Official Title of Study:

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

PROTOCOL(S) CV185-155

NCT Number: NCT02369653

Document Date (Date in which document was last revised): March 02, 2021

STATISTICAL ANALYSIS PLAN

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

PROTOCOL(S) CV185155

DATE: 02-MAR-2021

VERSION # 4.0

TABLE OF CONTENTS

[redacted]

1 BACKGROUND [redacted]

[redacted]

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.

Schedule of Analyses:

The final analyses for the study will be performed after all subjects either complete the study treatment period followed by a 6-day follow up period, or discontinue prematurely.

2 STUDY DESCRIPTION

Children and adolescents aged 1-18 years 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.

2.1 Study Design

The study is designed to compare the effect of prophylactic apixaban versus no administration of systemic prophylactic anticoagulant during planned 3-4 drug systemic induction chemotherapy, on the composite endpoint of adjudicated non-fatal asymptomatic and symptomatic VTE and VTE-related death during approximately 28 days of open-label treatment 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 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
- 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, use of 2.5-mg or 0.5-mg tablets is encouraged. Subjects <5 years and <35 kg may be administrated 0.5 mg tablets only Switching formulations during the course of the study is not encouraged but is allowed.
- a 6 - day (± 5 days) follow-up period starting the day after the Day 29 ± 5 days of 3-4 drug systemic induction chemotherapy

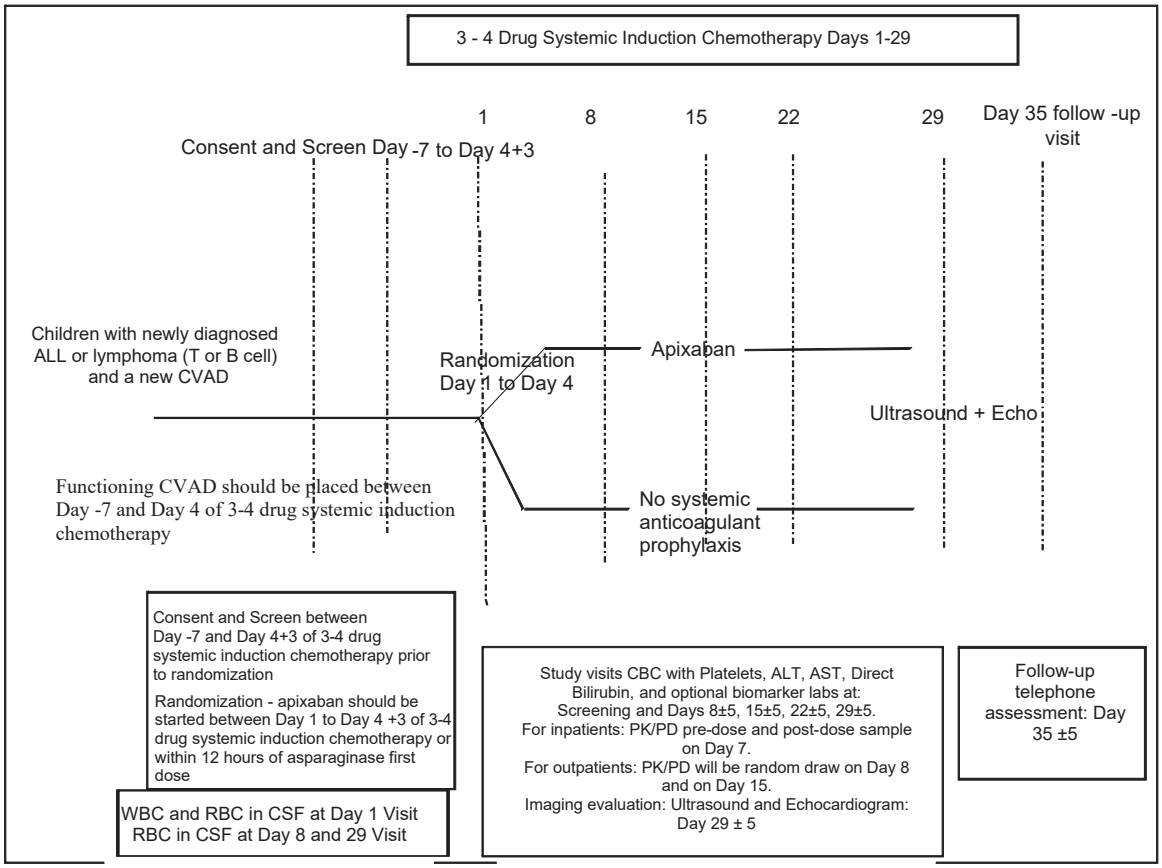
Subjects 1 to <18 years of age will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range as per Figure 2.1-1.

Table 2.1-1: 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 study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: CV185155 Study Schematic



2.2 Treatment Assignment

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 prophylactic anticoagulation) 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.

