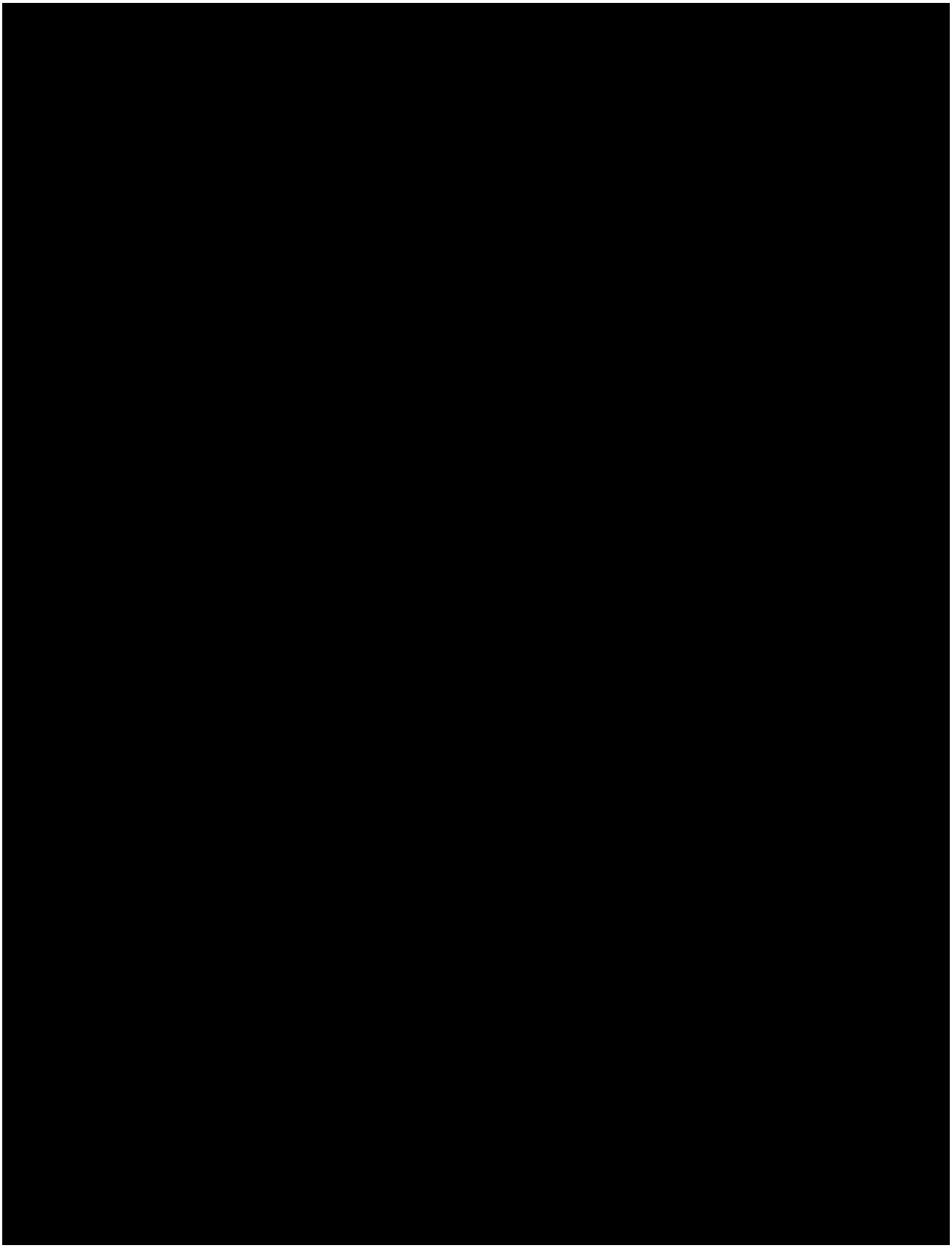
| Term | Definition |
|---|---|
| [redacted] | |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GFR | glomerular filtration rate |
| H | hour |
| HBsAg | hepatitis B surface antigen |
| [redacted] | |
| HCV | hepatitis C virus |
| [redacted] | |
| HRT | hormone replacement therapy |
| [redacted] | |
| ICH | International Conference on Harmonisation |
| Ie | id est (that is) |
| IEC | Independent Ethics Committee |
| IMP | investigational medicinal products |
| IND | Investigational New Drug Exemption |
| IRB | Institutional Review Board |
| [redacted] | |
| IU | International Unit |
| IV | intravenous |
| [redacted] | |
| Kg | kilogram |
| L | liter |
| LC | liquid chromatography |
| [redacted] | |

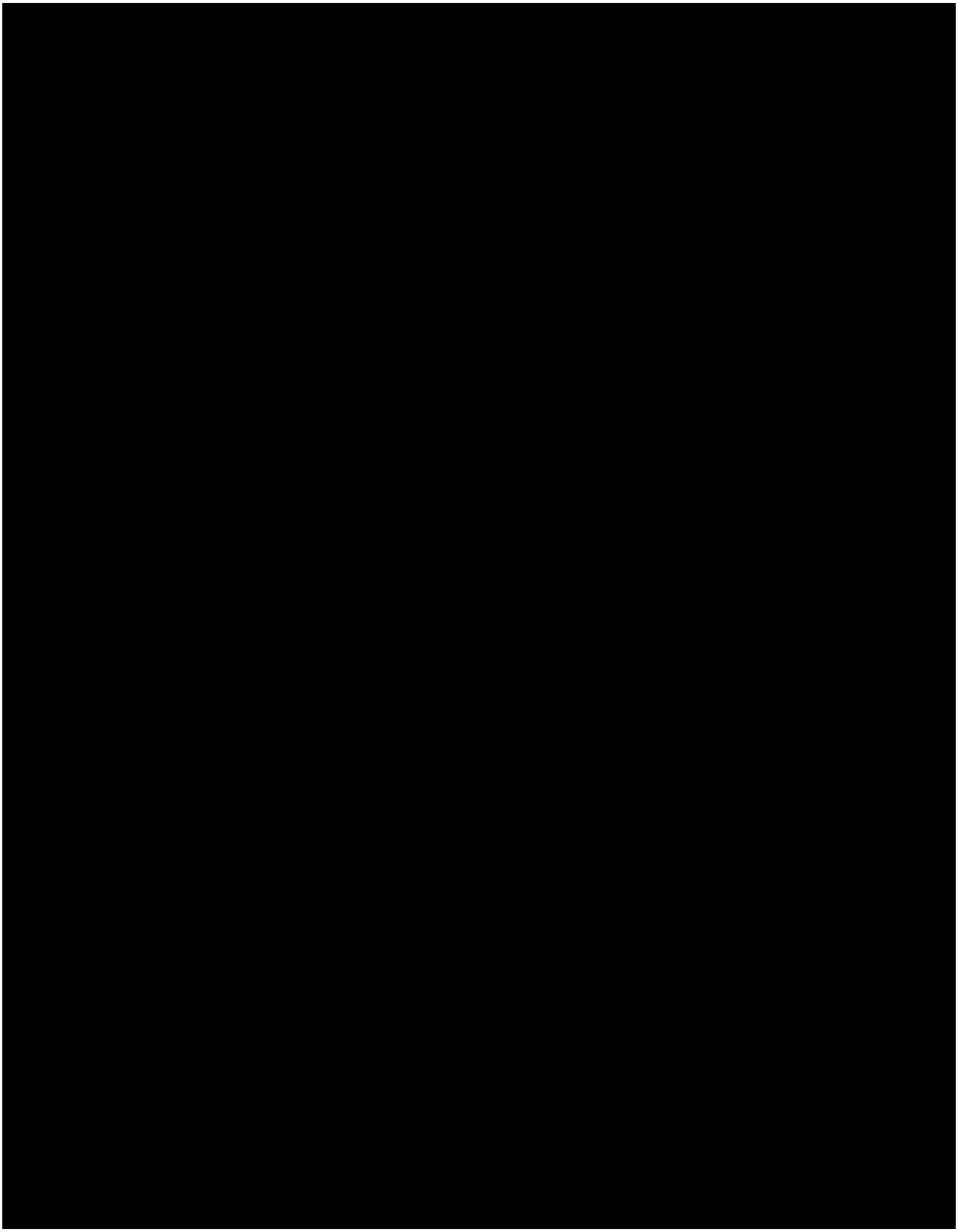
| Term | Definition |
|---|---|
| LP | Lumbar puncture |
| Mg | milligram |
| [redacted] | |
| Min | minute |
| mL | milliliter |
| [redacted] | |
| NIMP | non-investigational medicinal products |
| NSAID | nonsteroidal anti-inflammatory drug |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PO | per os (by mouth route of administration) |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| [redacted] | |
| RBC | red blood cell |
| SAE | serious adverse event |
| SD | standard deviation |
| [redacted] | |

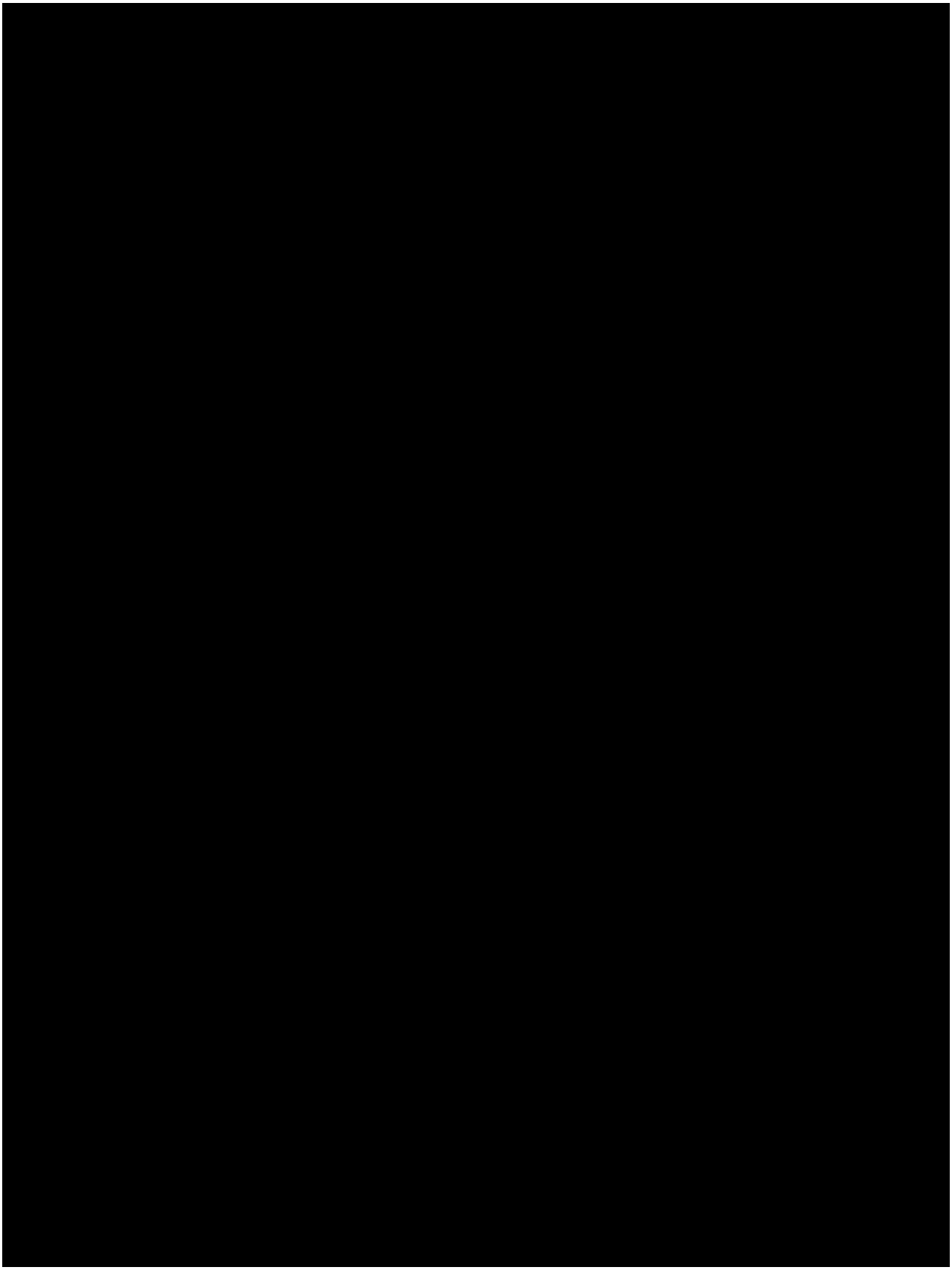
| Term | Definition |
|---|---|
| [redacted] | |
| WBC | white blood cell |
| [redacted] | |











# APPENDIX 1 ULTRASOUND PROCEDURE

## 1 ULTRASOUND IMAGING PROTOCOL

### 1.1 General Imaging Concepts and Principles

*Test protocols should be followed as closely as possible, but the examination should be representative of what is feasible in clinical practice. It is understood that the sequence of image acquisition and ability to obtain all suggested images will vary, depending on patient related factors such as age, clinical condition, ability to cooperate, etc. The extremity sonogram can be paired with other SOC procedures, such as lumbar puncture, as long as no additional sedation is required beyond what is used for the SOC procedure.*

*The Radiology Core Lab (RCL) will determine whether or not an exam is adequate for purposes of study inclusion.*

- For all sites, the first patient recruited will receive a rapid turnaround feedback on the technique quality of its Ultrasound.
- If a chest radiograph was obtained, the most recent film, prior to performance of the ultrasound, should be submitted along with the ultrasound examination
- Sedation or anesthesia should not be used for research purposes only.
- A thrombus will be defined as a space occupying lesion seen within a vessel or associated with a Central Venous Access Device (CVAD). It may be hyper- or hypo- intense. It may be mobile or adherent to a vascular or cardiac structure. It may be occlusive (if no blood flow is seen on Doppler imaging in that segment of the vessel) or non-occlusive. The absence of color flow Doppler will typically profile the thrombus. Thrombus will be differentiated from a "fibrin sheath/line cast" which is a more linear structure, often mimicking the appearance of a CVAD, is not mobile, and is the known location of a prior CVAD.
- If the patient has a suspected thromboembolic event and the patient is not cooperating with the radiological interventions, sedation is recommended as per the institutional guidelines.
- The majority of the vascular sonogram should be performed using the highest frequency linear transducer possible, usually 7 - 15 MHz. However, the brachiocephalic veins and superior vena cava should be assessed via the suprasternal notch, using a microcase (small footprint)/vector transducer (generally 3 - 10 MHz).
- A bilateral examination should be performed, even if the subject is asymptomatic. When no clot is seen in association with the PICC/CVL, sonography of the opposite/contralateral (non-PICC/CVL) side can be less extensive. To clarify, the side with the PICC/CVL (ipsilateral) side should be assessed using the full protocol, to the extent that is possible. If no clot is seen on the ipsilateral side, the contralateral side may be evaluated in a targeted manner as follows:
  For lower extremities: common femoral vein: long greyscale and long waveform views only.

  For upper extremities: subclavian vein: long greyscale and long waveform views only.

  However, if the site thinks there is a clot on the PICC/CVL (ipsilateral) side, a full examination on the contralateral side will be performed, following the full protocol, to the extent that this is possible.

