Impact of Daily Prophylaxis Dose Anticoagulation with a Factor Xa Inhibitor (Apixaban) in Patients with Sickle Cell Disease

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A randomized trial to evaluate if prophylactic dose Apixaban not only reduces the known hypercoagulable state, but more importantly, has a salutary effect on clinical pain scores in patients with Sickle Cell Disease

NCT02179177

Document Date; October 4, 2016

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1.0 Introduction and Background

In patients with SCD, the use of low dose anticoagulation as an outpatient may lead to a significant decrease in morbidity and as a result, decrease healthcare utilization and costs. Sickle cell disease (SCD) is most commonly affected by recurrent painful vaso-occlusive crisis (VOC) and although greater than 50% of patients with SCD have significant daily pain, only 5% of patients actually seek medical attention (Smith, 2008). Importantly, hospitalizations account for up to 90% of the medical care costs for patients with SCD (Yang, 1995). Review of data from the National Center for Health Statistics revealed the average direct costs per hospitalization (in 1996 dollars) was estimated at $6300, for a total direct cost of $475 million per year. The use of anticoagulation in SCD builds upon recent studies including our own (Shah, 2012; Ataga, 2007; Francis, 1989; Stuart 2001) which document a hypercoagulable state and has been found to be promising in smaller past studies.

Although few studies have attempted to evaluate clinical pain scores in the context of anticoagulation, several studies have examined the effects of anticoagulation on the coagulation system in SCD. Wolters et al documented that use of acenocoumarol at a mean INR of 1.64 resulted in a 50% decrease in plasma prothrombin fragment 1+2 in SCD patients during steady state. However, clinical evaluation was not performed in this initial small study (Wolters, 1995). Subsequently, Ahmed et al measured D-dimer in 37 sickle cell patients treated with low dose warfarin (mean dose of 1 mg) while in crisis. Their results revealed a significant decrease in D-dimer levels in patients treated with warfarin (Ahmed, 2004). These studies also documented no bleeding with low dose anticoagulation, along with the decrease in hypercoagulable markers.

Studies evaluating the clinical benefit of anticoagulation in patients with SCD began with Chaplin et al, who revealed that long term use of daily prophylactic subcutaneous heparin in four SCD patients over several years (mean 8.7 years) was beneficial. Minimal improvement in clinical pain was reported in one, and moderate improvement in three. Results also included no bleeding and no thrombocytopenia. In addition, there was a 73% reduction in days of hospitalization per year and 74% reduction in hours spent in emergency rooms per year during heparin administration. Pretreatment pain patterns recurred when heparin was discontinued (Chaplin, 1989). A larger study by Schnog et al examined 22 SCD patients in a double blind placebo controlled, cross-over pilot study. This study used acenocoumarol dosed to achieve an INR of 1.6-2 and followed patients for a total of 23 weeks. Results included reduction in all hypercoagulable markers; however, there was no decrease in the number of hospitalizations. Limitations of this study arose from the small sample size and the large number of patients excluded (Schnog, 2001). Furthermore, subcutaneous heparin and warfarin may not be the optimal antithrombotic agents to use in this particular clinical setting. Thus, the inconclusive results from previous studies indicate that further investigations are needed to more effectively evaluate the role of low dose anticoagulation in SCD.

2.0 Study Rationale

There is not only significant morbidity associated with patients with SCD, but also costs associated with the numerous hospitalizations. Small studies have been unable to show clear benefit of the use of low dose anticoagulation in SCD due to limited sample size or the inclusion of very specific populations. However, studies have shown a decrease in the level of elevated prothrombotic markers with anticoagulation, and one

study using full dose anticoagulation in patients with a generally milder form of SCD (with high protective hemoglobin) showed more rapid decrease in clinical pain with use of anticoagulation, suggesting a possible benefit of such therapy. Due to the paucity of data to support therapeutic dose LMWH in the more severe forms of SCD seen in the United States, we are currently performing an inpatient study to evaluate if prophylactic dose LMWH not only reduces the known hypercoagulable state, but more importantly, has a salutary effect on clinical pain scores. This study proposal attempts to critically avoid admissions by reducing daily pain scores and pain crisis as an outpatient by use of a novel oral anticoagulant.