[redacted]

2.4 Protocol Amendments

There were 5 protocol Amendments, and the summaries of major changes for each Amendment are presented in Table 2.4-1 below:

Table 2.4-1: CV185155 Protocol Changes

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 • 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 included in the Written Request filed with the FDA
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

Table 2.4-1: CV185155 Protocol Changes

Document	Date of Issue	Summary of Change
		Changed apixaban dosing scheme from a mg/kg dosing to a fixed-dose, body weight-tiered regimen Introduced the 0.5 mg tablet with dosing instructions and development rationale Clarified that the first dose of apixaban should began no later than 12 hours after the first dose of asparaginase Changed enrollment to include children ≥ 1 and < 18 years of age and ≥ 6 kg of weight 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 Indicated that children weighing between 9 and < 12 kg cannot be enrolled in the study until appropriate apixaban formulation/dose available Increased the window of visits from 3 days to 5 days 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 Indicated that Grade 1-2 chemotherapy induced neutropenia or hospitalization for the possibility of neutropenia do not have to be collected as adverse events 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 Clarified that the secondary endpoint of CVST included both fatal and non-fatal CVST Added to Secondary endpoints apixaban pharmacokinetics and anti-FXa activity [redacted] Increased the window of when the central venous catheter is inserted to Day -7 to Day 4 of when induction chemotherapy is started Clarified that subjects randomized to apixaban should begin apixaban treatment following randomization and before they start PEG 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

Table 2.4-1: CV185155 Protocol Changes

Document	Date of Issue	Summary of Change
		ultrasound and echocardiogram until Day 29 and should continue with the study treatment
		Allowed subjects to be enrolled who will have the administration of more than one dose of PEG-L asparaginase during the induction chemotherapy
		Allowed subjects to be enrolled who have a mixed-phenotype acute leukemia (MPAL) who will be treated with the COG ALL induction chemotherapy
		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
		Clarified that subjects with a total bilirubin ≤ 2XULN can be enrolled
		Clarified that subjects with an INR >1.4 can't be enrolled
		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
		Clarified that the screening period would be between Day -7 to Day 4 of induction chemotherapy
		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
		Excluded subjects with a risk of bleeding such as hemophilia and von Willebrand disease, etc
		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
		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
		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
		[redacted]
		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

Table 2.4-1: CV185155 Protocol Changes

Document	Date of Issue	Summary of Change
		Removed surveillance of subject contraception 1 month prior to dosing 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 Indicated that SAEs need to be collected up to 30 days after the last dose of study medication [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
Revised Protocol 02	14-Aug-2015	Incorporates Amendment 02
Amendment 02	14-Aug-2015	Dose adjustment [redacted] The age of subjects eligible for enrollment has been expanded to include children 2 to 18 years of age Clarified the study procedures that should be followed if a catheter is lost or replaced and planned replacements of the catheter is allowed Removed exclusion criteria of Central Nervous Status 3 and replaced with LP's > 3 over the course of the treatment period Clarified the exclusion criteria of 'Major Surgery' Clarified the timing of performing the radiographic imaging Aligned the Secondary safety endpoint and other safety endpoints with the Objectives Added to Exclusion Criteria the administration of any investigational drug including multiple doses of PEG-L asparaginase Added to Prohibited Therapies the chronic daily use of nonsteroidal anti-inflammatory drugs more than 7 days 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. To clearly define the time period around discontinuing apixaban prior to the lumbar punctures. To clearly define the exclusion criteria of uncontrolled severe hypertension at enrollment using the age, height and gender adjusted standard.

Table 2.4-1: CV185155 Protocol Changes

Document	Date of Issue	Summary of Change
Original Protocol	12-Dec-2014	Not applicable

2.5 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.

3 OBJECTIVES

3.1 Primary

- 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.

3.2 Secondary

- To assess the effect of prophylactic oral or enteric 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 oral or enteric 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.

[redacted]

[redacted]

4 ENDPOINTS

4.1 Primary Endpoints

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 that 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 (i.e., 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.

4.2 Secondary Endpoints

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

CRNM bleeding is defined as bleeding that satisfies one or both of the following:

1) overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition and
2) 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]

4.4 Pharmacokinetics

PPK, PK-AXA relationship, and exposure-response (safety/efficacy) relationship will be assessed as data permit.

5 SAMPLE SIZE AND POWER

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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The term "**Intended Treatment Period**" will refer to the period from day of randomization through Day 29 visit. This period will be the basis for the summaries of efficacy.

The term "**Treatment Period**" will refer to the period from the day of randomization through the end of treatment Day 29 visit or early discontinuation from study (whichever comes first).

The term "**On-treatment Period**" will refer to the period from the day of first dose through the last dose of study medication. This period will be the basis for the summaries of apixaban safety only, because only the apixaban arm will have dose information.

The term "**Follow-up Period**" will refer to the period starting the day after the Day 29 visit or early discontinuation to Day 35 days visit.