- Label all venous images with laterality (RT/LT), the vein name (with abbreviation as listed below), and segment of the vein interrogated where appropriate (central, mid, peripheral), in that order.
- Real-time Grey scale imaging with transducer compression of the vein should always be used in areas where the vein is accessible to compression
  - Compression technique: The transducer is pressed gradually down to fully compress the vein. Arteries resist compression and are visibly pulsatile. In some areas, overlying strictures (bones, ligaments) may hamper full compression. Compression should be applied with the transducer at 1 cm intervals over the entire length of the vessel.
- Color Doppler imaging improves vessel conspicuity and may help to better definition of the thrombus. However, it is important to remember that improper selection of color Doppler parameters can obscure thrombi, particularly non occlusive thrombi.
  - Pulsed-Doppler waveforms are used to document cardiac phasicity, respiratory, and compression-induced flow changes.
  - Techniques to elicit changes in venous waveforms are termed augmentation maneuvers and include the Valsalva maneuver, sniffing, deep breathing, and ipsilateral venous compression by the linear transducer. Normal cardiac phasicity, respiratory variation and augmentation by direct venous compression are all markers of venous patency. Observation of asymmetry between right and left side waveforms implies the presence of a venous clot. However, observation of normal, symmetrical venous Doppler waveforms does not exclude the possibility of a non-occlusive thrombus.

## 1.2 Imaging Protocol: Upper Extremity Central Venous Access Device (CVAD) or Peripherally Inserted Central Venous Cather (PICC)

- Most recent chest radiograph following line placement should be reviewed before ultrasound to determine the course of the CVAD or PICC and the location of the tip.

During the ultrasound exam, the course of the catheter should be demonstrated in all involved vessels. Attempt should be made to visualize the tip of the catheter if it is located in the SVC or brachiocephalic, not if it is in the right atrium.

Use the “Upper Extremity Worksheet” as a study protocol guide.

The following veins should be scanned on both sides**: Internal Jugular (IJ), Subclavian (SCV), Brachiocephalic (innominate) veins (BC), Superior Vena cava (SVC), Axillary (Ax), Brachial (Brach), Basilic (Bas), and Cephalic veins (Ceph).**

- **Internal Jugular vein**
  - Use high frequency linear transducer.
  - Internal Jugular vein should be followed from the base of the skull to the junction with the subclavian/brachiocephalic veins.
  - Evaluate internal jugular vein using Grey scale imaging in the transverse plane, following its course from superior (distal) to inferior (proximal) compressing every 1 cm. Take representative images with and without compression at the superior, mid and inferior aspect of the vein.
  - Evaluate internal jugular vein using Grey scale imaging in the transverse plane, following its course from superior (distal) to inferior (proximal) compressing every 1 cm. Using dual

screen, Take representative images without compression (left screen) and with compression (right screen) at the superior, mid and inferior aspect of the vein. Using the caliper/measuring tool, mark the margins of the non-compressed vein on the left image.
- Using dual screen, in the transverse plane, document grey scale (left screen) and color Doppler (right screen) views, without compression.
- Obtain a longitudinal image of the internal jugular vein, with Grey scale imaging, assessing for intraluminal thrombus.
- Obtain a longitudinal image of the internal jugular vein with color Doppler imaging, showing that the vessel fills uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
- Obtain pulsed Doppler wave form in the IJ vein the longitudinal plane, showing normal direction and phasicity/respiratory variation.

- **Subclavian vein**
  - Use high frequency linear transducer.
  - Evaluate the subclavian vein from lateral (peripheral) to medial (central) – from the junction with the axillary vein, to the junction with the internal jugular /brachiocephalic vein.
  - Evaluate entire subclavian vein in longitudinal plane using Grey scale imaging, evaluating for intraluminal thrombus, and take images that show the entire course of the vein.
  - Obtain color Doppler images of the subclavian vein in the longitudinal plane, showing that the vessel fills uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
  - Obtain pulse Doppler waveforms of both the subclavian vein and the adjacent subclavian artery to show the normal relationship between the two vessels and distinguish the subclavian vein from venous collaterals that can form in setting of longstanding occlusion. Perform augmentation maneuvers (squeezing arm), to demonstrate appropriate response in the subclavian vein.
- **Brachiocephalic/SVC**
  - From the suprasternal notch, use vector transducer/microcase if linear transducer does not allow visualization.
  - Obtain Grey scale coronal image showing the confluence of the subclavian and internal jugular veins into the brachiocephalic, evaluating for intraluminal thrombus. If possible obtain another Grey scale image angled down to see the more central portion of the brachiocephalic vein and SVC.
  - Obtain Color Doppler coronal image showing the confluence of the subclavian and internal jugular veins into the brachiocephalic. If possible obtain another Color Doppler image angled down to see the more central portion of the brachiocephalic vein and SVC. The goal is to show that the vessels fill in uniformly, excluding filling defect of thrombus.
  - If possible, obtain Pulse Doppler waveforms within the vessels showing normal direction and phasicity/respiratory variation (quiet breathing).
  - If possible, obtain Pulse Doppler waveforms within the vessels showing changes with augmentation maneuvers (Valsalva, sniffing, deep breathing).

## 1.3 Imaging protocol: upper extremity Peripherally Inserted Central Catheters (PICC)

Most recent chest radiograph following line placement should be reviewed before ultrasound to determine the course of the PICC and the location of the tip.

During the ultrasound exam, the course of the catheter should be demonstrated in all involved vessels, and the tip shown by US if it is proximal enough to be included in the protocol (not if the tip is in the right atrium).

In addition to the veins scanned for CVAD (see Section 1.2), the following veins should be scanned on both sides: **Axillary, Brachial, Basilic, and Cephalic veins**

- **Axillary Vein**
  - With linear transducer, image centrally (from junction with subclavian vein at level of first rib) to peripherally, where it ends at confluence of brachial and basilic.
  - Arm should be raised in the "pledge" position, with 90 degrees of abduction.
  - Evaluate axillary vein using Grey scale imaging in the transverse plane, following its entire course and compressing every 1 cm. Using dual screen, take representative images without compression (left screen) and with compression (right screen) at the distal, mid and proximal aspect of the vein. Using the caliper/measuring tool, mark the margins of the non-compressed vein on the left image.
  - Obtain longitudinal images of the axillary vein, with Grey scale imaging, assessing for intraluminal thrombus.
  - Obtain longitudinal images of the axillary vein with color Doppler imaging, showing that the vessel fills uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
  - Obtain pulsed Doppler wave form in the axillary in the longitudinal plane, showing normal direction and phasicity with augmentation (squeezing of the arm).
- **Brachial veins**
  - With linear transducer, image both of the paired veins on each side of the brachial artery, superiorly from the axillary vein, to just above the antecubital fossa.
  - Arm should remain abducted 90 degrees at the shoulder.
  - Evaluate brachial veins using Grey scale imaging in the transverse plane, following their entire course and compressing every 1 cm. Using dual screen, take representative images without compression (left screen) and with compression (right screen) at the distal, mid and proximal aspect of the vein. Using the caliper/measuring tool, mark the margins of the non-compressed vein on the left image.
  - Obtain longitudinal images of the brachial veins, with Grey scale imaging, assessing for intraluminal thrombus.
  - Obtain longitudinal images of the brachial veins with color Doppler imaging, showing that the vessel fills uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
  - Obtain pulsed Doppler wave form in the brachial veins in the longitudinal plane, showing normal direction and phasicity with augmentation (squeezing of the arm).
- **Cephalic Vein**
  - Lower arm back to neutral position to image the cephalic vein
  - With linear transducer, begin at the distal/central portion of the vein, where it ends in the subclavian, trace it to the antecubital fossa.

- Evaluate cephalic vein using Grey scale imaging in the transverse plane, following its entire course and compressing every 1 cm. Using dual screen, take representative images without compression (left screen) and with compression (right screen) at the distal, mid and proximal aspect of the vein. Using the caliper/measuring tool, mark the margins of the non-compressed vein on the left image.
- Obtain longitudinal images of the cephalic vein, with Grey scale imaging, assessing for intraluminal thrombus.
- Obtain longitudinal images of the cephalic vein with color Doppler imaging, showing that the vessel fills uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
- Obtain pulsed Doppler wave form in the cephalic vein in the longitudinal plane, showing normal direction and phasicity with augmentation (squeezing of the arm).

## 1.4 Imaging Protocol: Lower Extremity CVAD/(PICC)

Most recent abdominal radiograph following line placement should be reviewed before ultrasound to determine the course of the catheter and the location of the tip.

During the ultrasound exam, the course of the catheter should be demonstrated in all involved vessels, and the tip shown by US, bearing in mind this may not be possible depending on the location of the tip and habitus of the patient.

Use the "Lower Extremity Worksheet" as a study protocol guide.
The following veins should be scanned on both sides: **Inferior Vena Cava (IVC), common iliac (CIV), external iliac (EIV), common femoral (CVF), superficial femoral (SFV), popliteal veins (pop).**

- **Common femoral, femoral, popliteal veins**
  - Begin superiorly at the inguinal fossa with the common femoral vein, and trace the course of the common femoral, femoral, and popliteal veins inferiorly, to the popliteal fossa. Use high frequency linear transducer when possible. The deeper segments of the femoral vein may require use of the vector transducer in some patients.
  - Evaluate veins using Grey scale imaging in the transverse plane, following their entire course and compressing every 1 cm. Using dual screen, take representative images without compression (left screen) and with compression (right screen) at the superior, mid and inferior aspect of the vein. Using the caliper/measuring tool, mark the margins of the non-compressed vein on the left image.
  - Obtain longitudinal images of the veins, with Grey scale imaging, assessing for intraluminal thrombus.
  - Obtain longitudinal images of the veins with color Doppler imaging, showing that the vessels fill uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
  - Obtain pulsed Doppler wave form in the veins n in the longitudinal plane, showing normal direction and phasicity with augmentation (squeezing of the leg).
- **External iliac, common iliac, IVC**
  - Begin inferiorly at the external iliac vein where it meets the common femoral vein, and trace the course of the external iliac vein, common iliac vein, and IVC superiorly into the abdomen. Use high frequency linear transducer where possible, however lower frequency vector or curved transducer may be necessary.

- Grey scale images of the vessels in transverse plane (compress if possible)
- Grey scale images in longitudinal plane, assessing for intraluminal thrombus.
- Color Doppler images in longitudinal plane, showing that the vessels fill in uniformly, and excluding filling defect of fresh, hypoechoic thrombus.
- Pulse Doppler waveforms showing normal direction and phasicity/respiratory variation.
- The tip of the catheter may be in the abdominal or intrahepatic IVC.

For all exams, the catheters should be imaged and labeled on longitudinal grey scale images of relevant vessels. If the tip is demonstrated, cine clip demonstrating the tip should be obtained.

Study is positive for deep venous thrombosis if there is a filling defect within any of the assessed vessels. It may be echogenic or hypoechoic (visible by absence of color flow Doppler), central or peripheral, depending on the chronicity of the thrombus. It may be occlusive (if no blood flow is seen on Doppler imaging in that segment of the vessel) or non-occlusive

If intraluminal thrombus is seen within a vessel, a clip demonstrating the thrombus should be obtained, longitudinal to the vessel. The length of the thrombus should also be measured in the longitudinal plane. The anterior to posterior (AP) and transverse (TV) dimensions should be measured in the transverse plane.

If a prominent valve is encountered which could be mistaken for thrombus, a cine clip should be obtained demonstrating its motion.

If there is venous stasis with rouleaux formation, causing increased echogenicity of the blood, a cine clip should be obtained showing motion in the vessel, and demonstrating that it is not a thrombus.

**The thrombus will be categorized to:**

- Occlusive thrombus: intraluminal filling defect is seen (thrombus), and color Doppler images do not demonstrate blood flow past this defect
- Non-occlusive thrombus: intraluminal filling defect is seen (thrombus), however color Doppler images demonstrate blood flow past this defect
- No thrombus: no intraluminal filling defect identified in the vessel

**Presence of collateral vessels**

Collateral vessels are present if there are unnamed smaller caliber circuitous veins adjacent to the vessel in question.

**Report to accompany ultrasound images:**

For each protocol ultrasound, the Center will send the local radiology report, will complete a worksheet that will detail compliance with the imaging protocol and complete a data form detailing interpretation and findings.

# APPENDIX 2 ECHOCARDIOGRAM PROCEDURE

## 1 ECHOCARDIOGRAPHIC IMAGING PROTOCOL

### 1.1 Patient and Room Preparation

- ECG leads should be placed on every patient
- Optimize imaging conditions (darken the room, position ECG leads and other monitoring devices away from imaging positions, check to see that machine is sensing the ECG)
- If chest x-ray was used to guide the placement of the catheter it should be submitted with the Echocardiogram

### 1.2 General Imaging Concepts and Principles

- *Test protocols should be followed as closely as possible. The Echocardiography Core Laboratory (ECL) will determine whether or not an exam is adequate for purposes of study inclusion.*
- For all sites, the first patient recruited will receive a rapid turnaround feedback on the technique quality of its Echocardiogram.
- Sedation or anesthesia should not be used for research purposes only.
- A thrombus will be defined as a space occupying lesion seen within a vessel or associated with a CVAD. It may be hyper- or hypo-intense. It may be mobile or adherent to a vascular or cardiac structure. It may be occlusive (if no blood flow is seen on Doppler imaging in that segment of the vessel) or non-occlusive. The absence of color flow Doppler will typically profile the thrombus. Thrombus will be differentiated from a "fibrin sheath/line cast" which is a more linear structure, often mimicking the appearance of a CVAD, is not mobile, and is the known location of a prior CVAD.
- If the patient has a suspected thromboembolic event and the patient is not cooperating with the radiological interventions, sedation is recommended as per the institutional guidelines.
- For each new acoustic window, there should be a complete sweep of the relevant anatomy by 2D imaging
- After complete sweeps are recorded, specific areas of interest can be targeted for further evaluation using the zoom feature, in 2D, color Doppler (CD), pulsed wave (PW) Doppler, continuous wave (CW) Doppler, and/or color compare (CC) Doppler as described below. Do not over zoom.
- Color Imaging
  - The width and depth of the color sector should be adjusted to include only the relevant anatomy. Avoid using color sector boxes that fill up the entire 2D screen.
  - Use the highest Nyquist limit that provides color flow signal within the structure of interest
  - Avoid "color bleeding" by adjusting the color gain when lowering the Nyquist limit
  - Maintain the highest possible frame rate possible, no less than 20 frames per second
- Spectral Doppler (PW and CW)
  - Minimize the angle between the ultrasound beam and the direction of flow by adjusting transducer position (can disregard standard views). Use the audio feature to assist with optimizing the alignment with the flow jet to obtain the highest velocity with the minimal spectral dispersion

  - Adjust the gain, compress, and reject controls to depict a complete spectral "envelope" while optimizing signal-to-noise ratio
  - Adjust baseline and scale so the spectral "envelope" is (a) non-aliased, and (b) occupies ~ 75% of the velocity range
  - Use PW Doppler before CW Doppler
  - Start recording the Doppler tracing only after a full screen of Doppler data is on the screen. Record between 4 and 8 cardiac cycles.
- Clips should be limited to no more than 10 seconds
- Optimize the image BEFORE recording:
  - Locate the best acoustic window for each view
  - Adjust the depth and width of the sector to include only relevant image data
  - Adjust imaging parameters (transmit gain, horizontal and lateral receive gains, compress, frequency range, harmonic imaging, etc.) to obtain optimal image quality (strong signal from cardiovascular structures and minimal [but not absent] signal from the blood pool)
  - Maintain the focal zone at the level of the relevant anatomy
  - Imaging should be performed with the highest transducer frequency as possible, but trial use of lower frequency transducers if it improves image quality.
  - Depending on which probe is being used, trial images with and without harmonics
  - Particular attention should be paid to maintaining a frame rate over 20 Hz or frames per second during all acquisitions
- The order of the examination can be modified to accommodate patient- and diagnosis-specific circumstances. In addition to the above standard acoustic windows and imaging planes, the operator should exercise flexibility in transducer position and image orientation in order to obtain the best possible images and full delineation of the relevant anatomy and physiology.
- Example echocardiographic move clips and image stills demonstrating acoustic windows, sweeps, and quality of imaging of each of the views will be posted on an online website.