The development of novel anticoagulants such as oral direct factor Xa (FXa) inhibitors allows the realistic use of daily prophylactic dosing as an outpatient. Past studies as detailed earlier have been limited by attempts to use subcutaneous injections or frequent, close monitoring for acenocoumarol treatment, both which are not ideal for chronic daily use. Furthermore, the use of global assays such calibrated automated thrombography (CAT) have shown further details about thrombin generation in a population which is hypercoagulable at baseline. Our studies have revealed an increase in 'thrombin burst' and intrinsic hypercoagulability which can be monitored closely by CAT during treatment with a FXa inhibitor.

There is evidence of the potential role of anticoagulants for reduction in this hypercoagulable state, and importantly reduction in clinical pain. Studies of anticoagulation in outpatients with SCD have included the use of LMWH and acenocoumarol. Both have difficulty in administration, monitoring and ultimately compliance. The development of direct factor Xa (FXa) inhibitors which are administered orally and require minimal monitoring is ideal for chronic administration.

3.0 Study Design

This is a double blind, parallel group, placebo controlled feasibility study (see figure 1) with an enrollment target of 60 patients (30 per arm). All subjects that meet inclusion criteria as an outpatient, following a 1 month observation, will be randomized to receive an oral prophylactic dose factor Xa inhibitor (Apixaban 2.5mg po bid) or placebo for 6 months. Subjects will return for a 30 day (+/- 5 days) follow-up visit after the End of Treatment (EOT) visit. Initial randomization will occur by computerized randomization technique by the investigational drug services (IDS) at Duke University Medical Center.

3.1 Screening and Eligibility

All patients seen in our Adult Comprehensive Sickle Cell Center will be screened for eligibility. Currently, there are greater than 450 patients actively seen and an average of 60 patients seen per week. The same inclusion/exclusion criteria will be used for both arms of the study.

Inclusion Criteria

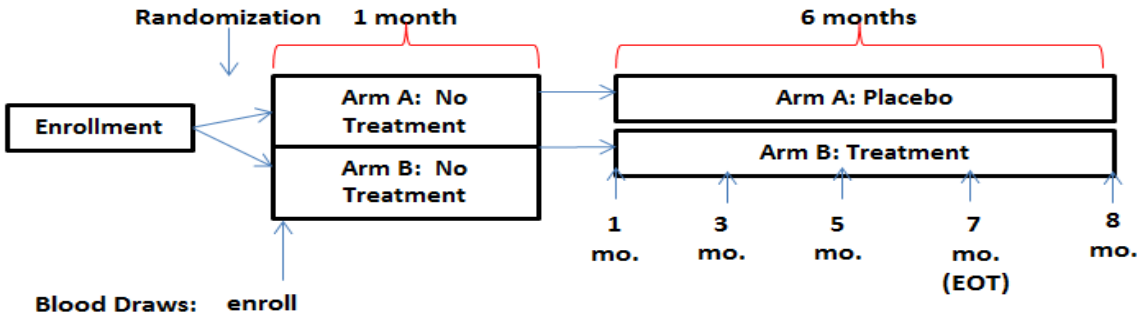
- documented HgbSS, SC or HgbS-beta^0 thalassemia,
- age ≥18 years old and ≤80, seen in outpatient clinic ≥2 times in past year, and
- seen for an acute care visit (hospitalization, emergency department, or day hospital visit) for pain >2 times in the past year.