6.2 Treatment Regimens

Subjects will be randomly assigned by the IVRS to either apixaban twice daily (see Table 2.1-1) or standard care (control) group. Apixaban will be provided by Bristol-Myers Squibb and is described in Table 6.2-1.

Table 6.2-1: 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 (In study CV185-155 not to be used in children < 5 years of age)	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.

6.3 Populations for Analyses

The following population will be used for the 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 ITT Population will be used for 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.

The relevant protocol deviations, used to determine exclusions, are listed in Section 7.2.

Safety Population

The safety population for safety endpoints includes all randomized subjects, since there is no intervention on top of standard of care in the control arm. Additional analyses will be performed for subjects treated with apixaban.

Pharmacokinetic (PK) Population

The analysis population for pharmacokinetic assessments will include subjects who have received at least one dose of apixaban and have a pharmacokinetic sample collected.

Pharmacodynamics (PD) Population

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.

Subgroup Populations

Table 6.3-1 shows the subpopulations of interest for analyses of efficacy and bleeding.

Table 6.3-1: Subgroups of Interest for Efficacy and Bleeding Assessments

Grouping Variable	Subgroups
Geographic region	North America Europe Latin America Asia/Pacific
Age (stratification variable)	< 10 years old ≥10 to < 18 years old
Age category	Young Children 1 year to <2 years Young Children 2 years to 6 years Children 6 years to <12 years Adolescents 12 years to <18 years
Ethnicity	Hispanic/Latino

Table 6.3-1: Subgroups of Interest for Efficacy and Bleeding Assessments

Grouping Variable	Subgroups
	Not Hispanic/Latino
Gender	Male Female
Race	White Black / African American Asian Other
Weight	< 35 kg ≥35 kg
Obesity	Non-obese (less than the 95th percentile of *age- and sex-specific BMI*)* Obese (Equal to or greater than the 95th percentile of *age- and sex-specific BMI*)*
ALL risk	Standard risk (WBC count less than 50,000/μL and age 1 to younger than 10 years) High risk (WBC count 50,000/μL or greater and/or age 10 years or older)
Central line	Peripherally inserted central catheters (PICC) lines All tunneled lines (including totally implanted devices/ports) All others ("non-tunneled line" and "other" from below, which will likely number 0 or at least a very small number of patients)

* *The definition that is based on Central for Disease Control and Prevention criteria*

7 STATISTICAL ANALYSES

SAS® version 9 or higher will be used for statistical analyses, tabulations and graphical presentations.

7.1 General Methods

Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Descriptive summaries for categorical variables will utilize counts and percentages.

Adverse events will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Adverse events will be summarized according to the MedDRA coded Preferred Terms (PT) by System Organ Class (SOC). Previous and concomitant medications will be coded using the WHO Drug Dictionary version.

Unless otherwise specified, baseline is defined as the last non-missing result with a collection date-time prior to the date-time of the randomization.

Testing for Treatment by Subpopulation Interaction

For efficacy subgroup analyses, Wald's chi-square test will be used to test whether treatment has a statistically significantly different ($p<0.1$) effect on the event rate of an endpoint across subgroups (e.g. male, female) based on a logistic model with terms for treatment, stratification variable age, subpopulation, and treatment by subpopulation interaction.

7.2 Study Conduct

7.2.1 Protocol Deviations

Subjects who deviate from protocol conditions (e.g., important inclusion/exclusion criteria) will be reported as having important protocol deviations. Important protocol deviations that are determined to affect the primary efficacy results are deemed Relevant Protocol Deviations. Relevant protocol deviations will be identified for all subjects who are randomized. Relevant Protocol Deviation Criteria are as follows:

- Subject randomized to apixaban group but not dosed with apixaban for > 3 consecutive days (excluding protocol defined interruptions)
- Error in treatment assignment resulting in a subject being dosed with an incorrect treatment for > 3 consecutive days
- Randomized subjects without a functioning CVAD placed between Day -7 and Day 4±3 of induction chemotherapy
- Randomized subjects with a prior history of documented DVT or PE in the past 3 months
- Randomized subjects with known inherited bleeding disorder or coagulopathy
- Prohibited and/or Restricted Treatments during study period
  - Any anti-platelet therapy with aspirin or thienopyridines such as clopidogrel, ticagrelor, or prasugrel.
  - 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.
  - 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.
  - 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 consecutive days is prohibited.

7.2.2 Coronavirus (Covid-19)

Focused summaries, as well as listings will be provided for the number and percent of participants affected by Covid-19 for the following areas:

Disposition: The number and percent of participants who were not randomized, prematurely discontinued study drug, or prematurely withdrew from the study (See Section 7.3.1) will also be summarized by the combination of primary reason for not being randomized, prematurely discontinued study drug, or prematurely withdrawn from the study and whether these reasons were Covid-19 related. Covid-19 related status events will also be listed.