## 1.3 Anatomic Structures of Interest and Abbreviations

- Left innominate vein (LIV)
- Right superior vena (RSVC)
- Inferior vena cava (IVC)
- Right atrium (RA)
- Atrial septum
- Tricuspid valve (TV)
- Right ventricle (RV)
- Pulmonary valve (PV)
- Main pulmonary artery (MPA)
- Left ventricle (LV)
- Aortic valve (AoV)

## 1.4 Imaging Protocol: Vital Signs. Record the following on the first image:

- Height in cm

- Weight in kg
- Systolic, diastolic, and mean blood pressure

## 1.5 Imaging Protocol Subcostal Windows (Move the Patient onto Their Back)

Full short-axis subcostal sweep through the entire heart (2D)

- The index mark is at ~ 3:00
- The sweep begins at a level showing the IVC and the aorta in cross-section below the diaphragm and progresses anteriorly-superiorly until the anterior wall of the right ventricular outflow tract is no longer visible, then sweep back to the cross-section of the upper abdomen.

Full long-axis subcostal sweep through the entire heart (2D)

- The index mark is at ~ 6:00
- Start position is the bi-caval view showing the IVC and SVC entering the right atrium. First sweep rightward to identify the right upper pulmonary vein, then sweep leftward through the ventricular apex, then back to the bi-caval view.

Short-axis sweeps through the IVC in long-axis (2D, CD, PW)

- Demonstrate the inferior vena cava from its right atrial connection to below the liver.

Short-axis sweeps through the RVC and RA junction (2D, CD, PW)

Short-axis and long-axis sweeps through the atrial septum to detect the presence of any atrial communication or patent foramen ovale (2D, CD, CCD)

- Demonstrate robust flow signal on both sides of the atrial septum, ventricular septum, left and right ventricular outflow tracts, and semilunar valves

Detailed short-axis and long-axis sweeps through the RA and LA looking for intra-atrial thrombus (2D)

## 1.6 Imaging Protocol Apical Windows (Move the Patient into a Left Decubitus Position)

Apical 4-chamber view (2D)

- The index mark is at ~3:00
- Begin at the 4-chamber view with a short (3-5 heart beats) clip
- Sweep posteriorly towards the diaphragm and then anteriorly to the level of the RV outflow tract, with particular attention to the atrium looking for thrombus

Focused zoom view with targeted sweeps through the MV (2D, CD)

Focused zoom view with targeted sweeps through the TV (2D, CD)

If a tricuspid regurgitation jet is present, interrogate the jet with CW

### 1.7 Imaging Protocol Parasternal Windows (Keep the Patient in a Left Decubitus Position)

Full parasternal long-axis sweep

- The index mark is at ~11:00
- Complete sweep rightward to the tricuspid valve and then leftward/anterior to the PV-MPA

Parasternal long-axis: focused zoom view with targeted sweeps through the MV (2D, CD)

Parasternal long-axis: focused zoom view with targeted sweeps through the AoV (2D, CD)

Parasternal long-axis: focused zoom view with targeted sweeps through the TV (2D, CD)

If a tricuspid regurgitation jet is present, interrogate the jet with CW

Parasternal long-axis: focused zoom view with targeted sweeps through the PV and MPA (2D, CD).

Full parasternal short-axis sweep

- The index mark is at ~ 2:00
- Begin with the aorta in the center of the screen and sweep to the apex of the LV, then sweep back (separate clip). Note: may have to move the transducer down a rib space to complete the sweep through the apex.

Parasternal short-axis: focused evaluation of ventricular function.

- At the level of mid-ventricle or papillary muscle tips
- The RV should be anterior (or on top) of the LV

Parasternal short-axis: focused zoom view with targeted sweeps through the PV and MPA (2D, CD, PD, CW)

### 1.8 Imaging Protocol Suprasternal Notch Windows (Move the Patient onto Their Back)

The index mark is at ~ 3:00

Sweeps through the left innominate vein (2D, CD, CCD)

Sweeps through the right superior vena cava (2D, CD, CCD)

### 1.9 Imaging Protocol Right Parasternal Windows (Move the Patient into a Right Decubitus Position)

Typically, the index mark is set at ~ 12:00 - 1:00

Sweep through the atrial septum and the entry of the SVC to the right atrium (2D, CD)

## 1.10 Imaging Protocol of Central Venous Access Devices (CVAD)

- If a CVAD is visible in any imaging window, additional attention should be paid to evaluate for associated thrombus
- The CVAD should be followed along its length with particular attention paid to the tip of the CVAD
- Imaging of the CVAD should be done in 2D, CD, and CCD
- If venous obstruction is suspected, additional PW and CW interrogation is required

**The thrombus will be categorized to:**

- Occlusive thrombus: intraluminal filling defect is seen (thrombus), and color Doppler images do not demonstrate blood flow past this defect
- Non-occlusive thrombus: intraluminal filling defect is seen (thrombus), however color Doppler images demonstrate blood flow past this defect
- No thrombus: no intraluminal filling defect identified in the vessel

**Presence of collateral vessels**

Collateral vessels are present if there are unnamed smaller caliber circuitous veins adjacent to the vessel in question.

**Report to accompany echocardiogram images:**

For each protocol echocardiogram, the Center will send the local echocardiography report, will complete a worksheet that will detail compliance with the imaging protocol and complete a data form detailing interpretation and findings.

## APPENDIX 3 DIAGNOSTIC ASSESSMENT OF SUSPECTED DVT

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential DVT, related or not-related to the central venous catheter, a dossier package should be created by the site to be sent for adjudication.

Hospitalized subjects will be assessed daily for signs and symptoms of DVT which include but are not limited to: phlebitis [eg, an inflammatory reaction within the vein, causing clinical findings of edema, pain/tenderness, or erythema of the involved extremity]; presence of congestion of tributary veins (eg, at the base of the neck, infraclavicular fossa, shoulder, or arm, according to catheter location and type); a palpable cord; catheter occlusion (inability to withdraw blood or infuse into an indwelling catheter); the presence of catheter-related infection, and signs and symptoms of pulmonary embolism (PE) (see Appendix 4).

Prior to discharge, subjects and/or caregivers will be taught signs and symptoms suggestive of VTE and instructed to contact the investigator immediately if any of these signs or symptoms are observed.

Diagnostic tests for presence of DVT include:

- Ultrasonography: See Appendix 1
- Echocardiography – See Appendix 2
- Magnetic resonance imaging (MRI)/Magnetic Resonance Venography (MRV) - The accuracy of MRV in diagnosis of DVT is similar to that of contrast venography performed with ionizing radiation. MRI/MRV will be performed according to the judgment of the clinical team caring for the patient. A DVT by MRI/MRV is diagnosed by a intraluminal filling defect, defined as
  - An area of reduced or absent filling that is at least partially surrounded by blood or with contrast medium in two or more projections, or
  - Lack of filling in a vessel in which there is a cut-off which has the configuration of a thrombus, or
  - Lack of normal flow void with expansion of the vessel.
- Computerized Tomography (CT)/Computerized Tomographic Venography (CTV) - Some centers will perform CT/CTV rather than MR/MRV for diagnosis of suspected DVT events. The criteria for a positive CT/CTV study are similar to those on MR/MRV.
- Venography – Venography may be performed when clinical suspicion for deep venous thrombosis is high, but ultrasound is negative or nondiagnostic. Installation of contrast into the vein (using the central line if a line study or another catheter) under fluoroscopy /digital subtraction angiography may show a thrombus.

**Symptomatic DVT detected at any time during the study:**

If a subject presents with signs and symptoms suggestive of a symptomatic DVT, conduct physical examination and perform diagnostic imaging tests within 48 hours of event. Specific recommendations are as follows:

- Conduct physical examination

- Treat for DVT per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Submit to the sponsor all relevant CRFs, clinical records and reports, CDs or DVDs of ultrasound, echocardiograms, venography, and other relevant information to support the diagnosis of a symptomatic DVT
- Report the DVT as an AE or SAE according to standard definitions and, if needed, clinical judgment

**Asymptomatic DVT detected during the assessment period:**

In the event that a DVT is incidentally detected while undergoing other imaging procedures required for the subject's care of his/her underlying condition, and the subject does not manifest any signs or symptoms of a DVT, the event will be considered an asymptomatic DVT. The subject should be managed and further investigated according to the investigator's standard of care. All diagnostic imaging tests should also be submitted for adjudication (CDs, DVDs, and reports). Specific recommendations are as follows:

- Conduct physical examination
- Treat for DVT per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Submit to the sponsor all relevant CRFs, clinical records and reports, CDs or DVDs of ultrasound, echocardiograms, line study, venography, and other relevant information to support the diagnosis of an asymptomatic DVT
- Report the DVT as an AE or SAE according to standard definitions and, if needed, clinical judgment

**Table 1: Evaluation and diagnosis for patients with suspected thrombosis[2]**

| | Site | Likely clinical signs and symptoms | Diagnostic method/s |
|---|---|---|---|
| Cardiac | Right atrial | CVAD occlusion, sepsis, congestive heart failure | ECHO |
| CVAD-related DVT | At or near CVAD | Swelling, pain, tenderness, erythema, dilated vessels, CVAD occlusion requiring revision or renewal, headache, swelling of face.<br>Red flags: recurrent CVAD-related infections<br>A significant CVAD-related DVT of the vessel harboring CVAD may be asymptomatic. Hence, high index of suspicion is required | ECHO, line study, venography, MRI/MRV, CT/CTV, and/or Doppler US depending upon the site of thrombosis[a] |

| Table 1: Evaluation and diagnosis for patients with suspected thrombosis[2] | | | |
|---|---|---|---|
| | **Site** | **Likely clinical signs and symptoms** | **Diagnostic method/s** |
| DVT | Upper venous system | Swelling, pain, tenderness, erythema, dilated vessels | Bilateral venogram is a "gold standard" for diagnosis of subclavian/brachial vessels TE MRI/MRV or CT/CTV can also be used.<br>Doppler USG necessary for jugular vein TE[a] MRV<br>Recommend ECHO to evaluate RAT |
| | Lower venous system | | Doppler USG to evaluate all sites. AVenogram is still the gold standard, but DVT can be diagnosed accurately by MRI/MRV or CT/CTV as well. |

[a] Detection of echogenic material within the lumen of a vein on a gray scale and presence of partial or complete absence of flow by pulse wave or color Doppler ultrasonography.

# APPENDIX 4 DIAGNOSTIC ASSESSMENT OF SUSPECTED PULMONARY EMBOLUS

This appendix has sections on symptomatic and asymptomatic pulmonary embolism (PE).

**Symptomatic PE detected during the Assessment Period:**

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential pulmonary embolism (PE), a dossier package should be created by the site to be sent for adjudication

Clinical impression of acute PE tends to be nonspecific, with low sensitivity and specificity. For this reason, additional diagnostic evaluations are needed. D-dimer assays are generally performed in the work-up of suspected PE and have good sensitivity and negative predictive value, but poor specificity and positive predictive value. In addition, at least one of the following diagnosis techniques should be used to assess suspected PE: computed tomography pulmonary angiography (CT-PA), ventilation-perfusion (V/Q) scanning, invasive pulmonary angiography, magnetic resonance pulmonary angiography (MR-PA), and/or echocardiography. The specific diagnostic testing performed should be chosen in accordance with available facilities at their institution and the safety for the patient.

CT pulmonary angiography (CT-PA) is used increasingly, with the largest adult study[3] suggesting a sensitivity of 83% (rising to 90% when venous –phase imaging was added, ie, CTA-CTV) and specificity of 96%. When high, intermediate, or low clinical probability was combined with a negative CT-PA, the predictive value negatives were 60%, 89%, and 96%. Additional testing is needed when the clinical probability is inconsistent with the results of the CT scan.

CT will be classified as follows:

1) CT Negative: No intraluminal filling defect (ILFD). NOTE: The EAC will consider the assessment of additional tests performed for a non-diagnostic spiral CT (eg, V/Q lung scan, pulmonary angiography)
2) CT Positive: ILFD in the central pulmonary arteries (pulmonary trunk; proximal right or left pulmonary arteries, right or left interlobar arteries, right or left segmental arteries)
3) CT indeterminate: Not all central pulmonary arteries (pulmonary trunk; proximal right or left pulmonary arteries, right or left interlobar arteries, right or left segmental arteries) are visualized, and an ILFD is not present

Ventilation-perfusion (V/Q) scanning: The probability of a PE is greatest when a V/Q scan suggesting high probability of PE is combined with a clinical picture highly suggestive of PE.[4] A normal V/Q scan virtually excludes PE. Results of a V/Q scan will be classified as follows:

A) Normal: No perfusion defects
B) High probability: Segmental perfusion defect (≥ 1), seen in at least two views, with normal ventilation at that spot
C) Lower Probability: A perfusion defect that does not qualify as High Probability. NOTE: The EAC will consider the assessment of additional tests performed for a lower probability

V/Q lung scan (ie, spiral CT, pulmonary angiography, venography, and compression ultrasound [proximal region])

D) Not done: V/Q lung scan not performed

Venography or compression ultrasound in the setting of a lower probability V/Q lung scan after suspected PE event: Venography and/or compression ultrasound of the proximal region will be classified as follows:

A) No acute DVT: No tests diagnostic for acute DVT were associated with the symptomatic PE
B) Acute DVT: Thrombus confirmed by diagnostic tests associated with a symptomatic PE
C) Not done: Venography or compression ultrasound not performed.

Echocardiography may demonstrate right ventricular enlargement, decreased right ventricular function, and tricuspid regurgitation. Fewer than half of patients with pulmonary embolus have an abnormal echocardiogram, although the likelihood of abnormalities is related to the severity of the PE.

Invasive (conventional) pulmonary angiography is the gold standard, but is rarely used. Pulmonary angiographic classification is as follows:

A) Normal: No ILFD and no sudden contrast cut-off in one or more vessels
B) Intraluminal Filling Defect (ILFD): An area of reduced or absent filling at least partially surrounded with contrast medium in two or more projections OR lack of filling in a vessel in which there is a cut-off which has the configuration of a thrombus
C) Sudden contrast cut-off: A sudden contrast cut-off (dye abruptly stops) involving one or more vessels
D) Indeterminate: Lack of filling of a region of the pulmonary arteries without being diagnostic for PE
E) Not done: Pulmonary angiography not performed

MR pulmonary angiogram (MR-PA): Criteria are similar to those of CT-PA. MR-PA for diagnosis of PE is generally inferior to CT-PA because of motion artifact.

Echocardiographic abnormalities are found in 30 - 40% of individuals; these comprise dilated right ventricle with diminished function and tricuspid regurgitation.

Patients will be classified with respect to PE events as follows:

**Positive PE Event**: To be classified as having a positive PE event, patients must meet at least one of the following criteria:

A) The CT-PA is assessed as positive for an ILFD;
B) The V/Q scan is assessed as High Probability;

C) The V/Q lung scan is assessed as Lower Probability and either venography or compression ultrasounds is diagnostic for acute DVT;

D) An invasive pulmonary angiogram is positive for an ILFD or a sudden contrast cut-off in one or more vessels > 2.5 mm in diameter; or

E) An autopsy confirms the presence of a PE.

**No PE event:** To be classified as having no PE event, patients must meet none of the criteria above:

**Non Diagnostic/Non-evaluable:** There is not enough information to make a determination of the presence or absence of a PE.