Exclusion Criteria

- Hospitalization or day hospital visit for pain crisis within the past 2 weeks
- Patients with ≥10 acute care visits within the past year will be excluded
- Creatinine >3.0 mg/dL
- creatinine ≥1.5 mg/dL AND **weight** ≤60 kg
- chronic use of antiplatelet or anticoagulation medication
- Patients with known vasculopathy or Moya-Moya
- platelet count <100 X 10^9/L
- AST or ALT >3 times normal
- chronic red blood cell transfusions (scheduled transfusions)
- packed red blood cell transfusion within the past 2 months
- Use of CYP3A4 and P-gp inhibitor medications

4.0 Specific Aim 1. Evaluate the impact of daily prophylactic dose anticoagulation (oral direct factor Xa inhibitor) on daily pain scores in outpatients with SCD.

Figure 1. Schematic of Scheduled Blood



4.1 Study Procedures Aim 1

Following randomization by IDS, and initial blood draw (Figure 1), patients will be given a daily pain logPatients will record daily pain scores and return in 1 month (+/- 5 days) at which time patients will then be given a 1 month supply of study drug. Patients will return monthly (+/- 5 days) to return daily pain logs, verify compliance to medication, review completion of daily pain logs, and give additional study drug for the next month. Patients must adhere to daily administration of study drug and miss no more than 2 doses per week. Clinical pain scores will also be performed with each visit. The primary pain assessment tool will be a 10-cm horizontal visual analog scale (VAS), with "0" corresponding to no pain at one end and "10" indicating the worst pain at the other. The daily pain log will include the VAS and if the patient classifies their pain as 'crisis' or not. Patients will be called monthly between in person visits to assess for AE/SAE and to reinforce the importance of medication compliance. Along with the VAS, there will be novel methods of pain assessment that may prove to better measure the impact of pain in these patients. One method is the *use of the validated PROMIS format . PROMIS uses a 5-point Likert-type format with response options ranging from never to always. A total score is calculated by obtaining a sum of scores across items, with higher scores indicating greater impact of the particular domain to a patient's daily living. Patients will have PRO performed on enrollment, after 1 month's use of study drug and at the end of 6 months' use of study drug. Patients will complete PROMIS on a mobile device and have all results*

recorded on the Duke secure server for further information. The second, a SMART application will be installed on patient's iPhones/iPads at their request to assist with monitoring of symptoms. Patients without an Apple device can have one loaned to them until completion of the study.

The devices will be returned to the study PI or coordinator per agreement at the time of enrollment. Patients admitted to the hospital will continue their study drug or placebo unless deemed medically inappropriate by admitting physician. Patients upon discharge are to resume study drug per supervision of study

principal investigator. Pain scores during hospitalization and for the subsequent 1 week will be recorded and used for secondary analysis of daily pain scores during crisis.

Patients who during the course of the study have laboratory findings which reveal creatinine ≥1.5 mg/dL AND weight ≤60 kg; platelets < 100 X 10^9/L; or develop AST or ALT >3 times normal, will have study drug stopped and will be terminated from the study.

Patients on hydroxyurea will be included in the study and sub-analysis will be performed to control for potential differences. All patients despite treatment with hydroxyurea will need to meet inclusion criteria of having clinically significant pain which requires >2 acute care visits.

4.2 Data and Statistical Analysis Aim 1

We power the study to test whether there is a significantly larger reduction in pain after administration of a daily prophylactic anticoagulation dose as compared to administration of a placebo. A total of 60 patients will be randomly assigned to each drug arm. The primary endpoint is the mean pain score per patient over each of four time periods. The design has two sources of variation: the variation between the patients receiving the same drug and the variation due to the interaction of time by the patients within drug arm. It is of interest to test whether the change in the pain score over the four time periods differs between the prophylactic anticoagulation dose arm and the placebo arm. From the literature the standard deviation of the mean pain score per patient is 1.5. Assume the true mean pain scores over the four time periods for the placebo and prophylactic anticoagulation dose arms are 3.9, 3.9, 3.9, 3.9 and 3.9, 3.12, 3.12, 3.12, respectively. Then, a total of 60 patients randomized equally to each drug arm will detect the difference in the change between the two arms in the mean pain scores over time, as specified by the preceding mean pain scores, with a power of at least 0.836 for a one-sided 0.05 test. Anticipating that 20% (10 patients) may have incomplete data (less than 75% of daily pain scores recorded or missing more than one dose of study drug per week), may be lost to follow up, or may drop out; we have also found a power of at least 78.4% for 50 patients.