Study Visits: Study visits not performed, or performed using an alternate method than specified in the protocol will be listed.

Imaging Not Performed: Reasons for not obtaining an image will be summarized, including whether the reason involved Covid-19. Missing data will be handled in the manner specified in Section 7.5.

Adverse Events: Covid-19 event will be treated as an event of interest. The number and percent of participants with a Covid-19 event will be summarized by SOC and preferred term (See Section 7.6), as well as listed.

Additional subset analyses may be performed excluding participant data affected by Covid-19, if the effect exceeds 10% of the study population.

7.3 Study Population

7.3.1 Subject Disposition

The number of subjects enrolled into the study, and the number of subjects enrolled but not randomized together with the reasons for not being randomized will be summarized. The reasons for not being randomized will be taken from the CRF pre-randomization status page.

The summaries described below will also be presented by age stratum when applicable.

The number of randomized subjects and the number of subjects discontinuing during each study period together with the reasons for discontinuation will be summarized by treatment group. The reasons for discontinuation will be taken from the end-of-treatment and the end-of-follow-up status pages of the CRF.

The frequency of subjects randomized in each country and in each region will be tabulated by randomized treatment group and for all randomized subjects combined.

7.3.2 Demography and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by randomized treatment group and for all subjects combined. Continuous variables will be summarized using mean and standard deviation. Categorical variables will be summarized using counts and percentages.

- Geographic region
- Country
- Age
- Age group (<10, 10≤18 years old)
- Gender

- Race
- Ethnicity
- Weight
- Weight group (<35, ≥35 kg)
- Height
- Platelet count
- Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate)
- Level of renal impairment (severe, moderate, mild, normal)

The summaries will be presented for the randomized/ITT population. All summaries will be further tabulated by age stratum.

In addition, medical history will be summarized for the randomized/ITT population.

Any imbalances between the treatment groups will be assessed in reviewing the summaries and any differences deemed clinically relevant to the efficacy or safety comparisons may be investigated by controlling for the characteristic in a supplemental analysis.

7.4 Extent of Exposure

7.4.1 Study Therapy

Extent of exposure to the study drug is defined as the number of days from first treatment to last treatment (date of last treatment - date of first treatment + 1). Summary of exposure to study drug will show the distribution of the number of days on drug together with the mean days of exposure, for the apixaban treatment group. Additionally, the extent of exposure will be summarized excluding any interruptions.

Treatment compliance (TC) will also be summarized for apixaban treatment group.

For each subject in the apixaban treatment group, treatment compliance (TC) with apixaban is defined as follows.

$$TC = \frac{number\ of\ doses\ taken\ (tablets\ or\ oral\ solution)}{(last\ dose\ date - first\ dose\ date + 1 - I)\ x\ 2 - k + R}\ x\ 100\%, \text{ where}$$

k=0, if two doses are given on the first day of apixaban

k=1, if one dose is given on the first day of apixaban

R: number of doses needed to be retaken because of the regurgitation, and

I: total number of days study drug was interrupted with a **protocol-defined** interruption.

Regarding protocol-defined interruptions, the number of days from first to last dose of apixaban will exclude the days that subjects have protocol defined dose interruption such as planned lumbar puncture, for conservative side, 2 days will be excluded for one planned lumbar puncture, and 3 days will be excluded for one traumatic lumbar puncture.

Extent of exposure to the study drug will be further tabulated by age stratum.

7.4.2 Concomitant Medications

The frequency of subjects receiving concomitant medications after randomization will be summarized by treatment group, medication class and drug name, using the randomized/ITT population.

7.5 Efficacy

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.

7.5.1 Primary Efficacy Analysis

The primary objective is compare the effect of prophylactic oral or enteric apixaban versus no administration of systemic prophylactic anticoagulant during induction chemotherapy, on the composite endpoint of adjudicated non-fatal asymptomatic and symptomatic DVT, pulmonary embolism (PE), and CVST; and VTE-related-death during intended treatment period.

To conclude superiority of apixaban versus standard care on the primary efficacy endpoint during intended treatment period, the upper bound of the two-sided 95% CI for the relative risk (p_a/ p_e) must be less than 1. This condition corresponds to a test of hypothesis H_0: $p_a = p_e$ against the alternative H_a: $p_a < p_e$ using the Mantel-Haenszel test stratified by age group (<10 years or ≥10 to <18 years) performed at the one-sided $\alpha = 0.025$ level. Here p_a and p_e represent the proportions of subjects with primary efficacy endpoints in the apixaban and standard care groups, respectively.

Two-sided 95% CI for the relative risk (p_a/p_e) will be reported for the primary efficacy endpoint. The p-value associated with the superiority test will also be reported.

The primary efficacy analyses will be performed based on the randomized/ITT population. Subjects with no symptomatic event and no ultrasound or echocardiogram assessment will be counted as not having an event.