If PE is considered likely or confirmed, patient should be managed and further investigated according to investigator standard of care. If these tests are negative or indeterminate, then further testing per investigator's choice should be performed.

Diagnostic imaging procedures performed such as ventilation-perfusion scanning or CT scans should also be submitted for adjudication.

To enable the Independent Event Adjudication Committee to appropriately classify the event in subjects with a history suggestive of PE who die suddenly, investigators will be encouraged to obtain an autopsy or other post-mortem studies reports

If a subject presents with a suspected symptomatic PE, a specific recommendations are as follows:

- Conduct a physical examination
- Evaluate with laboratory or diagnostic tests in accordance with feasibility and safety at your institution
- Treat for PE per investigator or center standard of care. (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Report as AE/SAE according to clinical judgment
- Collect relevant CRFs and reports to submit to the Sponsor
- Follow to resolution or stabilization
- Record as suspected PE in the CRF

**Asymptomatic PE detected during the Assessment Period:**

In the event that a PE is incidentally detected while undergoing other imaging procedures required for the subject's care of his/her underlying condition, and the subject does not manifest any signs and/or symptoms of a PE, the event will be considered an asymptomatic PE. The subject should be managed and further investigated according to the investigator's standard of care. All diagnostic imaging procedures performed such as CT pulmonary angiogram/VQ scan and US should also be submitted for adjudication as a suspected PE.

If a subject presents with an asymptomatic PE, specific recommendations are as follows:

- Conduct a physical examination
- Treat for PE per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Report as AE/SAE according to clinical judgment
- Collect relevant CRFs and reports to submit to the Sponsor
- Follow to resolution or stabilization
- Record as a suspected PE

**Table 2: Evaluation and diagnosis for patients with suspected pulmonary embolism[2]**

| | Site | Likely clinical signs and symptoms | Diagnostic method/s |
|---|---|---|---|
| PE | Pulmonary vasculature | Respiratory symptoms (dyspnea at rest or with exertion, pleuritic chest pain, hypoxia, cough, tachypnea,),<br>Respiratory signs (eg, tachypnea, tachycardia, loud P2)<br>DVT source (eg, catheter thrombosis)<br>Other: eg, syncope, "unexplained pneumonia, shock" | CT-PA<br>V/Q scan (if low probability for PE, venography or compression US may be helpful)<br>Pulmonary angiogram<br>(Echocardiogram – less useful)<br>(MR-PA – inferior to CT-PA) |

# APPENDIX 5 DIAGNOSTIC ASSESSMENT OF SUSPECTED CEREBRAL VENOUS SINUS THROMBOSIS (CVST)

To satisfy criteria for symptomatic CVST event positivity, 1) patients must be symptomatic, and 2) the diagnosis must be objectively documented by brain MRI with MR venography (MRI/MRV) or brain CT with CT venography (CT/CTV). In the event that a CVST is incidentally detected while undergoing other imaging procedures required for the subject's care of his/her underlying condition, and the subject does not manifest any signs and/or symptoms of a CVST, the event will be considered an asymptomatic CVST event.

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential CVST OR if an asymptomatic CVST is detected, a dossier package with medical records and CD/DVDs of imaging studies should be created by the site to be sent first to the Vendor for translation if needed and de-identification, and then to the EAC Coordinator for adjudication.

The presentation of cerebral vein and dural sinus thrombosis is highly variable, with onset that can be acute, subacute, or chronic. The most common symptom is headache, but other symptoms include altered consciousness/coma, cognitive dysfunction, focal or multi-focal deficits (eg, hemiparesis), or seizures. The signs and symptoms of cerebral sinus and vein thrombosis are dependent upon the particular site that has venous occlusion. For example, in cavernous sinus thrombosis, orbital pain, oculomotor palsies, and other occult signs are the predominant manifestation. With sagittal sinus thrombosis, motor deficits, bilateral deficits, and seizures are present. Lateral sinus thrombosis often presents with isolated headaches or intracranial hypertension. Severe signs and symptoms are often apparent with occlusion of the deep cerebral venous system.

Patients will be classified with respect to CVST events as follows:

**Positive symptomatic CVST Event:** To be classified as having a positive CVST event, patients must meet each of the following criteria:

A. Consistent symptoms (unexplained headaches, vomiting, visual problems or neurological deficits, seizure, drowsiness or any change in mental status, signs of raised intracranial pressure); AND

B. Confirmation of CVST on neuroimaging by either MRI/MRV or CT/CTV.

**No CVST event:** To be classified as having no CVST event, patients must meet none of the criteria above.

**Nondiagnostic/ Indeterminate:** There is not enough information to make a determination of the presence or absence of a CVST.

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential CVST, a dossier package should be created by the site to be sent for adjudication. Specific recommendations are as follows:

- Conduct physical examination
- Treat for CVST per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Submit to the sponsor all relevant CRFs, clinical records and reports, CDs or DVDs of MR/MRV, CT/CTV, and other relevant information to support the diagnosis of an CVST.
- Report the CVST as an AE or SAE according to standard definitions and, if needed, clinical judgment

**Table 3: Evaluation and diagnosis for patients with suspected Cerebral Venous Sinus Thrombosis[2]**

| | Site | Likely clinical signs and symptoms | Diagnostic method/s |
|---|---|---|---|
| CNS | Cerebral venous sinus thrombosis (CVST) | Unexplained headaches, vomiting, visual problems or neurological deficits, seizure, drowsiness or any change in mental status, signs of raised intracranial pressure | MRI/MRV<br>CT/CTV |

# APPENDIX 6 DIAGNOSTIC ASSESSMENT OF SUSPECTED ARTERIAL THROMBOEMBOLIC EVENTS

Each patient with suspected arterial thromboembolic outcome events will be classified as

a. Stroke
b. Myocardial infarction
c. Peripheral thromboembolic event

The signs and symptoms of a symptomatic arterial thromboembolic event will entirely depend upon the site of thrombosis. In the event that an arterial thromboembolic event is incidentally detected while undergoing other imaging procedures required for the subject's care of his/her underlying condition, and the subject does not manifest any signs or symptoms of an arterial thromboembolic event, the event will be considered an asymptomatic arterial thromboembolic event. The subject should be managed and further investigated according to the investigator's standard of care. Regardless of site of arterial thromboembolic events, all medical records and diagnostic imaging tests (CDs, DVDs, and reports)should also be submitted to the Vendor for translation and de-identification, and then to the EAC for adjudication.

Specific criteria for stroke and myocardial infarction are listed below.

*Classification of stroke*

An acute stroke will be defined as a new focal neurological deficit of sudden onset lasting at least 24 hours that is not due to a readily identified non-vascular cause, such as brain tumor or trauma.

All reported stroke events will be assessed either by imaging (CT or MRI) or autopsy.

Each stroke will be classified as

1) Primary hemorrhagic stroke: a stroke with documentation on imaging (eg, CT or MRI of hemorrhage in cerebral parenchyma, or subdural or subarachnoid hemorrhage. Evidence of hemorrhagic stroke obtained from lumbar puncture, neurosurgery, or autopsy can also confirm the diagnosis
2) Non-hemorrhagic stroke: a focal neurological deficit that results from a thrombus or embolus (and not due to a hemorrhage) that appears and is still partially evident at 24 hours
3) Infarction with hemorrhagic conversion: a stroke without evidence of hemorrhage on an initial scan, but with appearance of hemorrhage on a subsequent scan
4) Unknown type: a stroke type that could not be or was not determined by imaging or other means

*Classification of myocardial infarction (MI)*

An acute myocardial infarction is defined by the presence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, the diagnosis for myocardial infarction can be made in the setting of the patient population in this protocol as follows:

A. Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin, with at least one value above the 99th percentile of the upper limit of normal, and with at least one of the following.

a) Symptoms of ischemia
b) New or presumed new significant ST-segment-T wave (STTW) changes or new left bundle branch block (LBBB)
c) Development of pathological Q waves in the ECG (≥ .04 seconds in ≥ 2 continguous leads)
d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
e) Identification of an intracoronary thrombus by angiography or autopsy

OR

B. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

***Classification of Suspected Peripheral Arterial Thromboembolic Events***

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential arterial thromboembolic event, a dossier package should be created by the site to be sent for adjudication

**Symptomatic arterial thromboembolic event detected during the assessment period:**

If a subject presents with signs and symptoms suggestive of a symptomatic arterial thromboembolic event, conduct physical examination and perform diagnostic imaging commensurate with site of the arterial thrombus within 48 hours of event. Specific recommendations are as follows:

- Conduct physical examination
- Treat for arterial thromboembolic event per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Submit to the sponsor all relevant CRFs, clinical records and reports, CDs or DVDs of imaging tests, and other relevant information to support the diagnosis of arterial thromboembolic event
- Report the arterial thromboembolic event as an AE or SAE according to standard definitions and, if needed, clinical judgment

**Asymptomatic arterial thromboembolic event detected during the assessment period:**

In the event that an arterial thromboembolic event is incidentally detected while undergoing other imaging procedures required for the subject's care of his/her underlying condition, and the subject does not manifest any signs or symptoms of an arterial thromboembolic event, the event will be

considered an asymptomatic arterial thromboembolic event. The subject should be managed and further investigated according to the investigator's standard of care. All diagnostic imaging tests should also be submitted for adjudication (CDs, DVDs, and reports). Specific recommendations are as follows:

- Conduct physical examination
- Treat for arterial thromboembolic event per investigator standard of care (the American College of Chest Physicians evidence based clinical practice guidelines (9th Edition). may be used as a reference[1])
- Submit to the sponsor all relevant CRFs, clinical records and reports, CDs or DVDs of imaging tests, and other relevant information to support the diagnosis of arterial thromboembolic event
- Report the arterial thromboembolic event as an AE or SAE according to standard definitions and, if needed, clinical judgment

**Table 4: Evaluation and diagnosis for patients with suspected arterial thromboembolic events[2]**

| | Site | Likely clinical signs and symptoms | Diagnostic method/s |
|---|---|---|---|
| CNS | Cerebral arterial ischemic stroke ± hemorrhage | Unexplained headaches, vomiting, visual problems or neurological deficits, seizure, drowsiness or any change in mental status, signs of raised intracranial pressure | CT/CTA<br>MRI/MRA<br>Angiogram<br>Echocardiogram |
| Heart | Myocardial infarction | Chest pain, rhythm disturbance | EKG, troponin levels |
| Peripheral arterial thromboembolic events | Limb ischemia | Ischemic changes, poor perfusion, undetectable extremity pulses | Doppler ultrasound |
| | Kidney infarction ± hemorrhage | Hematuria | Renal US with Doppler |
| | Spleen infarction ± hemorrhage | Abdominal pain | Abdominal US with Doppler, contrast enhanced CT |

## APPENDIX 7 CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTION (CLABSI)[5]

At any time during the assessment period, if a subject experiences signs or symptoms that the investigator considers indicative of a potential CLABSI, a dossier package with medical records and laboratory studies should be created by the site to be sent first to the Vendor for translation if needed and de-identification, and then to the EAC Coordinator for adjudication.

Definition of CLABSI will be derived from that proposed by the CDC and adapted in COG protocol ACCL1034.

The patient must meet one of the following criteria:

**Criterion 1:** Patient has a recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site (Notes 1 and 2 below)

**Criterion 1:** Patient has a recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site. (if infection at another site can colonize central line)

**Criterion 2:**

- Patient has at least one of the following signs or symptoms: fever (> 38ºC), chills, or hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site and
- A common skin contaminant (ie, diphtheroids [*Corynebacterium* spp.], *Bacillus* [not *B. anthracis*] spp., *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.) is cultured from two or more blood cultures drawn on separate occasions.

**NOTES:**

1) In criterion 1, the phrase “one or more blood cultures” means that at least one bottle from a blood draw is reported by the laboratory as having grown organisms (ie, is a positive blood culture).
2) In criterion 1, the term “recognized pathogen” does not include organisms considered common skin contaminants (see criteria 2 and 3 for a list of common skin contaminants). A few of the recognized pathogens are *S. aureus*, *Enterococcus* spp., *E. coli*, *Pseudomonas* spp., *Klebsiella* spp., *Candida* spp., etc.
3) In criteria 2, the phrase “two or more blood cultures drawn on separate occasions” means 1) that blood from at least two blood draws were collected within two days of each other (eg, blood draws on Monday and Tuesday or Monday and Wednesday would be acceptable for blood cultures drawn on separate occasions, but blood draws on Monday and Thursday would be too far apart in time to meet this criterion), and 2) that at least one bottle from each blood draw is reported by the laboratory as having grown the same common skin contaminant organism (ie, is a positive blood culture). (See Note 4 for determining sameness of organisms.)

a) For example, an adult patient has blood drawn at 8 a.m. and again at 8:15 a.m. of the same day. Blood from each blood draw is inoculated into two bottles and incubated (four bottles total). If one bottle from each blood draw set is positive for coagulase-negative staphylococci, this part of the criterion is met.

b) For example, a neonate has blood drawn for culture on Tuesday and again on Saturday and both grow the same common skin contaminant. Because the time between these blood cultures exceeds the two-day period for blood draws stipulated in criteria 2 and 3, this part of the criteria is not met.

c) A blood culture may consist of a single bottle for a pediatric blood draw due to volume constraints. Therefore, to meet this part of the criterion, each bottle from two or more draws would have to be culture-positive for the same skin contaminant.

4) There are several issues to consider when determining sameness of organisms. If the common skin contaminant is identified to the species level from one culture, and a companion culture is identified with only a descriptive name (ie, to the genus level), then it is assumed that the organisms are the same. The speciated organism should be reported as the infecting pathogen (see examples below).

**Table 5: Examples of how to report speciated and unspeciated common skin contaminant organisms**

| Culture Report | Companion Culture Report | Report as… |
|---|---|---|
| S. epidermidis | Coagulase-negative staphylococci | S. epidermidis |
| Bacillus spp. (not anthracis) | B. cereus | B. cereus |
| S. salivarius | *Strep* viridans | S. salivarius |

5) Additional considerations not included in the CDC criteria

A. Recurrent infections will not be counted as new infections.

B. Criteria for recurrence of infection include:

a. The subsequent positive culture occurs in association with the same CVAD as the previous infection (the CVAD was not replaced with the previous infection)

b. The subsequent positive culture is due to the same organism/s as the previous infection without new organism/s cultured

c. The subsequent positive culture occurs within 4 weeks of the first infection

All 3 criteria must be present for a positive culture to be deemed a recurrent infection.

Different species isolated within a week of an initial isolate will be counted as one infection episode.

Different species identified at least one week after the initial isolate will be categorized as a new infection.

## APPENDIX 8 DEATH

At any time during the assessment period, if a death event occurs, a dossier package with medical records, imaging data, laboratory studies and any other relevant medical information should be created.

Deaths will be classified as

**A. VTE-related Death:**

(1) Fatal pulmonary embolism

(a) Autopsy reveals major pulmonary embolism (occlusion of at least two segmental pulmonary arteries or their equivalent), or

(b) Clinical course is compatible with pulmonary embolism AND there is not a more compelling alternative diagnosis to account for death.

(2) Fatal non-hemorrhagic stroke related to **paradoxical embolus**: ischemic stroke with the presence of venous thromboembolism and a right-to-left shunt (eg, patent foramen ovale, a pulmonary fistul) revealed by imaging, surgery or autopsy.

(3) Fatal MI related to **paradoxical embolus**: acute MI with the presence of venous thromboembolism and a right-to-left shunt (eg, patent foramen ovale, a pulmonary fistul) revealed by imaging, surgery or autopsy.