We expect two positive effects from prophylactic doses of apixaban on the patient reported outcomes:

- *PROs assessing fatigue, physical function, and pain impact will improve in patients administered daily prophylactic dose apixaban compared to placebo.*
- *We believe that there will be a significant correlation between PROs and pain scores.*

Statistical Analysis

The primary outcome of interest is to test the effect on the mean daily pain score due to the arm by time interaction. Secondary outcome will include comparison of daily pain scores while hospitalized between treatment arms and the number of hospitalizations during each treatment period.

All analyses will be performed using SAS version 9 or greater (SAS Institute Inc., Cary, NC). Data will be analyzed using descriptive statistics including mean and standard deviation. Comparisons are to be performed using SAS's PROC GLM with a model that accounts for all fixed and random effects in the design.

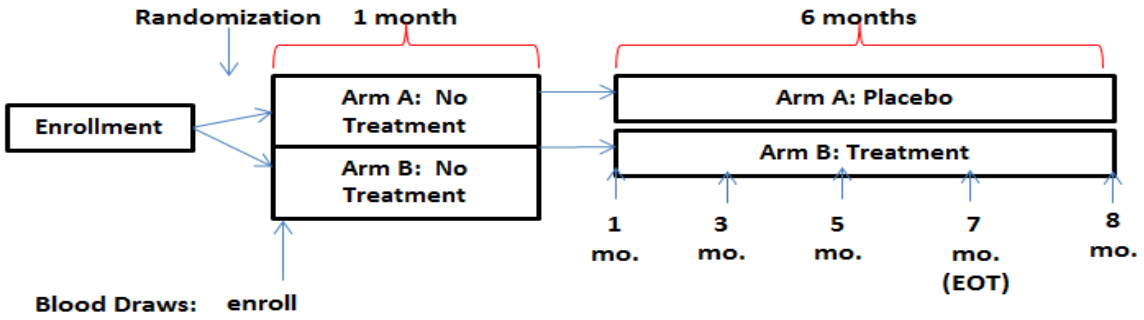
5.0 Specific Aim 2: Determine the effect of prophylactic dose anticoagulation on markers of thrombin generation during outpatient steady state as well as inpatient VOC.

As described in section 3.0, we will perform a double blind, parallel group, placebo controlled feasibility study with an enrollment target of 60 patients (30 per arm).

5.1 Study Procedures Aim 2

As described earlier (Figure 1), patients begin a 1 month observation following randomization. Patients will have blood drawn on enrollment and when they return in 1 month (+/- 5 days) to begin study drug. Subsequent blood draws performed at 2 month intervals while on study drug. Blood draws will occur between 2 and 4 hours from previous dose taken and ± 5 days regardless of hospitalization. Patients will be called monthly between in person visits to assess for AE/SAE and to reinforce the importance of medication compliance. Graded incentives may be given monthly to encourage patients to continue on study and return for follow up blood draws.

Figure 1. Schematic of Scheduled Blood



Platelet poor plasma will be separated and stored to allow batch testing for hypercoagulable markers and markers of inflammation. Markers of thrombin generation will include D-dimer, thrombin-antithrombin (TAT) complex, and CAT. Both D-dimer and TAT will be performed using enzyme-linked immunosorbent assay (ELISA). CAT will be performed using the Fluoroskan Ascent plate reader (TCoag) and phases to be analyzed include lag phase, slope, peak and endogenous thrombin potential. Markers of inflammation will also be measured at each of these time points (IL-6 and sVCAM) which are performed by ELISA.

Patients admitted to the hospital will continue their study drug or placebo unless deemed medically inappropriate by admitting physician. Patients upon discharge are to resume study drug per supervision of study principal investigator. Blood will be drawn for secondary analysis for hypercoaguability on any inpatient hospitalizations on day 1, 3 and 5 but will not be included in primary analysis.