7.5.1.1 Sensitivity Analyses for Primary Efficacy Endpoint

In order to assess the robustness of the effectiveness of apixaban relative to standard care, the following sensitivity analyses will be performed for the primary efficacy 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.

7.5.2 Secondary Efficacy Analysis

The key secondary objective is to assess the effect of prophylactic apixaban versus no administration of systemic prophylactic anticoagulant during induction chemotherapy, on single adjudicated endpoints of non-fatal asymptomatic DVT, symptomatic DVT, PE, and CVST; and VTE-related-death during intended treatment period.

Two-sided 95% CI for the relative risk (p_a/p_e) will be reported for the key secondary efficacy endpoint. The nominal p-value associated with the tests will also be reported.

[redacted]

7.5.4 Subgroup Analysis

Rates for the primary efficacy endpoint will also be summarized by treatment group and subgroups listed in Table Table 6.3-1. Ninety-five percent (95%) CIs for the ratio of event rates will be computed based on Mantel-Haenszel's method stratified by the stratification factor(s) as applicable

The analyses will be performed using events occurring during the Intended Treatment Period and for the Primary endpoint (when summarizing the primary efficacy endpoint). If the value of the

grouping variable cannot be determined for a subject, the subject will be excluded from the corresponding subgroup analysis. For each subpopulation analysis, if, in any treatment group, the number of subjects is ≤10 for a subgroup, then the grouping variable will not be included in the test of treatment by subpopulation interaction.

[redacted]

7.6 Safety

Safety presentations will be based on the Safety Population during the Treatment Period. In addition to the analyses and summaries based on the Treatment Period, the analyses and summaries for bleeding outcomes, AEs, SAEs, SAEs with death outcome, AEs leading to discontinuation, events of special interest, elevations in liver function tests (LFTs), and decreases in platelet counts will also be performed based on the On-Treatment period for apixaban treated subjects only.

For analyses of events during the Treatment Period, non-serious adverse events will be included in analyses if their onset occurs during the Treatment Period, or within 2 days after the end of the Treatment Period. Serious adverse events will be included in analyses if their onset occurs during the Treatment Period, or within 30 days after the end of the Treatment Period. For analyses of events during the On-treatment Period, events will be included if they occur during the On-treatment period, or within 2 days (non SAE) or 30 days (SAE) after the end of the On-treatment period. All events will be listed.

7.6.1 Bleeding Events

7.6.1.1 Bleeding Endpoints

For the primary safety endpoint (major bleeding) and the secondary safety endpoint (composite of major bleeding and CRNMB) during the treatment period, the 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 α=0.025 level. Construction of CIs for single event rates will be based on the Agresti Coull method.

All confirmed bleeding events will be listed, indicating the subject id, treatment group, age, gender, race, date of last dose of study drug prior to event and day of event relative to start of dosing.

7.6.1.2 Other Bleeding Related Safety Endpoints

For the CRNMB and minor bleeding during treatment period, event rate, 95% CI for event rate, relative risk, 95% CI for relative risk and nominal p-value will be displayed.

Number of platelet transfusions needed during the study will be summarized, and summary statistics including number and percentage will be presented by treatment group.

All bleeding events will be listed, including the subject id, treatment group, age, gender, race, event type, and reported event date.

7.6.2 Adverse Events

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). Listings and summaries will be based on the resulting SOCs and PTs.

The incidence of bleeding-related AEs during the Treatment Period will be summarized by SOC, PT and treatment group.

All reported AEs and SAEs will be listed, indicating the subject id, treatment group, age, gender, race, day of onset relative to start of dosing, resolution date, investigator-assessment of relationship to study drug, investigator-assessment of intensity of event, action taken regarding study drug and whether treatment was required for the event.

Summary information (the number and percentage of subjects) regarding AEs (for serious and non-serious events) will be tabulated by SOC, PT and treatment group for:

- all events
- deaths
- related events
- all events categorized by intensity

The frequency of subjects discontinuing study drug due to AEs will be tabulated by SOC, PT and treatment group.

Most common AEs (reported in more than 5% of subjects in any treatment group) will also be summarized by PT and treatment group.

Laboratory AEs are laboratory results identified by the Investigator as AEs and thus reported on the AE pages of the CRF. Any such AE occurring during the Treatment Period will be included in the respective AE summaries.

7.6.3 Laboratory Data

The frequency of subjects with laboratory marked abnormalities (MAs) during the Treatment Period based on pre-specified criteria will be tabulated by treatment group, for each analyte.

Laboratory measurements (for liver function only) and their changes from baseline will be summarized at baseline and at the end of study by treatment group.