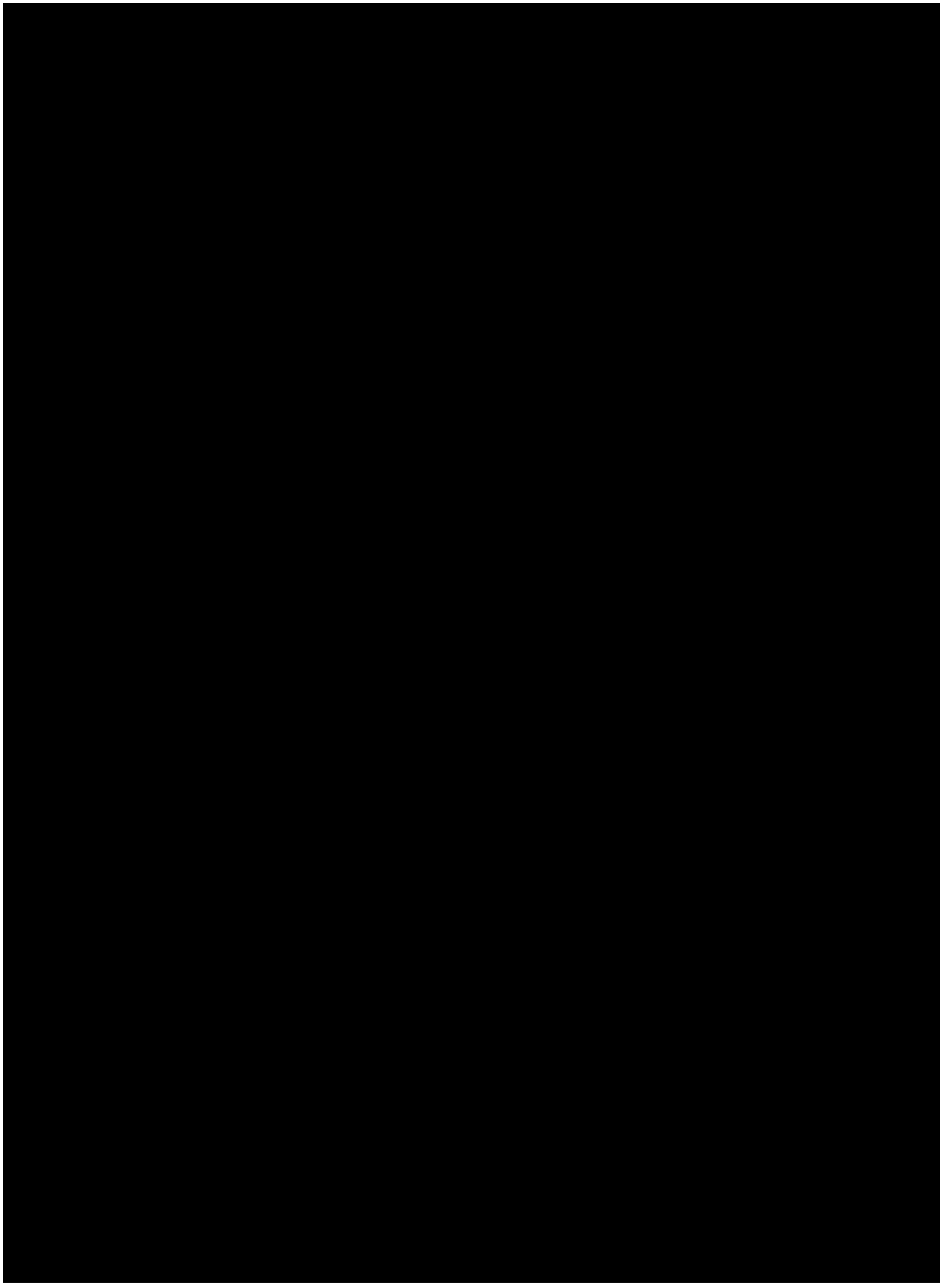
**B. Fatal Bleeding**

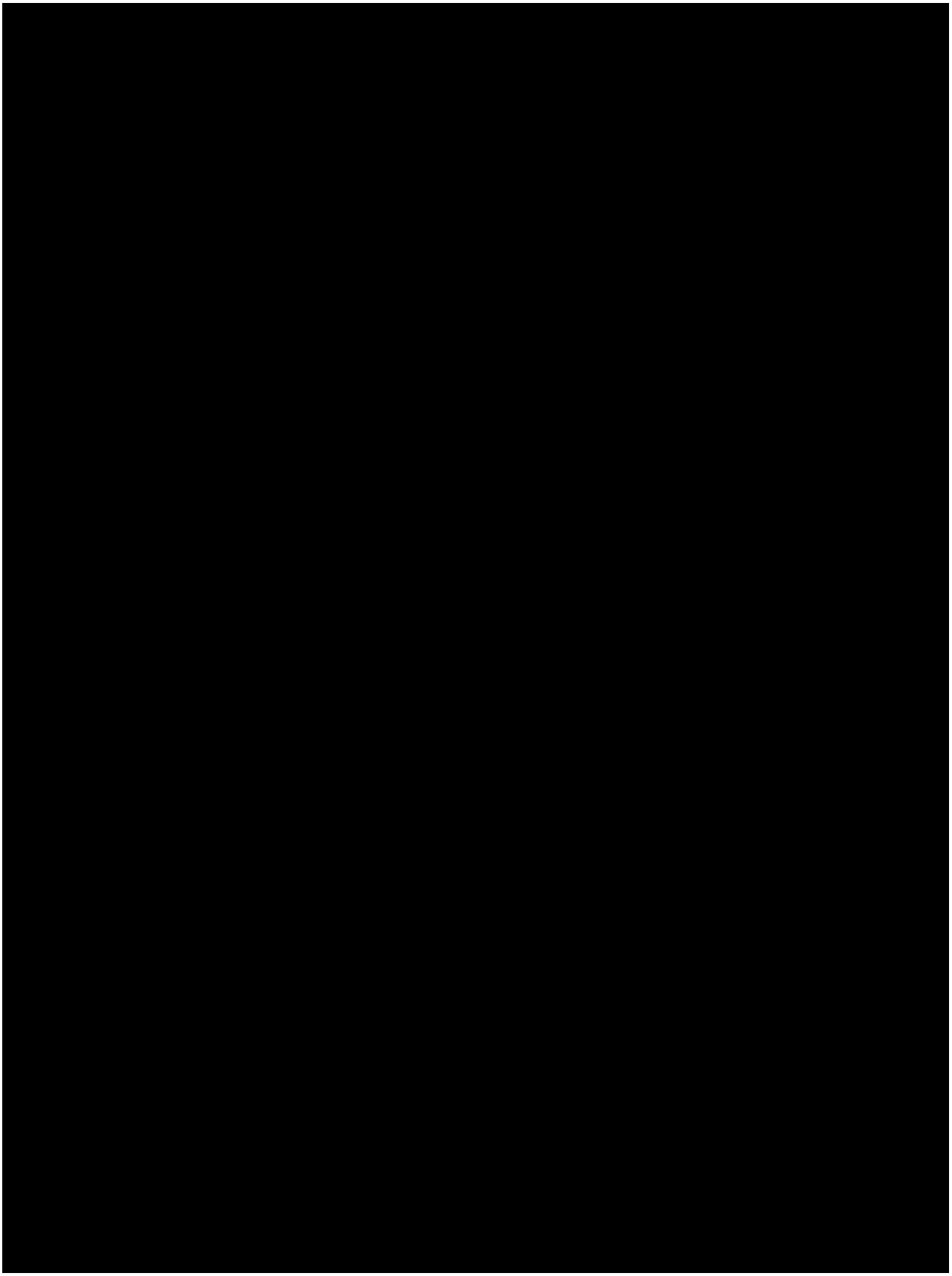
(a) Death will be classified as related to fatal bleeding if there is overt bleeding (including autopsy evidence) AND there is not a more compelling alternative diagnosis to account for death.

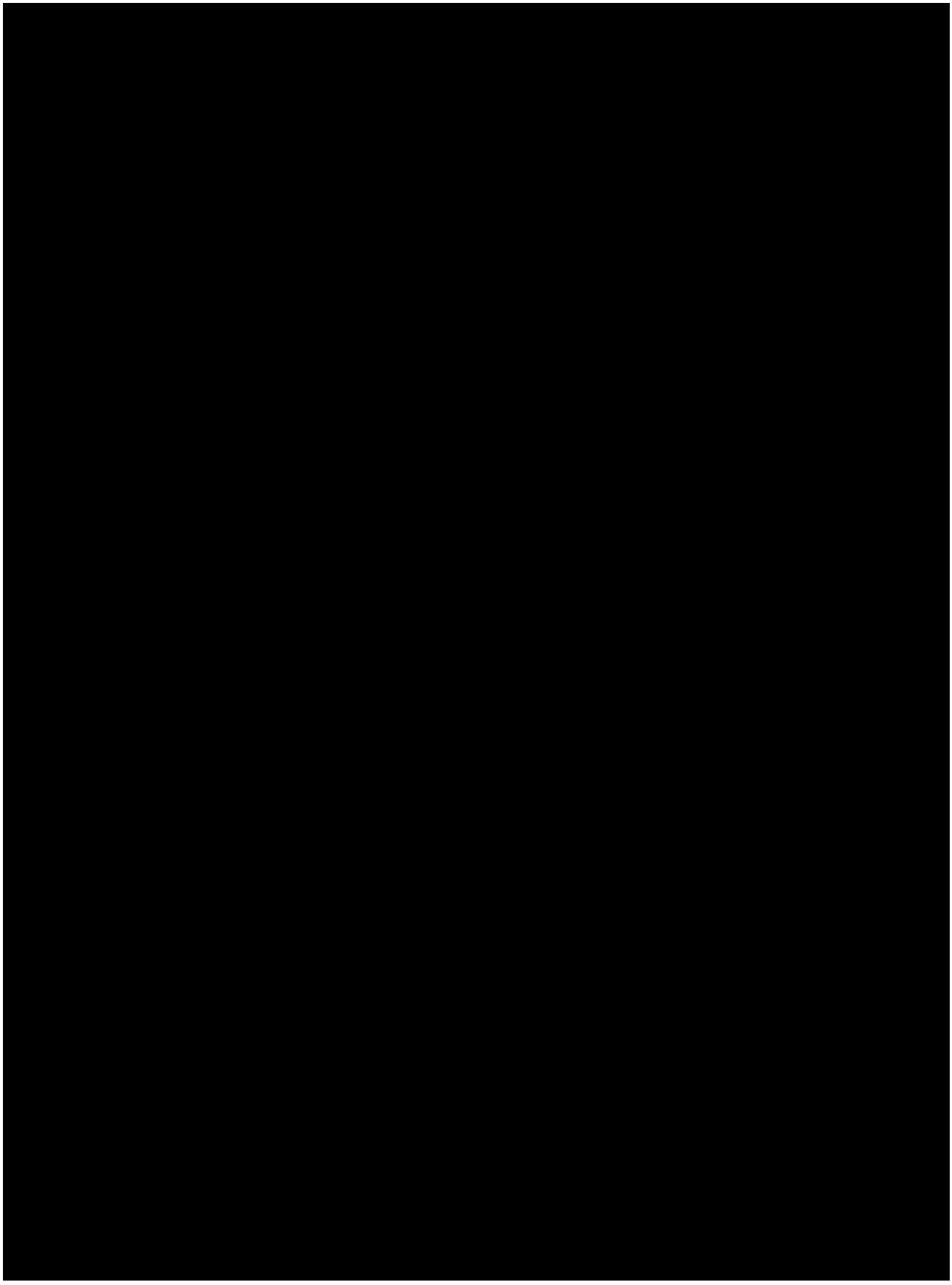
(b) Death associated with pulmonary hemorrhage will usually be attributed to underlying pulmonary embolism.

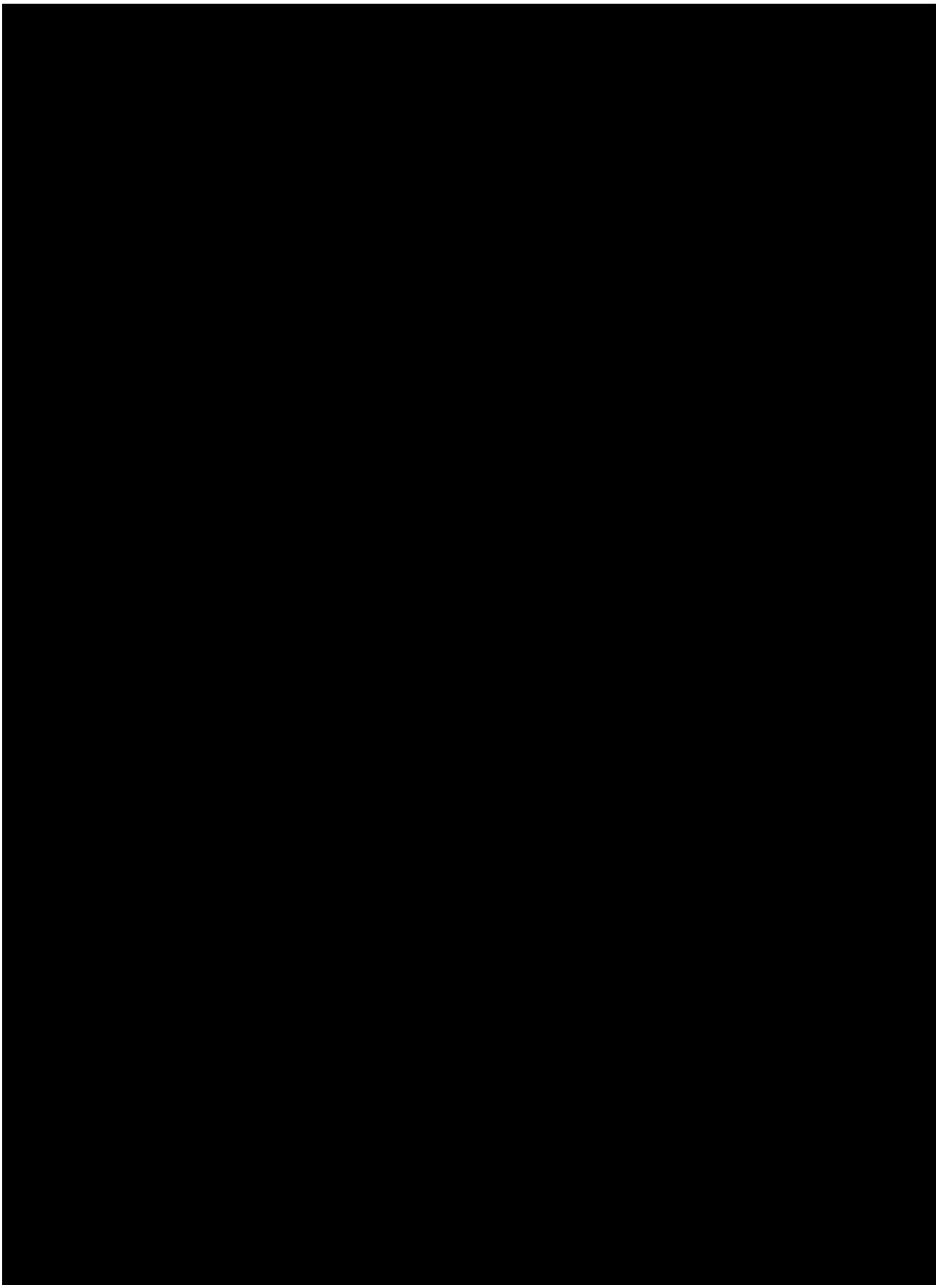
**C. Other** (eg, malignancy, infection, tumor lysis syndrome, cardiovascular – related, respiratory failure – related , central nervous system (CNS) – related, withdrawal of support, study drug toxicity other than bleeding (specify), and Other not mentioned).