5.2 Data and Statistical Analysis

Sample Size

The same design used in Aim 1 applies to Aim 2. We analyze the change in thrombin generation from enrollment to 2 months following initiation of study drug. We hypothesize that the anticoagulation drug will

cause a decrease in thrombin generation from baseline to two months. From the literature the standard deviation of the D-dimer measure per patient is 500. With a total of 60 patients randomized equally to each drug sequence, and conservatively assuming no correlation between D-dimer values from baseline to 2 months on the same patient, we achieve a power of 0.863 to detect a mean D-dimer difference in the change from baseline to 2 months between the placebo and the daily prophylactic anticoagulation dose groups of 250 mg/l {= [(1000-750) - (1000-1000)] mg/l} for a one-sided 0.05 test.

No studies to date have evaluated the influence of anticoagulants on thrombin generation as measured by CAT, therefore sample size and expected differences are calculated based on available studies examining D-dimer.

Statistical Analysis

For our primary outcome, we will compare mean changes in thrombin generation (D-dimer, TAT and phases of CAT) for patients treated with prophylactic dose anticoagulation and placebo. Secondary outcomes will include correlation of hypercoagulable and inflammatory markers to clinical outcomes (such as pain, hospitalization, and number of acute care visits).

In addition, we expect that 50% of the patients to be hospitalized and continue their medication (placebo or drug) as assigned at randomization. For these patients, thrombin generation D-dimer measures will be collected at admission, 3 days and 5 days. Therefore, as a secondary aim, for these hospitalized patients we will analyze the difference between the placebo and drug groups in the change over time in the mean D-dimer values.

Planned Analysis of Primary Endpoint

Following the enrollment of the 60 patients, and completion of the 7 month study period for each patient, all data will be subsequently analysed with the assistance of the Duke Translational Medical Institute. Barry Moser, PhD is our lead stastician who will continue to provide statistical support and analysis through this study.

Primary analysis of daily pain scores will be performed for patients on treatment with Apixaban and compared to patients on placebo, to determine if treatment decreases daily pain scores. In addition, we will compare changes in thrombin generation from enrollment to 2 months for patients treated with Apixaban versus placebo.

Secondary analysis will be performed to evaluate differences when patients are hospitalized and on study drug versus placebo, as well as healthcare utilization for patients treated with Apixaban.

6.0 Study Visit Procedures (See Appendix A)

6.1 Screening/Randomization Visit

The investigator or designee will:

- Obtain written informed consent
- Obtain relevant medical history
- Determine eligibility
- Conduct pregnancy test (WOCBP only)
- Obtain blood samples for research laboratory tests
  - Research labs include: D-dimer, thrombin-antithrombin, and calibrated automated thrombography, IL-6, sVCAM
- Assess concomitant medication use

- Randomize subject
- Perform Pain Score
- Distribute Pain log
- Perform Patient Reported Outcome Computerized Questionnaire (PROMIS)
- Install SMART app on subject's phone or provide subject with a device

6.1.2 Observational Period (30 days)

Via a telephone contact at 2 weeks, the investigator or designee will:

- Assess concomitant medication use
- Review pain log completion guidelines
- Assess adverse events

6.1.3 Month 1

The investigator or designee will:

- Obtain blood samples for research laboratory tests
  - Research labs include: D-dimer, thrombin-antithrombin, and calibrated automated thrombography.
- Assess concomitant medication use
- Perform Pain Score
- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events

6.1.4 Month 1, 2, 3, 4, 5, 6, 7 and 8 (telephone) – 2 weeks following last clinic visit

Via a telephone contact, the investigator or designee will:

- Assess concomitant medication use
- Review pain log completion guidelines
- Assess adverse events

6.1.5 Month 2

The investigator or designee will:

- Assess concomitant medication use
- Perform Pain Score
- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events
- Perform Patient Reported Outcome Computerized Questionnaire (PROMIS)

6.1.6 Month 3

The investigator or designee will:

- Obtain blood samples for research laboratory tests
  - Research labs include: D-dimer, thrombin-antithrombin, and calibrated automated thrombography.
- Assess concomitant medication use
- Perform Pain Score
- Assess study drug compliance

- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events

6.1.7 Month 4

The investigator or designee will:

- Assess concomitant medication use
- Perform Pain Score
- Assess study drug compliance
- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events

6.1.8 Month 5

The investigator or designee will:

- Obtain blood samples for research laboratory tests
  - Research labs include: D-dimer, thrombin-antithrombin, and calibrated automated thrombography, IL-6, and sVCAM.
- Assess concomitant medication use
- Perform Pain Score
- Assess study drug compliance
- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events

6.1.9 Month 6

The investigator or designee will:

- Assess concomitant medication use
- Perform Pain Score
- Assess study drug compliance
- Dispense study drug
- Assess pain log completion compliance
- Assess adverse events

6.1.10 Month 7 (End of Treatment)

The investigator or designee will:

- Assess concomitant medication use
- Perform Pain Score
- Assess study drug compliance
- Assess pain log completion compliance
- Assess adverse events
- Perform Patient Reported Outcome Computerized Questionnaire (PROMIS)

6.1.11 Month 8 (Follow-Up)

The investigator or designee will:

- Obtain blood samples for research laboratory tests

- Research labs include: D-dimer, thrombin-antithrombin, and calibrated automated thrombography.
- Assess concomitant medication use
- Perform Pain Score
- Assess pain log completion compliance
- Assess adverse events

7.0 Study Duration

Enrollment for this study will be completed within the first 12 months (average 5 patients per month), followed by 8 months to allow completion of study by all patients.

8.0 Data and Safety Monitoring Board.

The Duke University Data and Safety Monitoring Board (DSMB) is a Committee that has been established for the purpose of monitoring clinical studies. The DSMB has multiple responsibilities including:

- Assessing risk and complexity of those clinical trials that have been submitted for review
- Determining the appropriate level of data and safety monitoring
- Reviewing the reports of all serious adverse events (SAEs) that have been experienced by participants in those active clinical trials that are being monitored by the DSMB
- Reviewing the regularly submitted (usually at least yearly) data and safety monitoring reports that are required of all active clinical trials.
- Recommending appropriate actions (closure, increased monitoring, etc.) to the Principal Investigator.

9.0 Data Safety and Monitoring Plan

We will be using the descriptive terminology developed by the National Cancer Institute for use in reporting adverse events: Common Toxicology Criteria for Adverse Events (CTCAE) version 4.0, dated May 29, 2009. The website for the CTCAE is http://evs.nci.nih.gov/ftp1/CTCAE/About.html. The CTCAE includes a grading (severity) scale for each adverse event term.

9.1 Adverse Event Reporting

9.1.1 Collection of Safety Information

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.)

9.1.2 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose:</u>

- 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 [e.g., 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.)
- Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.3.6 for reporting pregnancies.)

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

- a visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- elective surgery planned before signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

9.1.3 Nonserious Adverse Events

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

9.2 Assignment of Adverse Event Intensity and Relationship to Investigational Product

The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

Related: There is a reasonable causal relationship to investigational product administration and the adverse event.

Not Related: There is not a reasonable causal relationship to investigational product administration and the adverse event.

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

9.3 Collection and Reporting

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.)

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to investigational product, action taken, and treatment required. If treatment for the AE was administered, it should be recorded in the medical record.
The investigator shall supply the sponsor and Ethics Committee with any additional requested information, notably for reported deaths of subjects.