Shift analysis will be performed to evaluate qualitative changes that occurred during the Treatment Period. Shift tables (for liver function only) will display, by treatment group, the frequency of subjects with the following combination of values at baseline and during the Treatment Period:

- no change (low to low: L-L, normal to normal: N-N, high to high: H-H)
- abnormal to normal (low to normal: L-N, high to normal: H-N)
- normal to abnormal (normal to low: N-L, normal to high: N-H)
- abnormal to abnormal (low to high: L-H, high to low: H-L),

where low refers to values that are <LLN, high refers to values that are >ULN and normal refers to values in-between the normal limits. Two sets of shift tables will be presented:

- one for labs with MA criteria based on high values (regardless of whether the MA criteria also considers low values) - the post-dose value considered for the tabulation will be the largest value obtained during the Treatment Period;
- another for labs with MA criteria based on low values (regardless of whether the MA criteria also considers high values) - the post-dose value considered for the tabulation will be the smallest value obtained during the Treatment Period.

In addition, liver-related elevations and discontinuations will be tabulated by treatment group. The tabulation will include the number and proportion of subjects with

- post-dose elevation of AT >3 ×ULN (AT refers to either one of ALT or AST)
- post-dose elevation of AT >5 ×ULN
- post-dose elevation of AT >10 ×ULN
- post-dose elevation of AT >20 ×ULN
- post-dose elevation of conjugated bilirubin >2 ×ULN
- post-dose elevation of AT >3 ×ULN and conjugated bilirubin >2 ×ULN on the same date
- Liver-related discontinuations

The number and proportion of subjects with post-dose elevations of AST, ALT, conjugated bilirubin, ALP, or CK will also be tabulated by treatment group including:

- AST elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- AST or ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN
- both AST and ALT elevations >3×ULN, >5×ULN, >10×ULN, or >20×ULN on the same date
- ALP elevations >2×ULN
- CK >10×ULN

Similar tabulations for the number and proportion of subjects with elevations of AST, ALT, total bilirubin, ALP, or CK as described in the previous paragraph will be presented by treatment group and by nominal visit (including baseline).

The following considerations apply to all liver-related laboratory tabulations described above:

- AT elevation refers to ALT or AST elevations regardless of whether they occurred concomitantly
- elevations will be counted if they occur during the Treatment Period; Only values that meet the criteria and are larger than the baseline value will be included in the tabulations. If baseline

value is missing then all values for that particular lab that meet the criteria will be included in the tabulations.

- values will be counted towards the categories of "AST and ALT elevations", or "AT and Total Bilirubin elevation" if both AST and ALT or both AT and Total Bilirubin, respectively, meet the criteria and at least one of the values in the component is larger than the baseline value.
- values will be counted towards the categories of "AST or ALT elevations" if either AST meets the criteria and is larger than the AST baseline value or ALT meets the criteria and is larger than the ALT baseline value.
- For each subject and lab or lab combination, the largest value measured during the Treatment Period will be counted for the Treatment Period summaries that do not take nominal visit into consideration
- For each subject and lab or lab combination, the largest value measured within each visit window during the Treatment Period will be counted for the summaries by nominal visit.

The number and proportion of subjects with decreased platelet counts to <20,000/mm^3 will be tabulated by treatment group and by nominal visit (including baseline) and by treatment group for all measurements during the Treatment Period. The following considerations apply to these summaries:

- decreases will be counted if they occur during the Treatment Period; only platelet counts that meet the criteria and are smaller than the baseline count will be included in the tabulations. If baseline value is missing then all platelet counts that meet the criteria will be included in the tabulations
- for each subject, the smallest platelet count obtained during the Treatment Period will be counted for the Treatment Period summaries that do not take nominal visit into consideration
- for each subject, the smallest platelet count obtained within each visit window during the Treatment Period will be counted for the summaries by nominal visit.

7.6.4 Vital Signs

Individual vital sign measurements (systolic BP, diastolic BP and heart rate) will be listed.

7.7 Pharmacokinetics

Analyses of PK data will be performed using the PK dataset. Listings of PK concentrations and AXA of apixaban by time will be provided.

The pharmacokinetics of apixaban using a population PK assessment and the relationship between apixaban exposure, anti-Xa activity and safety and efficacy endpoints are out of the scope of the CSR.

[redacted]

8 CONVENTIONS

8.1 Safety Data Conventions

Except as noted in Section 7.6, and as applicable, safety data will be handled consistent with BMS safety data conventions summarized below. These conventions include descriptions on how to analyze AE data as well as how to handle partial dates, missing dates, and unknown end dates when analyzing safety data.

For the analyses of efficacy and bleeding endpoints, imputation of missing or partial dates for efficacy and bleeding events will follow the convention outlined, but rather than using the hierarchy "first active study medication date, consent date, visit date corresponding to the visit at which the event was reported", should instead use the following hierarchy

- "first active study medication date, randomization date, consent date" for efficacy and bleeding endpoints other than death
- "last contact date" for death.
-

A. Subject Population

Key Guidelines
All subjects that receive one or more doses of study treatment constitute the population included in the primary safety analysis. The analysis and reporting of safety data will be performed on an as assigned (open label trials) or as randomized (randomized trials) basis. Exception: If a subject received the incorrect medication for **the entire period** of treatment, the subject will be analyzed in the treatment group associated with the incorrect medication. Important safety events that occur while the subject is on an incorrect treatment will be specifically discussed in the text of the Clinical Study Report.