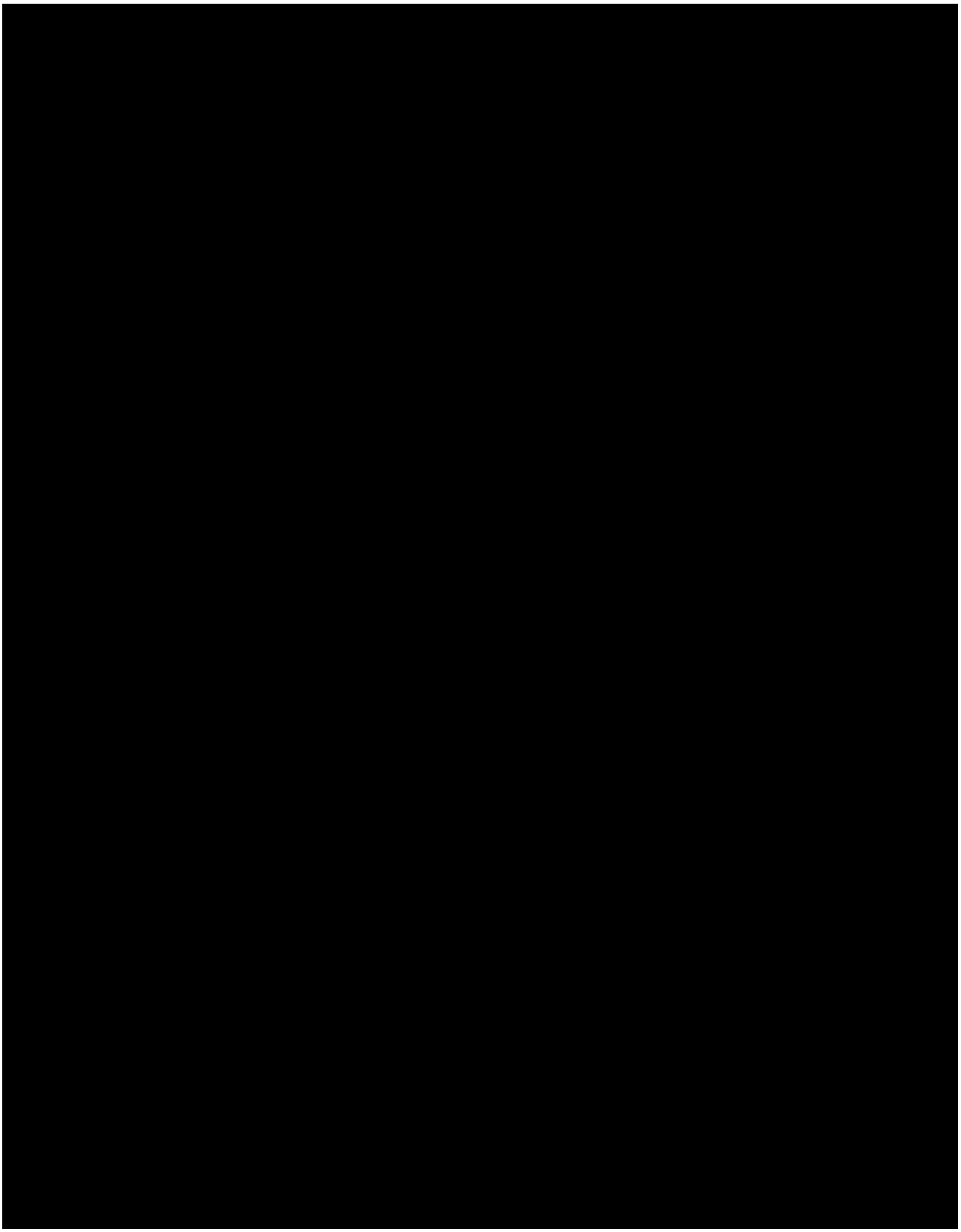
**D. Unknown Cause**: No data are available to assign a cause of death.