All AE/SAEs will be reported to the DSMB and BMS. The DSMB will review these data at their regular meeting and notify the Principal Investigator if safety appears to be an issue. After 12 months of this study (or completion of 20 patients, whichever comes first), all of the safety data, including information on any deaths, will be presented to the DSMB in a tabular format. The investigators will also prepare an overall report to accompany the tables. The DSMB will review the report and determine if there is a safety concern. If there are significant adverse events, the DSMB may recommend that the study be terminated. All AE/SAEs will be included in the final study report.

9.3.1 Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 70 days of discontinuation of dosing of the investigational product. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should notify BMS of any SAE occurring after this time period that is believed to be related to the investigational product or protocol-specified procedure.

All SAEs whether related or unrelated to the study drug, apixaban, must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed or emailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Serious adverse events, whether related or unrelated to investigational product, must be recorded on the SAE page and reported expeditiously to BMS (or designee) to comply with regulatory requirements. An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

All SAEs must be immediately reported by confirmed facsimile transmission (fax) and mailing of the completed SAE page. In some instances where a facsimile machine is not available, overnight express mail may be used. 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.) In selected circumstances, the protocol may specify conditions that require additional telephone reporting.

If the investigator believes that an SAE is not related to the investigational product, 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 page.

If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow-up SAE report should be sent immediately to the sponsor. As follow-up information becomes available it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

9.3.2 Handling of Expedited Safety Reports

In accordance with local regulations, BMS will notify investigators of all SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). investigator notification of these events will be in the form of an expedited safety report (ESR).

Other important findings which may be reported by the sponsor as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

9.3.3 Nonserious Adverse Events

The collection of nonserious AE information should begin at initiation of investigational product. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

If an ongoing nonserious AE worsens in its intensity, or if its relationship to the investigational product changes, a new nonserious AE entry for the event should be completed. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of investigational product, or those that are present at the end of study participation. Subjects with nonserious AEs at study completion should receive post-treatment follow-up as appropriate.

All identified nonserious AEs must be recorded and described in the medical record.

9.3.4 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.
The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

9.3.5 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 must be reported as an SAE.

9.3.6 Pregnancy

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling WOCBP in this clinical study, the investigator must review the guideline about study participation for WOCBP which can be found in the GCP Manual for Investigators. The topics include the following:

- General Information
- Informed Consent Form
- Pregnancy Prevention Information Sheet

- Drug Interactions with Hormonal Contraceptives
- Contraceptives in Current Use
- Guidelines for the Follow-up of a Reported Pregnancy.

Before study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All WOCBP MUST have a negative pregnancy test within 72 hours before receiving apixaban. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive apixaban and must not be enrolled in the study.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). The investigator must immediately notify BMS of this event and record the pregnancy on the Pregnancy Surveillance Form (not an SAE form). Initial information on a pregnancy must be reported immediately to BMS, and the outcome information provided once the outcome is known. Completed Pregnancy Surveillance Forms must be forwarded to BMS according to SAE reporting procedures.

Any pregnancy that occurs in a female study participant or a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The study staff will continue to follow the pregnant female throughout the course of the pregnancy until an outcome is known. In addition, the investigator must report to BMS and follow-up on information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

The study staff will continue to follow you throughout the course of the pregnancy, including perinatal and neonatal until an outcome is known. The study staff will collect information for your infant(s) from the medical chart and through phone contact with the parent/parents. The information will include any complications or abnormalities at birth. The study staff will also document the following information: date of birth, sex, birth weight, head circumference and Apgar score (**A**ppearance, **P**ulse, **G**rimace, **A**ctivity, **R**espiration). The study staff will continue to collect information about your infant for a minimum of 8 weeks after birth.

9.3.7 Adverse Events of Special Interest

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential adverse event (AE) of special interest. All occurrences of potential adverse event of special interest, meeting the defined criteria, must be reported as SAEs (see Section 7.2.1 for reporting details).

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected:

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis..

SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Reconciliation will occur every three months and once just prior to database lock/Final Study Report (FSR). The investigator will request a safety data reconciliation report to aepbusinessprocess@bms.com. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. The data elements listed on the GPV&E safety data reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

9.3.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded in the medical record.

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