B. Inclusion of Events in Primary Analysis

Key Guidelines
All adverse events with an onset date during the treatment phase of a study will be included in the primary safety analysis. This analysis strategy conforms to the "treatment -emergent" concept as described in ICH-E9. Adverse events with an onset date prior to the first day of the active treatment phase of a study are not included in the primary safety analysis. This is regardless of the possible continuance of the adverse event into the treatment phase of the study. Pre-existing conditions or adverse events with an onset date prior to the active treatment phase of a study that worsen with regard to intensity (e.g. mild to moderate) or change from unrelated to study medication to unknown relationship or at least possibly related during the treatment phase of a study are included in the primary safety analysis. At a minimum, non-serious adverse events with an onset date on or before the last date of dosing and serious adverse events with an onset date within 30 days of the last date of dosing are included in the primary safety analysis. Depending on the investigational product being researched (e.g. biologics with long half-life, oncology trials, etc.), an extended observational period may be defined for the primary safety analysis - provided the extended period is defined in the analysis section of the protocol. For development programs where the use of a pre-study treatment observational phase is important in determining the baseline status of a subject, baseline subtraction of events should be undertaken as a supplemental analysis. In such cases, this supplemental analysis is to be specified in the analysis plan.

C. Analysis Periods

Key Guidelines
Analysis periods must be defined in the statistical analysis plan. Typical study periods include: • Pre-treatment period - from first visit until initiation of the next study phase. • Baseline period - an observational period before the initiation of active study treatment used to establish a baseline for subjects. This phase is optional as some studies progress from pre-treatment phase to treatment phase. • Treatment period - begins on the first day study treatment (BMS investigational compound or placebo/active comparator) is administered. The duration of the treatment phase is defined in the protocol and includes the length study treatment is administered • Long-term extension period - defined by a protocol as a follow-on period of study treatment administration after a short-term study. This phase begins on the first day of long-term extension dosing. • Post-treatment period - begins the day after the last dose of study therapy. Crossover studies have a layer of complexity due to the planned switching of treatment assignments. The various phases of a crossover study are defined during the set-up and initiation of a study. On the day the next study treatment starts, a new treatment phase of the study begins.

D. Selection of Adverse Events for Counting

Key Guidelines

Where a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in adverse event frequency tables.

Where a subject has multiple adverse events within the same system organ class in a single analysis period, the subject will only be counted once at the system organ class level in adverse event frequency tables.

When a subject has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event
- Onset date and time

If relationship is not already reported as Not related versus Related by the investigator, the reported categories will be collapsed into these two categories – Not related and Related. Related events will include those reported as certainly, probably, or possibly related to study medication and those of unknown relationship. Related events will take precedence over Not related events in determining the event to include in summary tables.

More intense events will take precedence over less intense events in determining the event to include in summary tables.

Earlier onset date-time events will take precedence over later onset date-time events in determining the event to include in summary tables.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

E. Medical Dictionary

Key Guidelines
The Medical Dictionary for Regulatory Activities (MedDRA) will be used when reporting adverse events, medical history findings and/or physical examination findings in standard terminology. Analysis and reporting of MedDRA data will always be performed using the latest version of the MedDRA dictionary in production at BMS. Unless otherwise requested by a health authority, only the primary MedDRA hierarchy will be used for regulatory submission reports. MedDRA is an industry standard terminology that is maintained by an external organization. Updates to this dictionary can have significant impact on the analysis and reporting of our clinical data. The impact of updates implemented during the course of a study must be assessed and documented (e.g. changes in verbatim coding between interim and final databases). To avoid the potential of multiple codes being assigned to a single verbatim term, whenever data is integrated across multiple versions of MedDRA the data will be recoded, analyzed and reported in the latest version of MedDRA in production at BMS. When integrated data is recoded, an impact assessment must be performed to reconcile differences in coding between the individual studies and the integrated database.

F. Partial or Missing Adverse Events Data

Key Guidelines
Missing and incomplete data will be processed according to data processing guidelines detailed in the study data review plan. When an analysis must be performed with incomplete or missing data, the following guidelines can be used to derive data for use in the analysis. Onset Dates If the onset date for an adverse event is missing or incomplete, an imputed date will be derived to slot the event to an appropriate analysis period. This derived date will not be reported in summary tables or listings. Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence): • First active study medication date • Consent date • Visit date corresponding to the visit at which the event was reported (for non-serious adverse events only) If a valid non-missing date is not available for any of these dates, the derived onset date will be set to missing. If an onset date is incomplete, the derived onset date will be calculated using the following algorithm Calculate a surrogate date as the first non-missing valid date from the following list (in order of precedence): • First active study medication date • Consent date • Visit date corresponding to the visit at which the event was reported (for non-serious adverse events only) If a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing. Based on the information provided, set the derived date to the earliest possible date. If only a year is provided, set the derived date to January first of that year. If a year and month is provided, set the derived date to the first day of that month. If the surrogate date is non-missing then: If the derived date is equal to or after the surrogate date use the derived date as calculated If the derived date is prior to the surrogate date and the surrogate date is consistent with the partial data provided for the onset date, use the surrogate date as the derived date If the derived date is prior to the surrogate date and the surrogate date is not consistent with the partial data provided for the onset date then set the derived onset date to be the latest possible date based on the partial onset date information provided. If only a year is provided, set the derived date to December 31st of that year. If a year and month is provided, set the derived date to the last day of that month. If the surrogate date is missing (i.e. all three dates used to determine the surrogate date are missing) then use the derived date as determined in section 3-II. Resolution Dates Dates will not be derived for missing or partial resolution dates Intensity If an adverse event is reported with an unknown intensity, a derived intensity of 0.5 will be used for the event. The derived intensity will only be used in determining the event to be counted in frequency tables it will not be displayed in listings or tabulations of the data.

G. Laboratory Data Analysis

Key Guidelines

Analyze laboratory safety data using either a Marked Abnormality or a standard toxicity grade approach. The data analysis plan should outline the approach used and specify the criteria. The criteria must be pre-defined and consistent for all studies within a program. Additional laboratory safety analyses (e.g. mean change from baseline) may also be performed and should be consistent throughout a program. Implausible and improbable laboratory results will be corrected, if appropriate, at the source (i.e. laboratory) of the data. If a laboratory confirms a result which has been identified as implausible or improbable, the result will be included in the analysis and its impact, if necessary, addressed in the text of the study report.

H. Programming for Death Events Reporting

Key Guidelines
Programming for death events reporting for annual safety reports, investigator brochure updates, etc …, that is performed on a not reconciled clinical database, must include all death data being collected in the subject CRF. SAE and subject status are examples of CRF modules to be taken into account for the programming. This list is of course not exhaustive.

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8.2 Baseline Measurements

For all laboratory measures, the baseline value is the last assessment taken prior to randomization. When there is a missing baseline assessment it will not be imputed, thus, subjects are excluded from any changes from baseline analysis for which they have a missing baseline value.

8.3 Day Ranges for Analysis of Time Points

For this study, "Day 1" refers to the start of planned 3-4 drug systemic induction chemotherapy, and not necessarily the day of randomization or first dose of apixaban. Study visits are timed from the start of induction therapy. Subjects do not always adhere strictly to the visit schedule timing in the protocol.

The imaging data for the primary efficacy analysis for primary endpoint up to Day 40 will be included in analyses.

The day ranges for the analyses of laboratory and vital sign measurements are defined in Table 8.3-1.

Table 8.3-1: Day Ranges for Analysis of Vital Sign and Laboratory Measurements

Nominal Visit	Target Day	Day Ranges
Baseline	Pre-dose up to 2 days prior to randomization	Prior to or on the day of randomization
Day 8	8	Day 5 - 10, but exclude values prior to or on day of randomization
Day 15	15	Day 11 - 20

Table 8.3-2: Day Ranges for Analysis of Vital Sign and Laboratory Measurements

Day 22	22	Day 21 - 27
Day 29	29	Day 28 -34
Follow-up	35	Day 35 - 40

8.4 Multiple Measurements

Laboratory Measurements

For tabulations of changes from baseline or shift analyses, if multiple laboratory measurements are obtained within the same nominal visit, then the measurement obtained on the day closest to the target day for that nominal visit will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses.

For tabulations of incidence of marked abnormalities (e.g. ALT >3xULN), if multiple laboratory measurements are obtained within the same nominal visit, then the worst measurement within the nominal visit window nominal visit will be used.

9 CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Pharmacokinetic, exposure, and exploratory biomarker results may be reported separately.

Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific Data Presentation Plan (DPP).

10 DOCUMENT HISTORY

The document history is shown in Table 10-1

Table 10-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue
2.0		Incorporated all the protocol amendments since Version 1.0 was signed off through Amendment 04, dated 08-Dec-2017. Version 2.0 was reviewed, but not signed off.
3.0		Incorporated protocol amendment 05. Modified and clarified analysis populations, including specifying primary analysis population for efficacy and safety endpoints as Randomized/Intent-to-treat. Modified sample size calculations to include calculation based on the primary analysis population. Included additional sensitivity analyses to address missing data. Clarified dosing duration and date ranges. Corrected various typographical, grammatical, and other non-content errors.
4.0		Minor modifications, including typographical, grammatical, and other non-content errors.