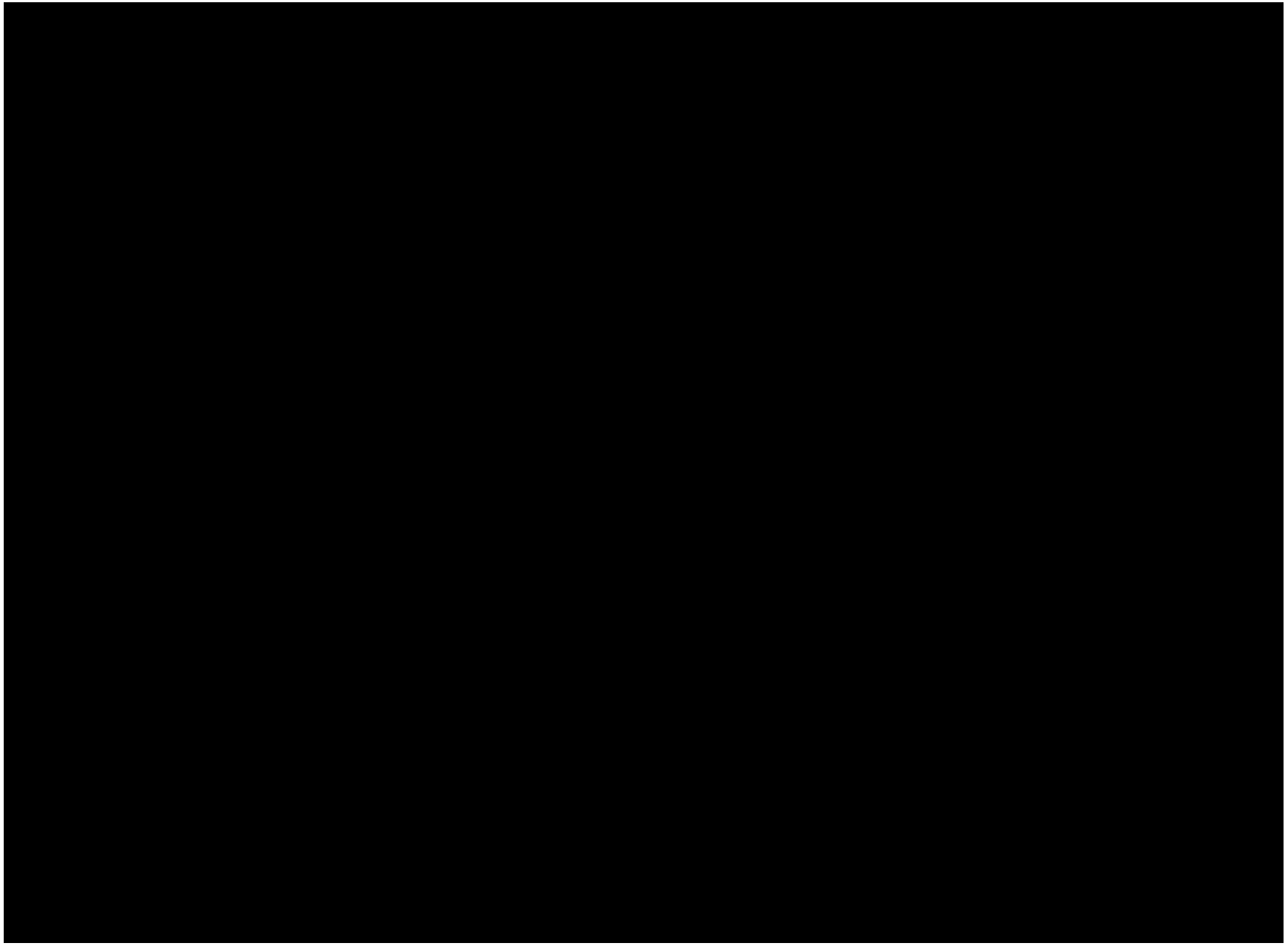


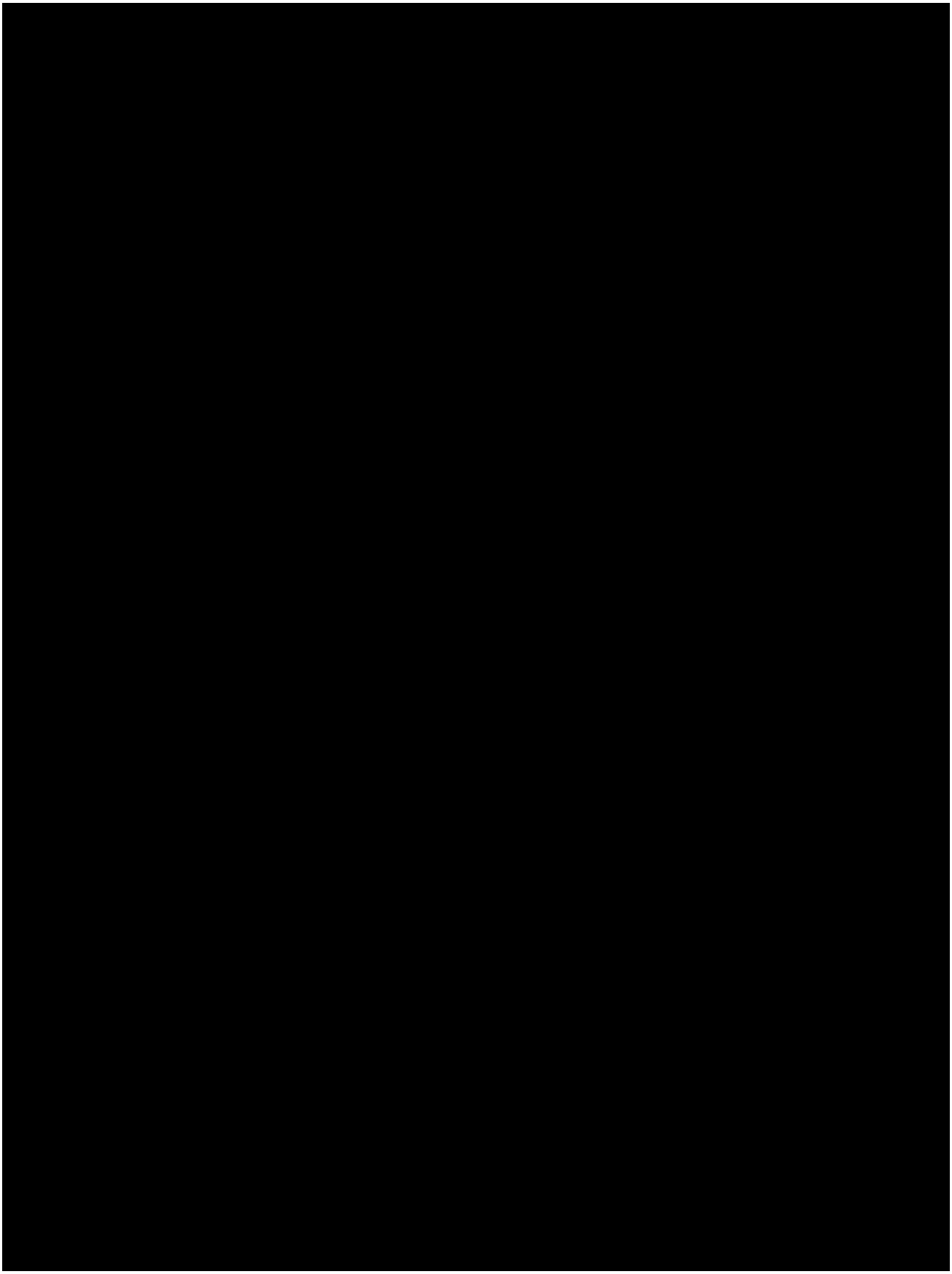


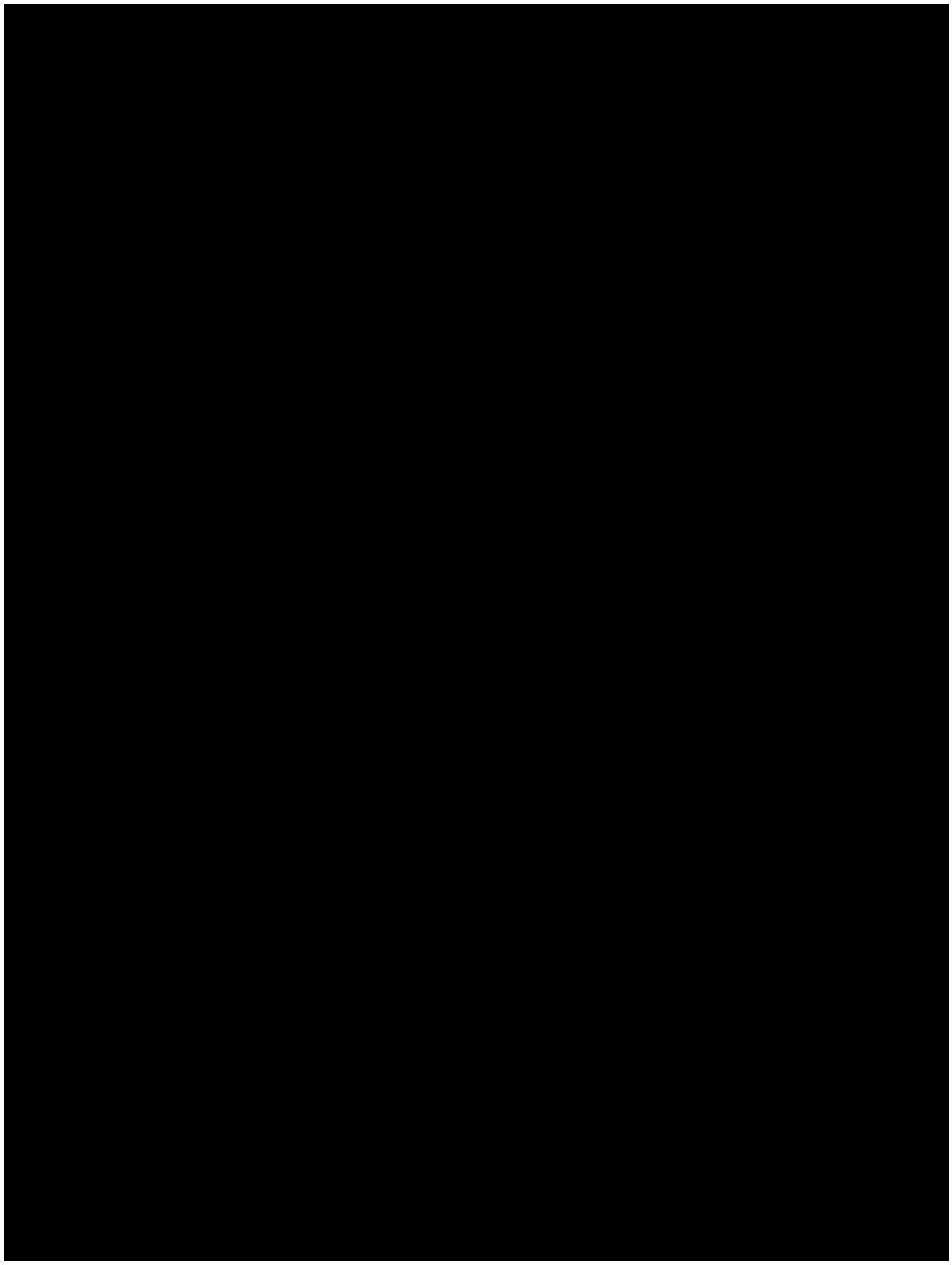


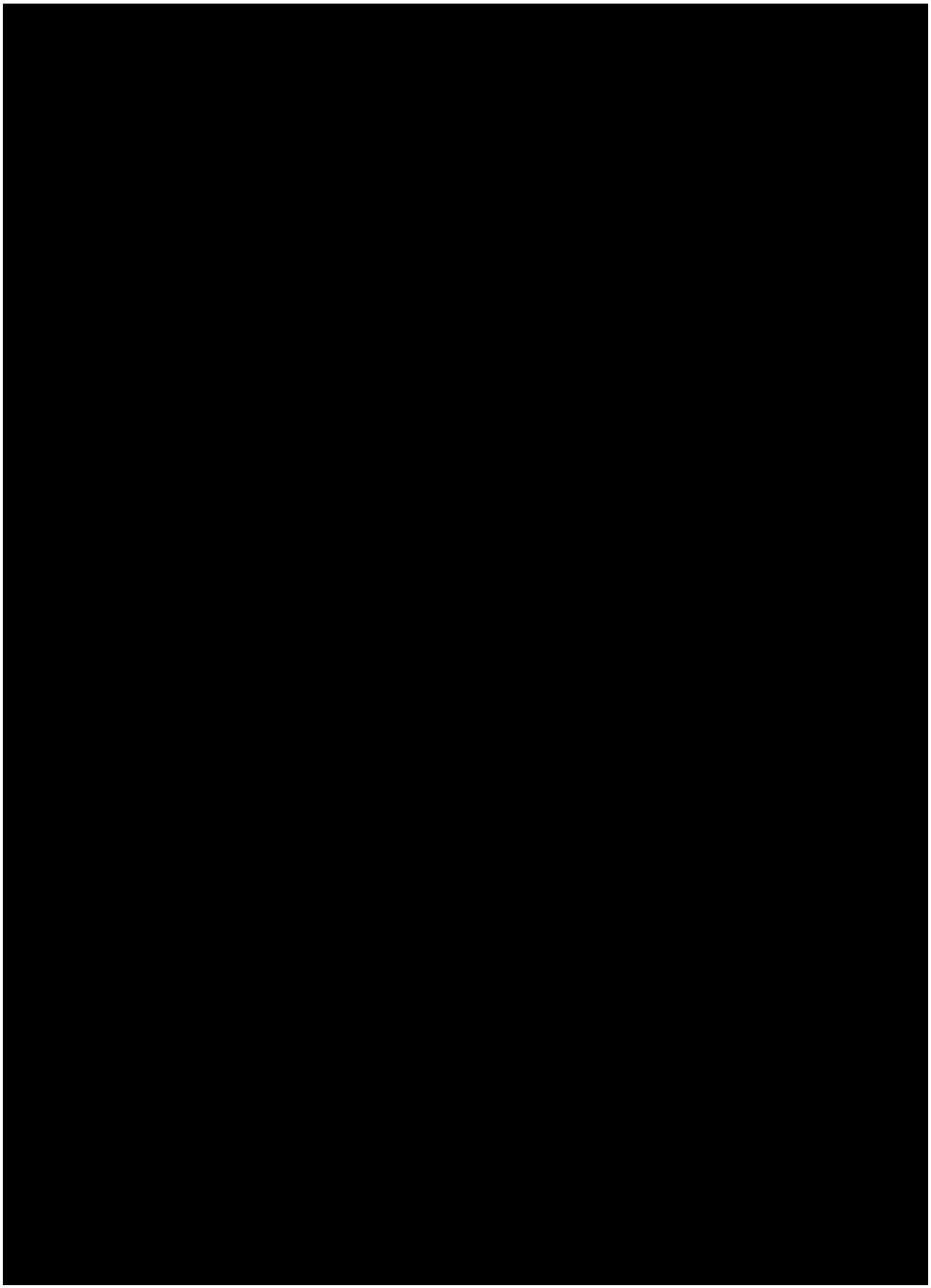


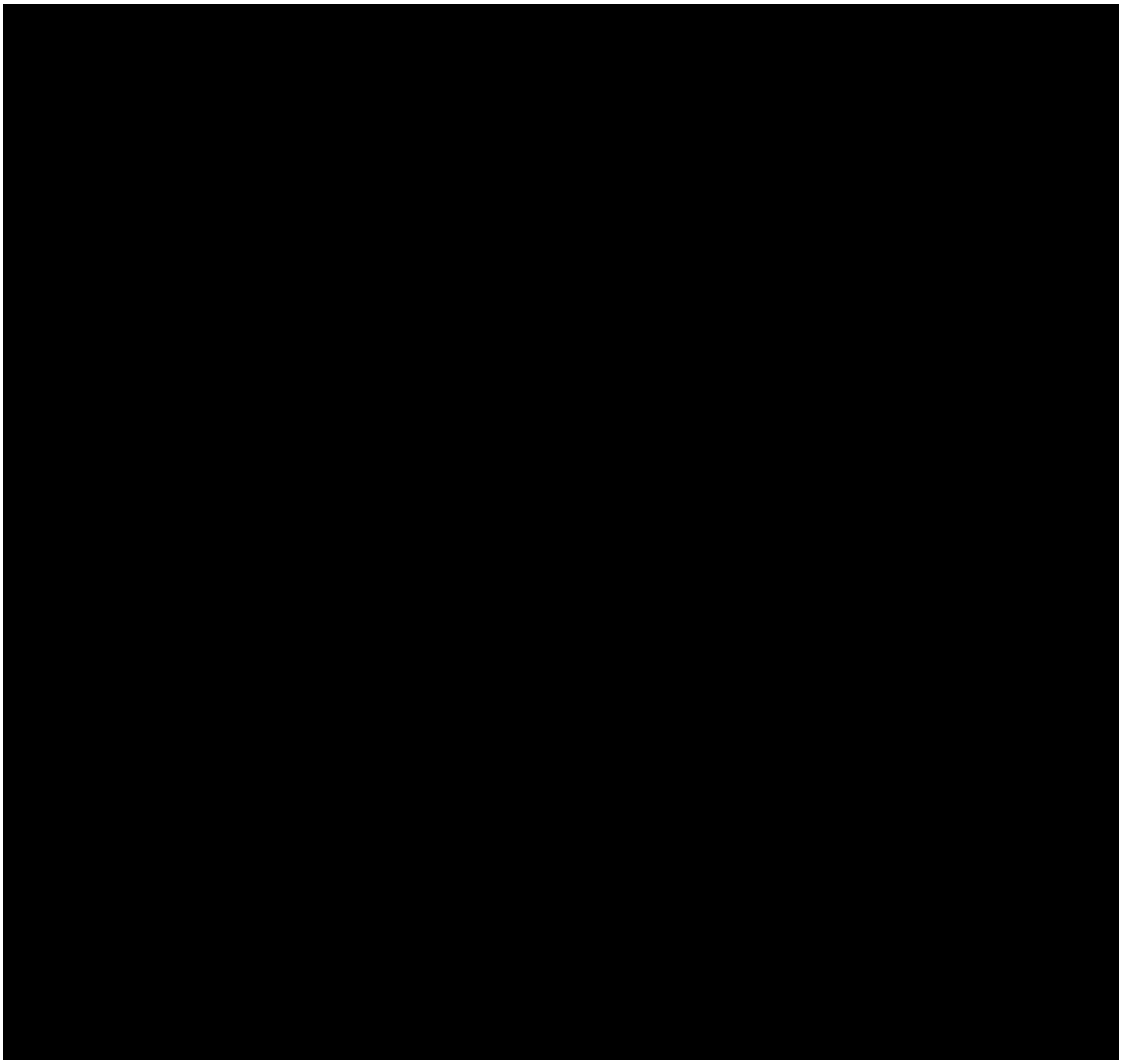


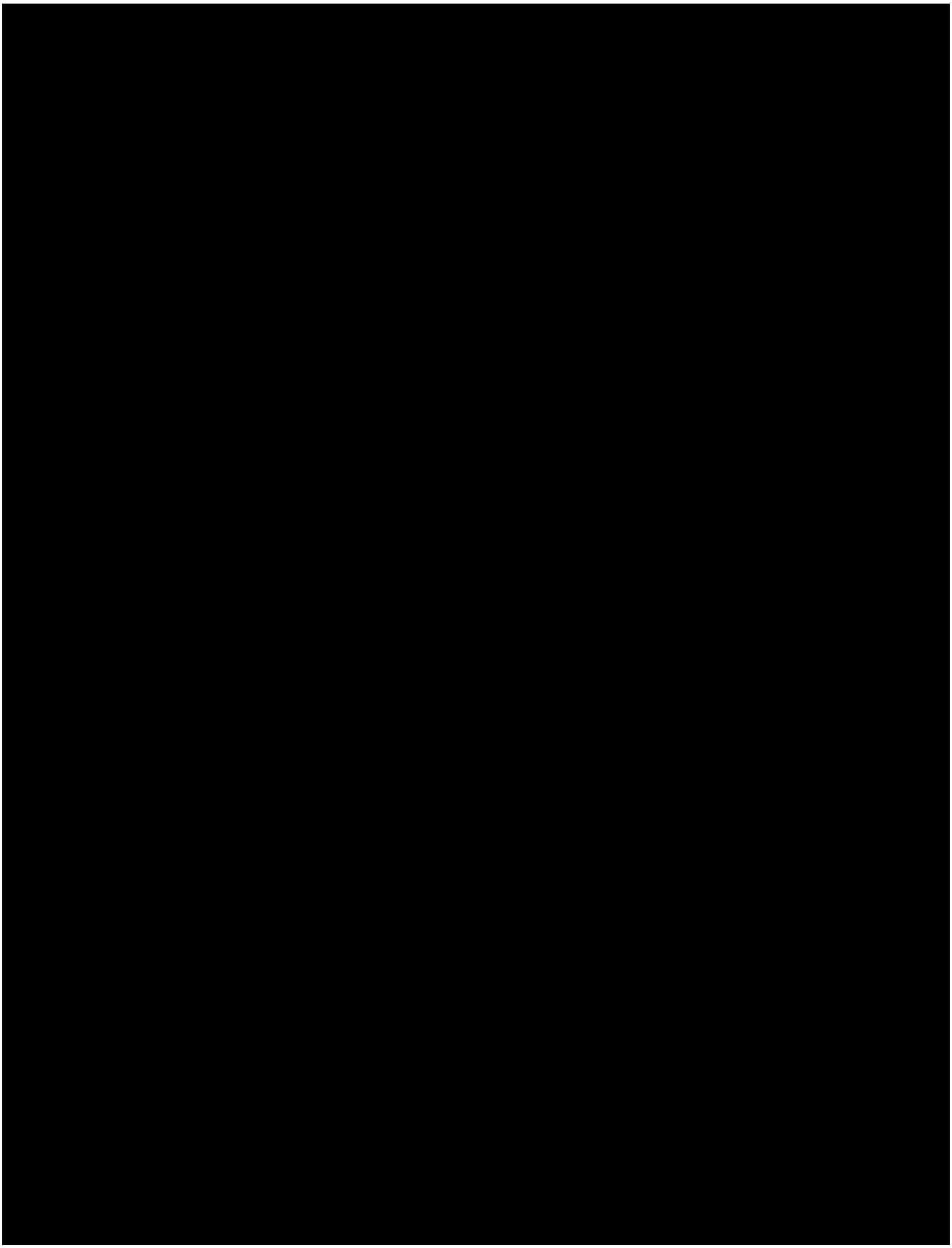












## APPENDIX 10 COMMON STRONG INHIBITORS OF BOTH CYTOCHROME P450 3A4 (CYP3A4) AND P-GLYCOPROTEIN (P-GP) (NOT ALL INCLUSIVE)[26]

Apixaban is hepatically metabolized by cytochrome P-450 3A4 (CYP3A4) and is a substrate for the efflux transporter P-glycoprotein (P-GP). Co-administration of drugs that are strong inhibitors of both CYP3A4 and P-GP can increase apixaban blood concentrations. Patients with renal insufficiency or of low body weight may be at increased risk of excessive anticoagulation due to CYP and P-gp drug interactions, and avoidance of certain drug combinations should be considered.

Examples of strong inhibitors of CYP3A4 are prohibited while subjects are on treatment with BMS-562247. Some examples of strong inhibitors of CYP3A4 are:

| | |
|---|---|
| Clarithromycin | nelfinavir |
| telithromycin | ritonavir |
| itraconazole | saquinavir |
| ketoconazole | indinavir |
| voriconazole | cobicistat |
| posaconazole | |

Strong inducers of P-gp and CYP3A4 are expected to decrease apixaban blood concentrations and can result in failure of therapeutic anticoagulant effect.

Examples of strong inducers of both CYP3A4 and P-gp are:

| | |
|---|---|
| Rifampin | phenytoin |
| carbamazepine | St. John's wort |

These lists are not meant to be all inclusive. Please consult individual drug labels for further information.

**Management suggestions:**

Avoid co-administration of strong inhibitors of both CYP3A4 and P-gp. Bleeding risk is expected to be further increased in patients with renal insufficiency, depending upon severity.

The efficacy of routine coagulation testing to evaluate the degree of anticoagulation with apixaban is limited.

Avoid co-administration of strong inducers of both CYP34 and P-gp.

# APPENDIX 11 COMMON NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) (NOT ALL INCLUSIVE)

## Over-the-Counter NSAIDS

| BRAND NAME | GENERIC NAME |
|---|---|
| Advil, Motrin | ibuprofen |
| Aleve | naproxen sodium |
| Ascriptin, Bayer, Ecotrin | aspirin |

## Prescription NSAIDS

| BRAND NAME | GENERIC NAME |
|---|---|
| Anaprox | naproxen sodium |
| Celebrex | celecoxib |
| Clinoril | sulindac |
| Daypro | oxaprozin |
| Disalcid | salsalate |
| Dolobid | diflunisal |
| Feldene | piroxicam |
| Indocin | indomethacin |
| Lodine | etodolac |
| Mobic | meloxicam |
| Naprosyn | naproxen |
| Relafen | nabumetone |
| Toradol | ketorolac tromethamine |
| Vimovo | naproxen/esomeprazole |
| Voltaren | diclofenac |

# APPENDIX 12 OUTLINE OF CHILDREN'S ONCOLOGY GROUP (COG) INDUCTION THERAPY PHASE IA

**Table 6: Outline of Children's Oncology Group (COG) Induction Therapy Phase IA**

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|---|---|---|---|
| Intrathecal Cytarabine (IT ARAC) | IT | Age (yrs) → Dose<br>1-1.99 → 30 mg<br>2-2.99 → 50 mg<br>≥ 3 → 70 mg | Given at time of diagnostic lumbar puncture (LP) OR Day 1[a] | Note age-based dosing |
| VinCRIStine (VCR) | IV push over 1 minute+ | 1.5 mg/m²/dose | Days 1, 8, 15 &22 | +Or infusion via minibag as per institutional policy<br>Maximum dose: 2 mg |
| Dexamethasone (DEX)<br>Patients < 10 years ONLY | PO<br>(may be given IV) | 5 mg/m²/dose BID | Days 1 - 14 | Total daily dose: 10 mg/m2/day, divided BID |
| PredniSONE (PRED)<br>Patients ≥ 10 years ONLY | PO<br>(may be given IV) | 30 mg/m²/dose BID | Days 1 - 28 | Total daily dose: 60 mg/m2/day, divided BID<br>Note: IV methylprednisolone may be substituted for oral predniSONE at 80% of the dose |
| DAUNOrubicin (DAUN) | IV push over 1-15 minutes | 25 mg/m²/dose | Days 1, 8, 15 & 22 | |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours | 2500 International Units/m² | Day 4 | Note: pegaspargase must be administered on Day 4.<br>Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) → Dose<br>1-1.99 → 8 mg<br>2-2.99 → 10 mg<br>3-8.99 → 12 mg<br>≥ 9 → 15 mg | Days 8 & 29<br>CNS3 also on Days 15 & 22 | Note age-based dosing |

[a] On Day 1 OR at the time of diagnostic lumbar puncture (LP) if < than 72 hours from the start of protocol therapy.

## APPENDIX 13 GFR ASSESSMENT

Inadequate renal function is defined as <30% of 1 standard deviation (SD) below normal GFR for age and size as determined by the Schwartz formula [eGFR (ml/min/1.73m2) = 0.413 * (height (cms)/serum creatinine (mg/dL). If serum creatinine concentration is measured in SI units (umoles/L), divide this number by the conversion factor of 88.4 to get the SI units (mg/dL) before inserting into the Schwartz formula to calculate eGFR.

**Table 7: GFR Assessment**

| Age (sex) | Normal GFR (for reference only. Not for study qualification) (Mean GFR ± SD) (mL/min/1.73m2) | GFR for study qualification[a] (Mean GFR) (mL/min/1.73m2) |
|---|---|---|
| 1 week (males and females) | 41 ± 15 | ≥ 8 |
| 2 - 8 weeks (males and females) | 66 ± 25 | ≥ 12 |
| > 8 weeks to < 2 years (males and females) | 96 ± 22 | ≥ 22 |
| 2 - 12 years (males and females) | 133 ± 27 | ≥ 30 |
| 13 - 17 years (males) | 140 ± 30 | ≥ 30 |
| 13 - 17 years (females) | 126 ± 22 | ≥ 30 |
| 1 week (males and females) | 41 ± 15 | ≥ 8 |
| 2 - 8 weeks (males and females) | 66 ± 25 | ≥ 12 |

[a] Patient may be enrolled if GFR is at or greater to this value as determined by Schwartz formula[27]

## APPENDIX 14 BLOOD PRESSURE (BP) LEVELS FOR GIRLS AND BOYS BY AGE AND HEIGHT PERCENTILE [28]

Instructions for using this BP Chart:

1) Measure the patient's blood pressure using an appropriate size cuff.
2) Select appropriate chart for a female or male patient.
3) Using the "age" row and "height" column determine if the BP is within the ULN.

## BP Levels for Boys by Age and Height Percentile

| Age, y | BP Percentile | SBP, mm Hg | | | | | | | DBP, mm Hg | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Percentile of Height | | | | | | | Percentile of Height | | | | | | |
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 80 | 81 | 83 | 85 | 87 | 88 | 89 | 34 | 35 | 36 | 37 | 38 | 39 | 39 |
| | 90th | 94 | 95 | 97 | 99 | 100 | 102 | 103 | 49 | 50 | 51 | 52 | 53 | 53 | 54 |
| | 95th | 98 | 99 | 101 | 103 | 104 | 106 | 106 | 54 | 54 | 55 | 56 | 57 | 58 | 58 |
| | 99th | 105 | 106 | 108 | 110 | 112 | 113 | 114 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| 2 | 50th | 84 | 85 | 87 | 88 | 90 | 92 | 92 | 39 | 40 | 41 | 42 | 43 | 44 | 44 |
| | 90th | 97 | 99 | 100 | 102 | 104 | 105 | 106 | 54 | 55 | 56 | 57 | 58 | 58 | 59 |
| | 95th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 99th | 109 | 110 | 111 | 113 | 115 | 117 | 117 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| 3 | 50th | 86 | 87 | 89 | 91 | 93 | 94 | 95 | 44 | 44 | 45 | 46 | 47 | 48 | 48 |
| | 90th | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95th | 104 | 105 | 107 | 109 | 110 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 99th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 71 | 71 | 72 | 73 | 74 | 75 | 75 |
| 4 | 50th | 88 | 89 | 91 | 93 | 95 | 96 | 97 | 47 | 48 | 49 | 50 | 51 | 51 | 52 |
| | 90th | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 63 | 64 | 65 | 66 | 66 | 67 |
| | 95th | 106 | 107 | 109 | 111 | 112 | 114 | 115 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| | 99th | 113 | 114 | 116 | 118 | 120 | 121 | 122 | 74 | 75 | 76 | 77 | 78 | 78 | 79 |
| 5 | 50th | 90 | 91 | 93 | 95 | 96 | 98 | 98 | 50 | 51 | 52 | 53 | 54 | 55 | 55 |
| | 90th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 65 | 66 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 99th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| 6 | 50th | 91 | 92 | 94 | 96 | 98 | 99 | 100 | 53 | 53 | 54 | 55 | 56 | 57 | 57 |
| | 90th | 105 | 106 | 108 | 110 | 111 | 113 | 113 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| | 99th | 116 | 117 | 119 | 121 | 123 | 124 | 125 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| 7 | 50th | 92 | 94 | 95 | 97 | 99 | 100 | 101 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| | 90th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 70 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 110 | 111 | 113 | 115 | 117 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 82 | 82 | 83 | 84 | 85 | 86 | 86 |
| 8 | 50th | 94 | 95 | 97 | 99 | 100 | 102 | 102 | 56 | 57 | 58 | 59 | 60 | 60 | 61 |
| | 90th | 107 | 109 | 110 | 112 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 75 | 76 |
| | 95th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 99th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 83 | 84 | 85 | 86 | 87 | 87 | 88 |
| 9 | 50th | 95 | 96 | 98 | 100 | 102 | 103 | 104 | 57 | 58 | 59 | 60 | 61 | 61 | 62 |
| | 90th | 109 | 110 | 112 | 114 | 115 | 117 | 118 | 72 | 73 | 74 | 75 | 76 | 76 | 77 |
| | 95th | 113 | 114 | 116 | 118 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 120 | 121 | 123 | 125 | 127 | 128 | 129 | 84 | 85 | 86 | 87 | 88 | 88 | 89 |
| 10 | 50th | 97 | 98 | 100 | 102 | 103 | 105 | 106 | 58 | 59 | 60 | 61 | 61 | 62 | 63 |
| | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 99th | 122 | 123 | 125 | 127 | 128 | 130 | 130 | 85 | 86 | 86 | 88 | 88 | 89 | 90 |
| 11 | 50th | 99 | 100 | 102 | 104 | 105 | 107 | 107 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 124 | 125 | 127 | 129 | 130 | 132 | 132 | 86 | 86 | 87 | 88 | 89 | 90 | 90 |
| 12 | 50th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 60 | 61 | 62 | 63 | 63 | 64 |
| | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 99th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 86 | 87 | 88 | 89 | 90 | 90 | 91 |
| 13 | 50th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 60 | 60 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 130 | 131 | 133 | 135 | 136 | 137 | 87 | 87 | 88 | 89 | 90 | 91 | 91 |
| 14 | 50th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 60 | 61 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 87 | 88 | 89 | 90 | 91 | 92 | 92 |
| 15 | 50th | 109 | 110 | 112 | 113 | 115 | 117 | 117 | 61 | 62 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 134 | 135 | 136 | 138 | 140 | 142 | 142 | 88 | 89 | 90 | 91 | 92 | 93 | 93 |
| 16 | 50th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| | 99th | 136 | 137 | 139 | 141 | 143 | 144 | 145 | 90 | 90 | 91 | 92 | 93 | 94 | 94 |
| 17 | 50th | 114 | 115 | 116 | 118 | 120 | 121 | 122 | 65 | 66 | 66 | 67 | 68 | 69 | 70 |
| | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |
| | 99th | 139 | 140 | 141 | 143 | 145 | 146 | 147 | 92 | 93 | 93 | 94 | 95 | 96 | 97 |

The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for boys with height percentiles given in Table 3 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645, and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

## BP Levels for Girls by Age and Height Percentile

| Age, y | BP Percentile | SBP, mm Hg | | | | | | | DBP, mm Hg | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Percentile of Height | | | | | | | Percentile of Height | | | | | | |
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 83 | 84 | 85 | 86 | 88 | 89 | 90 | 38 | 39 | 39 | 40 | 41 | 41 | 42 |
| | 90th | 97 | 97 | 98 | 100 | 101 | 102 | 103 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 95th | 100 | 101 | 102 | 104 | 105 | 106 | 107 | 56 | 57 | 57 | 58 | 59 | 59 | 60 |
| | 99th | 108 | 108 | 109 | 111 | 112 | 113 | 114 | 64 | 64 | 65 | 65 | 66 | 67 | 67 |
| 2 | 50th | 85 | 85 | 87 | 88 | 89 | 91 | 91 | 43 | 44 | 44 | 45 | 46 | 46 | 47 |
| | 90th | 98 | 99 | 100 | 101 | 103 | 104 | 105 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 99th | 109 | 110 | 111 | 112 | 114 | 115 | 116 | 69 | 69 | 70 | 70 | 71 | 72 | 72 |
| 3 | 50th | 86 | 87 | 88 | 89 | 91 | 92 | 93 | 47 | 48 | 48 | 49 | 50 | 50 | 51 |
| | 90th | 100 | 100 | 102 | 103 | 104 | 106 | 106 | 61 | 62 | 62 | 63 | 64 | 64 | 65 |
| | 95th | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| | 99th | 111 | 111 | 113 | 114 | 115 | 116 | 117 | 73 | 73 | 74 | 74 | 75 | 76 | 76 |
| 4 | 50th | 88 | 88 | 90 | 91 | 92 | 94 | 94 | 50 | 50 | 51 | 52 | 52 | 53 | 54 |
| | 90th | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 64 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th | 105 | 106 | 107 | 108 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 71 | 72 |
| | 99th | 112 | 113 | 114 | 115 | 117 | 118 | 119 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| 5 | 50th | 89 | 90 | 91 | 93 | 94 | 95 | 96 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 90th | 103 | 103 | 105 | 106 | 107 | 109 | 109 | 66 | 67 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 70 | 71 | 71 | 72 | 73 | 73 | 74 |
| | 99th | 114 | 114 | 116 | 117 | 118 | 120 | 120 | 78 | 78 | 79 | 79 | 80 | 81 | 81 |
| 6 | 50th | 91 | 92 | 93 | 94 | 96 | 97 | 98 | 54 | 54 | 55 | 56 | 56 | 57 | 58 |
| | 90th | 104 | 105 | 106 | 108 | 109 | 110 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 72 | 72 | 73 | 74 | 74 | 75 | 76 |
| | 99th | 115 | 116 | 117 | 119 | 120 | 121 | 122 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| 7 | 50th | 93 | 93 | 95 | 96 | 97 | 99 | 99 | 55 | 56 | 56 | 57 | 58 | 58 | 59 |
| | 90th | 106 | 107 | 108 | 109 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 116 | 73 | 74 | 74 | 75 | 76 | 76 | 77 |
| | 99th | 117 | 118 | 119 | 120 | 122 | 123 | 124 | 81 | 81 | 82 | 82 | 83 | 84 | 84 |
| 8 | 50th | 95 | 95 | 96 | 98 | 99 | 100 | 101 | 57 | 57 | 57 | 58 | 59 | 60 | 60 |
| | 90th | 108 | 109 | 110 | 111 | 113 | 114 | 114 | 71 | 71 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 99th | 119 | 120 | 121 | 122 | 123 | 125 | 125 | 82 | 82 | 83 | 83 | 84 | 85 | 86 |
| 9 | 50th | 96 | 97 | 98 | 100 | 101 | 102 | 103 | 58 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 90th | 110 | 110 | 112 | 113 | 114 | 116 | 116 | 72 | 72 | 72 | 73 | 74 | 75 | 75 |
| | 95th | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 99th | 121 | 121 | 123 | 124 | 125 | 127 | 127 | 83 | 83 | 84 | 84 | 85 | 86 | 87 |
| 10 | 50th | 98 | 99 | 100 | 102 | 103 | 104 | 105 | 59 | 59 | 59 | 60 | 61 | 62 | 62 |
| | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 99th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 84 | 84 | 85 | 86 | 86 | 87 | 88 |
| 11 | 50th | 100 | 101 | 102 | 103 | 105 | 106 | 107 | 60 | 60 | 60 | 61 | 62 | 63 | 63 |
| | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 99th | 125 | 125 | 126 | 128 | 129 | 130 | 131 | 85 | 85 | 86 | 87 | 87 | 88 | 89 |
| 12 | 50th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 61 | 61 | 62 | 63 | 64 | 64 |
| | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 99th | 127 | 127 | 128 | 130 | 131 | 132 | 133 | 86 | 86 | 87 | 88 | 88 | 89 | 90 |
| 13 | 50th | 104 | 105 | 106 | 107 | 109 | 110 | 110 | 62 | 62 | 62 | 63 | 64 | 65 | 65 |
| | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| | 99th | 128 | 129 | 130 | 132 | 133 | 134 | 135 | 87 | 87 | 88 | 89 | 89 | 90 | 91 |
| 14 | 50th | 106 | 106 | 107 | 109 | 110 | 111 | 112 | 63 | 63 | 63 | 64 | 65 | 66 | 66 |
| | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| | 99th | 130 | 131 | 132 | 133 | 135 | 136 | 136 | 88 | 88 | 89 | 90 | 90 | 91 | 92 |
| 15 | 50th | 107 | 108 | 109 | 110 | 111 | 113 | 113 | 64 | 64 | 64 | 65 | 66 | 67 | 67 |
| | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| | 99th | 131 | 132 | 133 | 134 | 136 | 137 | 138 | 89 | 89 | 90 | 91 | 91 | 92 | 93 |
| 16 | 50th | 108 | 108 | 110 | 111 | 112 | 114 | 114 | 64 | 64 | 65 | 66 | 66 | 67 | 68 |
| | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 132 | 133 | 134 | 135 | 137 | 138 | 139 | 90 | 90 | 90 | 91 | 92 | 93 | 93 |
| 17 | 50th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 64 | 65 | 65 | 66 | 67 | 67 | 68 |
| | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |
| | 99th | 133 | 133 | 134 | 136 | 137 | 138 | 139 | 90 | 90 | 91 | 91 | 92 | 93 | 93 |

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for girls with height percentiles given in Table 4 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645 and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

# APPENDIX 15 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

## DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

### Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

## CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception (highly effective and/or less than highly effective) listed below is required during study duration and for 30 days after treatment has been discontinued.

Local laws and regulations may require use of alternative and/or additional contraception methods.

| **Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of <1% per year when used consistently and correctly.*[a] |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation (These methods of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b]<br>– oral (birth control pills)<br>– intravaginal (vaginal birth control suppositories, rings, creams, gels)<br>– transdermal |
| • Progestogen-only hormonal contraception associated with inhibition of ovulation[b]<br>– oral<br>– injectable |
| **Highly Effective Methods That Are User Independent** |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited)[b]<br>• Intrauterine device (IUD)[c]<br>• Intrauterine hormone-releasing system (IUS) (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited) [b,c]<br>• Bilateral tubal occlusion |
| • Vasectomized partner<br>*A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* |
| • Sexual abstinence<br>*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 treatment. 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.*<br>• It is not necessary to use any other method of contraception when complete abstinence is elected.<br>• WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2.<br>• Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence |

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

| **Less Than Highly Effective Contraceptive Methods That Are User Dependent**<br>*Failure rate of >1% per year when used consistently and correctly.* |
|---|
| • Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously<br>• Diaphragm with spermicide<br>• Cervical cap with spermicide<br>• Vaginal Sponge with spermicide<br>• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited) |
| **Unacceptable Methods of Contraception** |
| • Periodic abstinence (calendar, symptothermal, post-ovulation methods)<br>• Withdrawal(coitus interruptus).<br>• Spermicide only<br>• Lactation amenorrhea method (LAM) |

## CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.

No additional contraceptive measures are required to be used.

## COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 6.4 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting