Cover Page

APB Study: Apixaban Pharmacokinetics in Bariatric Patients

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The Johns Hopkins University School of Medicine
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APB Study: Apixaban Pharmacokinetics in Bariatric Patients
A study to determine the pharmacokinetics and pharmacodynamics of apixaban in obese patients who undergo bariatric surgery.

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Obesity is now the leading health problem of the 21st century. Weight reduction by conservative methods including diet and exercise has had poor success rates. There has been a substantial increase in the use of bariatric surgery to provide sustained weight loss and thus a reduction in the medical comorbidities that are associated with obesity. However, because these procedures may alter the anatomical and physiological aspects of the gastrointestinal system, there is a possibility of altered pharmacokinetics to medications particularly when taken orally. Furthermore, patients typically lose anywhere from 50 to 75% of their estimated excess body mass approximately one to two years following surgery. This successful therapeutic outcome of the surgery may be causing long term changes in the pharmacokinetics that are independent of any direct anatomical or physiologic changes induced by the procedure.

Physicians and surgeons are very interested in oral anticoagulants for this special patient population. To date, there is no approved dosing for the obese patient (especially when considering surgical

intervention such as bariatric surgery). VTE is one of the top two causes of morbidity and mortality in the bariatric surgical patient. In the ninth edition of the Antithrombotic Therapy and Prevention of Thrombosis guideline published by the American College of Chest Physicians (1), it is reported that virtually all bariatric surgical patients have at least a moderate risk of VTE, with many patients at high risk. (2) The approach to VTE prophylaxis used by most bariatric surgeons today is a combination of non-invasive and pharmacologic techniques, including sequential compression devices, anti-embolic stockings, anticoagulation, and early ambulation. Traditionally VTE prophylaxis has been accomplished with subcutaneous injection however with the introduction of new oral anticoagulant medications many practitioners are using these anticoagulants without demonstration of effectiveness in this population.

The Johns Hopkins Center for Bariatric Surgery is interested in conducting a pharmacokinetic study of apixaban (an oral anticoagulant with FDA approval for use of VTE prophylaxis and treatment) in the obese adult population to determine if bariatric surgery influences apixaban exposure. More interesting would be to see how the dose may need to change pre- vs. post-bariatric surgery (this will be important for physicians as more and more patients undergo this procedure worldwide and many may require anticoagulation in their future healthcare).

2. Objectives (include all primary and secondary objectives)

Specific Aim 1: To determine the pharmacokinetics of apixaban in obese patients scheduled to have bariatric surgery with a body mass index (BMI) of 35 kg/m^2 or greater.

Hypothesis 1a: Obese patients prior to bariatric surgical intervention, compared to normal weight historical controls, will have a decrease in both Cmax and AUC when given a single dose of 5 mg of apixaban.

Specific Aim 2: To determine the pharmacokinetics of apixaban in the bariatric surgical patient who has undergone Roux-en Y gastric bypass (RYGB) or Vertical Sleeve Gastrectomy (VSG) at 1, 6, and 12 months post-op.

Hypothesis 2a: Patients who have recently undergone RYGB surgery (1 month post-op) will have a decrease in both the Cmax and AUC, relative to pre-op values, when given a single dose of 5 mg of apixaban.

Hypothesis 2b: Patients who have recently undergone VSG surgery (1 month post-op) will have a decrease in both the Cmax and AUC, relative to pre-op values, when given a single dose of 5 mg of apixaban. The magnitude of the decrease in Cmax and AUC will be less than that seen in RYGB patients.

Rationale: Anatomic alteration of the GI tract will immediately reduce absorption in all post-operative bariatric patients. In RYGB patients, the attenuated small bowel and altered bile acid composition will lead to decreased absorption of the drug, whereas in sleeve gastrectomy patients prolonged gastric emptying may affect pharmacokinetics.

These findings will be important when considering the use of apixaban as an oral anticoagulation option for perioperative VTE prophylaxis in the bariatric population, both in the acute hospital setting and after discharge in patients requiring extended VTE prophylaxis or treatment.

Hypothesis 2c: After undergoing bariatric surgery, patients at 6, and 12 months post-op will have an increase in Cmax and AUC, relative to pre-op values, when given a single dose of 5 mg of apixaban.

Hypothesis 2d: After undergoing RYGB, patients at 6, and 12 months post-op will have a greater increase in both Cmax and AUC, relative to pre-op values, than VSG patients relative to pre-op values when given a single dose of 5 mg of apixaban.

Rationale: Patients who are 6 to 12 months post-bariatric surgery generally have a 30-50% decrease in excess body weight. This decrease in body weight reduces volume of distribution of drug, potentially affecting Cmax. Results of the published Phase 1 apixaban study found that exposure to a dose of apixaban was inversely related to body weight. Therefore, we should expect higher plasma levels of apixaban in patients who are 6 to 18 months post-bariatric surgery when compared to pre-op values.

Findings of the Phase I study (3,4)
An open-label, parallel-group, non-randomized, single-dose study in healthy male and female subjects was conducted to assess the effects of body weight on the pharmacokinetics of a single 10 mg dose of apixaban. Following screening, patients were enrolled in one of three groups: low body weight (≤50kg, N=18), normal body weight (65-85kg, N=18) or high body weight (≥120kg, N=19).

Compared to normal body weight:
• There was a 27% increase in Cmax and 20% increase in AUC in patients with low body weight
• There was a 31% decrease in Cmax and 23% decrease in AUC in patients with high body weight

The effect of RYGB vs. sleeve gastrectomy on long-term pharmacokinetics is difficult to predict because of the opposing effects of greater weight loss with reduced absorption in the RYGB patient.

These findings will be important when considering apixaban as an oral medication for long-term post-op bariatric patients who may require anticoagulation for stroke, myocardial infarction, atrial fibrillation or orthopedic procedures such as hip or knee replacements. (5, 6)

Specific Aim 3: To measure the effect of apixaban on Factor Xa activity (chromogenic anti-Xa activity assay) in bariatric surgical patients pre-operatively then at 1, 6, and 12 months post-operatively.

Hypothesis 3a: In spite of the changes in pharmacokinetics, the pharmacodynamics response (measured with a chromogenic anti-Xa activity assay) will not differ by more than 10% in comparing pre-surgical response to that at 1, 6, and 12 months after surgery.

Rationale: The changes in pharmacokinetics should not lead to a different concentration-response relationship in the chromogenic anti- Xa activity of individual patients following dosing with apixaban 5 mg. Were there to be a significant change in pharmacodynamics, other factors due to the altered anatomy or substantial weight loss would need to be invoked to explain that altered relationship.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

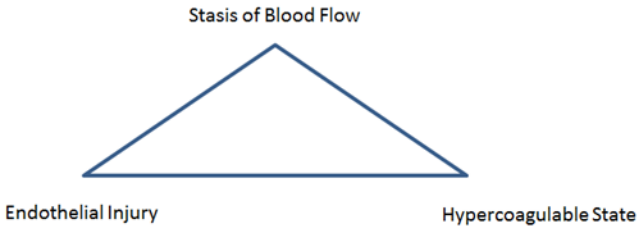
Defining Venous Thromboembolism

VTE includes both deep vein thrombosis (DVT), blood clots that form in the deep veins of the body, and pulmonary emboli (PE), blood clots that form in the deep veins of the body and then break free and enter the arteries of the lungs. VTE affects all races, ethnicities, both genders and all age groups. (1)

There is a fine balance between clot formation and fibrinolysis. Normally these two physiologic states are in dynamic equilibrium preventing patients from bleeding or clotting excessively. Numerous factors affect this delicate balance. These factors can be grouped into three broad categories, also known as Virchow's triad (after the German physician Rudolf Virchow):

1. Vascular injury (endothelial damage)
2. Activation of blood coagulation (hypercoagulability)
3. Venous stasis

Figure 1 Virchow's Triad



Burden of Venous Thromboembolism in the Bariatric Surgical Patient

VTE and its sequelae constitute one of the most significant causes of morbidity and mortality in hospitalized and post-operative surgical patients. In the United States alone, an estimated 300,000 to 600,000 (1 to 2 per 1,000) patients each year are diagnosed with VTE, and 60,000 to 100,000 die of VTE. (3) Among people who have had a DVT, one-half will have long-term complications such as swelling, pain, discoloration, and scaling in the affected limb (post-thrombotic syndrome). (7) Spyrpoulos et al completed a healthcare claims analysis on the economic burden of VTE and found that the cost of VTE ranges from $7594 to $16, 644 per patient. (8) This equates to a total annual cost of 2 to 10 billion dollars. VTE is one of the top two causes of morbidity and mortality in the bariatric surgical patient. In the ninth edition of the Antithrombotic Therapy and Prevention of Thrombosis guideline published by the American College of Chest Physicians (1), it is reported that virtually all bariatric surgical patients have at least a moderate risk of VTE, with many patients at high risk. (9, 10) Despite these impressive figures, there exists no FDA-approved or universally accepted protocol for pharmacologic VTE prophylaxis in morbidly obese patients.

Prophylaxis of Venous Thromboembolism in Bariatric Surgical Patients

To date, there remains no consensus as to the optimal regimen for prevention of VTE in the bariatric surgical patient. The approach to VTE prophylaxis used by most bariatric surgeons today is a combination of non-invasive and pharmacologic techniques, including sequential compression devices, anti-embolic stockings, anticoagulation, and early ambulation. In 2000, Wu and colleagues surveyed members of the American Society of Metabolic and Bariatric Surgery (ASMBS) and found that while virtually all of those who completed the survey practiced some form of DVT prophylaxis, nearly half nonetheless experienced patient mortality due to PE. They found considerable variation among surgeons with respect to preferred means of prophylaxis. (11) Because of this, best practices for VTE prophylaxis in bariatric surgical patients are unfortunately based not on evidence but on the experience and opinion of experts in the field. Furthermore, there is little published evidence to direct primary care and specialty physicians on the medical management of post-bariatric patients who years following their weight loss surgery might require oral anticoagulation prophylaxis or therapy.

Narrative Summary of Methods of VTE Prophylaxis

Chemoprophylactic VTE Prevention

To date there remains no class 1 evidence to formulate specific recommendations regarding the use of anticoagulation medication. The American College of Chest Physicians recognizes three main drug classes: heparin, including low-dose unfractionated heparin (UFH) and low-molecular weight heparin (LMWH), fondaparinux (anti-factor Xa inhibitor), and aspirin.

Aspirin acts as an effective platelet inhibitor at low doses (50-100 mg daily). It acts on the cyclooxygenase-1 and prevents thrombosis. Scientists and physicians have considered aspirin for possible VTE prophylaxis. Unfortunately, the results have not measured up (12) and the American College of Chest and Physicians Guidelines do not recommend the use of aspirin alone as prophylaxis for VTE for any patient population. (13)

Unfractionated Heparin (UFH) was first discovered by Mclean (a second year medical student at Johns Hopkins University) in 1916. (10) It is a naturally occurring polysaccharide and is derived from either porcine intestine or bovine lung. UFH binds to antithrombin (AT) III and enhances AT to inactivate factors IIa, Xa, IXa, and XIIa. This then prevents the conversion of prothrombin to thrombin and fibrinogen to fibrin. (14) UFH consists of polysaccharide molecular chains of varying lengths (5000 to 40,000 Daltons). Heparin is administered intravenously or subcutaneously but is inactivated in the GI tract. It binds non-specifically to various plasma proteins and therefore causes an unreliable dose-response. It has a rapid onset of action and a short half-life. Intravenous administered heparin is measured by the activated partial thromboplastin time (aPTT).

Low Molecular Weight Heparins (LMWH) are obtained by fractionating or depolymerizing unfractionated heparin through various chemical or enzymatic processes creating short chains of polysaccharides that have an average molecular weight of less than 8000 Daltons (15). LMWH also binds to and enhances the activity of AT, but has a preferential and longer lasting

effect on factor Xa and does not selectively bind to specific proteins like heparin. As a result this drug is more predictable and has less inter-patient variability, and has a longer duration of action when compared to heparin and the risk of developing DVT is significantly reduced. (16-17) LMWHs do not require monitoring of either aPTT or INR.

There are numerous varieties of LMWH based on their molecular weight and include Enoxaparin, Dalteparin, Nadroparin, Parnaparin, Certoparin. Bemiparin, Reviparin and Tinzaparin. Enoxaparin is the most commonly used and studied LMWH in the bariatric literature. It is derived from the intestinal mucosa of pigs.

Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor. Fondaparinux inhibits factor Xa by selectively binding to antithrombin III (AT), a blood protein responsible for inactivating enzymes in the clotting cascade. When fondaparinux sodium is introduced into the circulatory system it binds to AT and effectively neutralizes its activity. This in turn disrupts the blood coagulation cascade and prevents thrombin formation. (18) Fondaparinux has no direct effect on thrombin. It is administered subcutaneously and has a long half-life. While this medication cannot be used in patients with renal impairment, a potential advantage of fondaparinux over LMWH or unfractionated heparin is a greatly reduced risk for heparin-induced thrombocytopenia (HIT).(19)

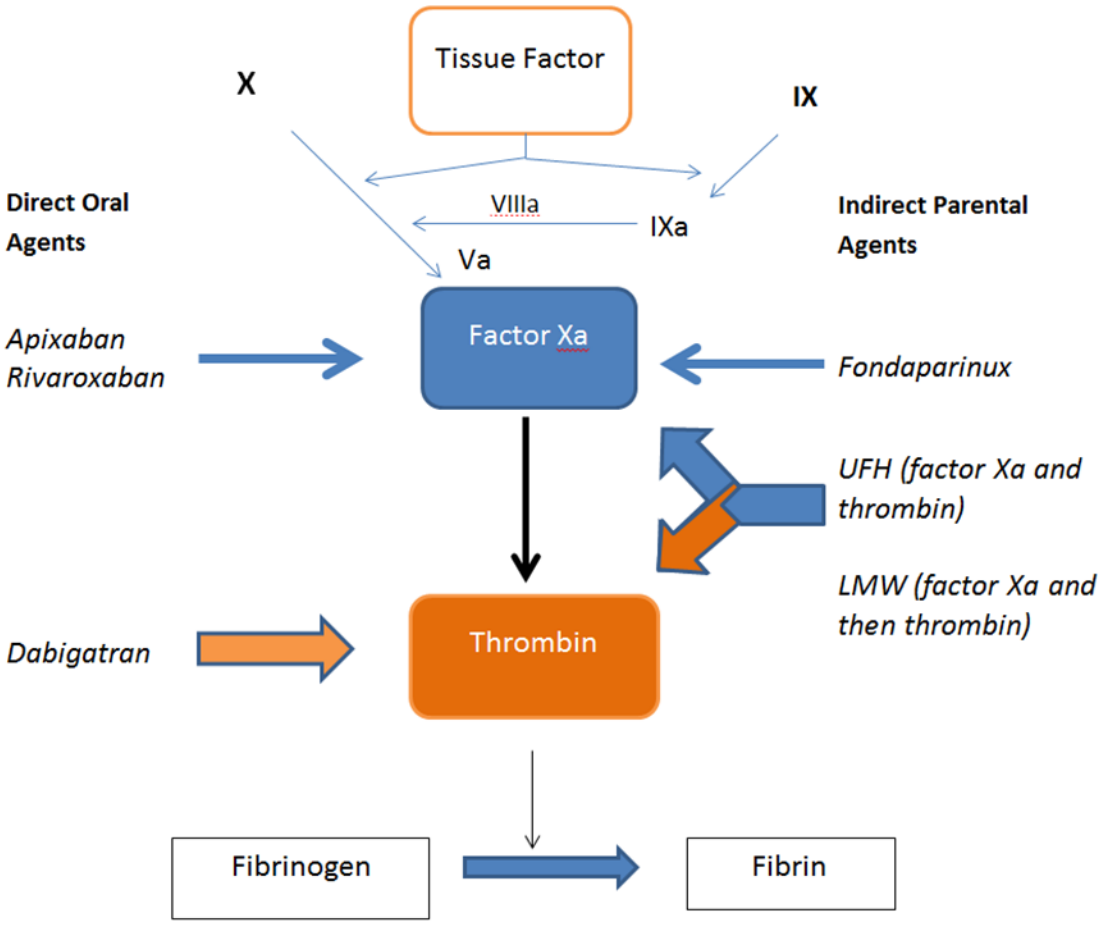
Whereas fondaparinux directly prevents DVT formation by selective binding to a specific protein, enoxaparin indirectly prevents DVT formation by prolonging the natural lag phase of thrombin formation in the body. (20)

New Oral Anticoagulants (NOACs) are currently available for prophylaxis against venous thromboembolism in patients undergoing total hip or knee replacement surgery. Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor which inhibits both free and fibrin-bound thrombin. Randomized controlled trials have shown that dabigatran is as effective in the prevention of VTE in total hip replacement.(21) Rivaroxaban (Xarelto) is an orally activated direct factor Xa inhibitor (4 hours after the dose is taken and the factor Xa activity does not return to normal for 24 hours thus once daily dosing is possible). (22) This drug has FDA approval for the initial treatment of DVT and PE and for the prevention of recurrent DVT and PE. Apixaban (Elquis): Like Rivaroxaban, **Apixaban** is a direct factor Xa inhibitor. Apixaban first became available in Europe in 2011 and is used there for preventing venous thromboembolism in hip and knee surgery. This drug was initially approved in the United States for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. (23) More recently, it has received FDA approval for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement surgery.

A recent review and meta-analysis of these new oral anticoagulants has concluded that they were equally as good as enoxaparin but did have a higher bleeding tendency. The drugs did not differ significantly for efficacy and safety. (24)

NOACs do not require routine coagulation monitoring and seem to be the way of the future for ease of administration efficacy and tolerability. Additional research is needed to determine how these new oral anticoagulants should be used in special populations such as the obese medical or surgical patient.

Figure 1 Mechanism of Action of Anticoagulants



*Derived from Dwek et al 2012

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

Patients will be recruited from our preoperative bariatric surgical clinic (Roux-en Y gastric bypass, and vertical sleeve gastrectomy). Each patient will undergo a thorough history and physical exam (routine standard of care for bariatric patients) to document demographics including: age, sex, height, weight, body mass index and absence of the exclusion criteria. See Table 1 for sequence and timing of study procedures.

Table 1. Sequence and Timing of Study Procedures

Overview of Study Visits: Specific Aims 1, 2 and 3				
Study Visit Before and After Intervention		Specific Aim 1	Specific Aim 2	Specific Aim 3
		Pharmacokinetics (Prior to Surgery)	Pharmacokinetics (Following Surgery)	Pharmacodynamics
1	3 to 5 Weeks Prior to Bariatric Surgery (study participant receives one 5 mg dose of apixaban)	X		X
2	1 Month (4 to 6 weeks) Post-bariatric surgery (study participant receives one 5 mg dose of apixaban)		X	X
3	6 Months (6 to 8 months) Post-bariatric surgery (study participant receives one 5 mg dose of apixaban)		X	X
4	12 Months (12 to 14 months) Post-bariatric surgery * (study participant receives one 5 mg dose of apixaban)		X	X
5	Final Exit Interview Visit (two weeks following final visit)	Review any adverse events that may have occurred throughout entire study		

Note: Research participants in each group (RYGB, n=15; VSG, n=15; Total n=30) will undergo the study protocol detailed above.
*The patient ideally will have lost at least 30% to 50% of excess body weight by 12 months

Study population: Obese patients with a body mass index (BMI) of 35 kg/m^2 or greater that have been approved for bariatric surgery at the Johns Hopkins Center for Bariatric Surgery from January 2015 until all patients recruited. (See Table 3. Timeline of Study)

Consenting subjects will be hospitalized overnight in the JHBMC Clinical Research Center. A single dose of 5 mg apixaban will be administered by experienced CRU nursing staff, and blood samples for apixaban concentration and factor Xa activity will be collected before administration of the apixaban dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 48 and 72 hours after dosing.

The participant will be hospitalized and monitored for a 24 hour duration and then released home when they meet discharge criteria. The participant will then be asked to return back to the CRU for one blood draw at 48 hours and one blood draw at 72 hours. At hours 48 and 72 hours we will have ±4 hour window to allow for travel and check in for the participant.

The apixaban concentrations will be measured at Pfizer (all specimens will be stored and batched for shipment to a commercial laboratory), and the factor Xa activity measured at JHH under the leadership and guidance of Dr. Thomas Kickler Director of the Lab. (As per Dr. Kickler's expertise he has recommended the ***chromogenic assay*** that measures factor Xa activity using reagents from Siemens.)

Dose schedule, duration, and concurrent medications:

A single dose of 5 mg of apixaban will be given at approximately one month before bariatric surgery, then 1, 6 and 12 months followingbariatric surgery. Alterations in the pharmacokinetics of the bariatric surgical patient could be due to the anatomic changes in the gastrointestinal tract, the resulting weight loss or both. By examining patients who have had undergone the surgery but have not lost adequate weight loss, we can separate the effects of these two variables. There will be no required concurrent medications. Excluded medications are strong dual inhibitors and inducers of CYP3A4 and P-glycoprotein inhibitors and inducers (see Table 2). This table has been provided by Dr. Michael Streiff who is an anticoagulant expert and co-investigator of this study.

Table 2. Excluded medications

Drug Class	Examples	Impact of co-administration	Suggested Managment
Combined P-glycoprotein and strong CYP 3A4 inhibitor	boceprevir, cobicistat, conivaptan, delavirdine, diltiazem, dronedarone, all HIV protease inhibitors (eg. ritonavir), imatinib,indinavir,itraconazole,ketoconazole, nefazodone, posaconazole, telaprevir, telithromycin, voriconazole	Significant increase in apixaban levels and increased potential for bleeding complications	AVOID USE. Risk higher with renal impairment
Combined P-glycoprotein and moderate CYP 3A4 inhibitor	amoidarone, azithromycin, chloramphenicol, cimetidine, erythromycin, clarithromycin, cyclosporin, diltiazem, dronedarone, felodipine, fluconazole, grapefruit, lapatinib, mifepristone, nicardipine, quinidine, ranolazine, tamoxifen, telithromycin, ticagrelor, verapamil	Moderate increase in apixaban levels in patients with normal renal function. Significant increase in apixaban levels in patients with severe renal function (CrCl < 30 ml/min)	Prescribe apixaban with caution in patients with normal renal function. AVOID USE in patients with severely impaired renal function (CrCl < 30 ml/min), age > 80 years or low body weight (< 60 kgs).
Combined P-glycoprotein inducer and strong CYP 3A4 inducer	carbamazepine, dexamethsone, phenytoin, rifampin, St John's wort	Significant reduction in apixaban levels. Effects may persist for several weeks following discontinuation	AVOID USE
Inducers of p-glycoprotein	doxorubicin, prazosin, tipranavir, trazodone, vinblastine	Significant reduction in apixaban levels. Effects may persist for several weeks following discontinuation	AVOID USE
Strong inducers of CYP 3A4	barbiturates, bosentan, efavirenz, etravirine, fosphenytoin, nafcillin, nevirapine, oxarbazepine, phenytoin, primidone, rifabutin, rifapentine	Significant reduction in apixaban levels. Effects may persist for several weeks following discontinuation	AVOID USE

Drug Interactions with Apixaban: P-glycoprotein is a drug transporter that mediates apixaban absorption. P-glycoprotein inhibitors can increase apixaban absorption while inducers will reduce its absorption. The metabolism of apixaban is mediated by p450 liver microsomal enzyme CYP3A4. CYP3A4 inhibiotrs will increase apixaban levels while inducers will decrease levels.

b. Study duration and number of study visits required of research participants.
Study duration: two years
Number of study visits: four (one month prior to surgery and 1, 6 and 12 months following surgery).

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.
There will be no effect on routine clinical care.

e. Justification for inclusion of a placebo or non-treatment group.
N/A

f. Definition of treatment failure or participant removal criteria
The participants will be removed from the study if they develop a clinically significant illness or a major bleeding complication attributed to apixaban (as opposed to minor issues, which need not remove the participant from the study).

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
If the subject discontinues early, will we conduct an exit interview with final assessment.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Men or women, 18 to 65 years old with a BMI of 35 kg/m^2 or greater who will be undergoing bariatric surgery (VSG and RYGB).
- Signed written informed consent
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- Women must not be breastfeeding

Exclusion Criteria:

- History of documented clotting/coagulation disorder.
- History of cancer (within the last year)
- Any diagnosis requiring anti-coagulation
- History of hypersensitivity reaction to apixaban
- Active clinically significant bleeding
- GFR < 30
- Participant who has moderate-severe liver disease (Child-Pugh B or C)

- Participants currently receiving any type of anticoagulation or blood thinning medications, including heparin, low molecular weight heparins, Plavix, aspirin, NSAIDS
- Participant who is taking any of the excluded medications (see Table 2 above)

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

Drug procurement, handling, accountability and destruction will be carried out by the Johns Hopkins Bayview Research Pharmacy. Administration of the drug will be completed by nursing staff in the CRU. These nurses will be trained and familiar with the protocol.

We chose apixaban because it is delivered orally, eliminating the need for subcutaneous injection of anticoagulation prophylaxis, and has a new indication in orthopedic surgery for DVT. Administration of a 5 mg single does is expected to result in similar exposure to that observed in patients treated with 2.5 mg twice daily for the prevention of VTE following elective knee or hip replacement.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

The dose of apixaban proposed for this study is consistent with the FDA -approved dose for VTE prophylaxis and will be given by the usual route of administration (orally). It is labeled for VTE prophylaxis in patients undergoing hip or knee replacement, but not in those whose VTE risk is only obesity and not in patients undergoing bariatric surgery. Safety information can be found in the FDA-approved package insert.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

Apixaban is an FDA approved oral anticoagulant. This study is not intended to assess clinical outcomes for obese patients undergoing bariatric surgery who take a single dose of apixaban, but rather is a pharmacokinetic and pharmacodynamic comparison of absorption and elimination of apixaban before vs. after bariatric surgery. Apixaban doses up to 50 mg have been well tolerated in previous studies in healthy volunteers. (25, 26, 27) Therefore, a single 5 mg dose of apixaban in this patient population is expected to be safe and well tolerated. Safety information can be found in the FDA-approved package insert.

Apixaban 5 mg tablets will be supplied by BMS and delivered to the Johns Hopkins Bayview Research Pharmacy for processing and administration/

PRODUCT	Packaging	APPEARANCE	Storage and handling
Apixaban 5mg tablets	Commercial Bottles of 60 tablets	Yellow, round, biconvex, film coated tablets with "893" debossed on one side and "2 ½" on the other side	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)

7. Study Statistics

a. Primary outcome variable.

To determine the durability or change in pharmacokinetics and pharmacodynamics of apixaban in patients with a body mass index (BMI) of 35 kg/m^2 or greater following one of two bariatric surgical procedures (pre-operative versus post-operative vertical sleeve gastrectomy or Roux-en-Y gastric bypass patients).

b. Secondary outcome variables.

1. To compare/contrast the pharmacokinetics and pharmacodynamics of apixaban in bariatric surgical patients who have undergone RYGB vs. VSG.

2. To determine how the pharmacokinetics of the drug may differ when there is significant post-operative surgical weight loss (>40% estimated excess body weight) 12 months following surgery versus those patients who have suboptimal weight loss following bariatric surgery (< 40% of estimated excess body weight).

c. Statistical plan including sample size justification and interim data analysis.

We propose to study 15 subjects in each arm (RYGB vs. VSG) and use them as their own controls. We have accounted for loss to follow-up (even with a 36% (5 in each group) drop-out rate, we would have enough subjects (10 per group) to demonstrate a 36 % change in AUC with an alpha error of 0.05 and a beta error of 0.2 (Power of 80%). If there is no loss to follow-up and all patients remain in the study, this will allow us to demonstrate a 29% change in AUC with an alpha error of 0.05 and a beta error of 0.2.

These calculations were calculated based on the following data from Upreti et al.: Ratio of geometric mean point estimated for high body weight (>120 kg) vs. normal body weight for C_{max} = 0.692 (0.586, 0.818) and AUC (INF) = 0.77 (0.652, 0.912).

Routine pharmacokinetic data will be determined, including C_{max}, T_{max} and AUC for each subject at each dosing time, and compared within subjects and between subjects and between groups. Factor Xa activity will be compared to apixaban concentration at each time point.

d. Early stopping rules.

While we do not expect to have any serious adverse events related to the administration of a single dose of 5 mg of apixaban as required in this study, we will interrupt the study and report to the IRB if 10% or more of our first 12 subjects suffer a serious adverse event "definitely

related" or "probably related" to the administration of apixaban. In such a case, we will not resume the study until the investigators, the sponsor, and the IRB are satisfied that there are alternative explanations for the events not related to apixaban, or the study procedures are altered to reduce the risk of such events for future participants. After the first 20 subjects, if there is ever a point where 10% or more of the subjects suffer a serious adverse event either "definitely" or "probably" related to apixaban, the same approach will be taken.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

The only risks related to pharmacokintectic and pharmacodynamics studies are minor bleeding and/or bruising at the IV insertion site and the possibility of vasovagal reactions to blood draws.

The risks associated with use of apixaban are as follows:

Bleeding: As with other anticoagulants, subjects administered with apixaban are to be carefully observed for signs of bleeding.

Stroke: Stroke has been reported occasionally in studies of apixaban (multiple dosing studies). However, given that this is a single dose study – the likelihood of such a complication is rare. As part of good clinical practice, the investigators will remain vigilant.

b. Steps taken to minimize the risks.

To minimize the risks we will use experienced phlebotomists from the CRU to place the venous catheters for blood drawing or to draw the blood via venipuncture if preferred by the subject. Those drawing the blood will be familiar with the possibility of vasovagal reactions, and will have the subject lay down with legs elevated if the subject becomes symptomatic. The patients will be monitored for a full 24 hours after ingesting the single dose of apixaban. The participant will then return at 48 hours and at 72 hours at which time we can check in with the patient and ensure there are no side effects to the medication or complications. We will also closely monitor subjects before, during, and after study visits.

All records will be secured in research offices. Computers that contain patient data are password protected.

WOMEN OF CHILD-BEARING POTENTIAL (WOCBP)

Sexually active Women of Child-Bearing Potential (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 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 24hours 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.

ADVERSE EVENT REPORTING

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to Bristol Meyers Squibb (BMS) Worldwide Safety.

Adverse Events

- 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.
- The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:
  - Related: There is a reasonable causal relationship between study drug administration and the AE.
  - Not Related: There is not a reasonable causal relationship between study drug administration and the AE.
- The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.
- 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 adverse events).

Serious Adverse Events

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

- 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 for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on 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 above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

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

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Adverse Events of Special Interest

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 suspectived cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.**

***NOTE:** The following hospitalizations are not considered SAEs:*

- 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 (eg, routine colonoscopy)
- Medical/surgical admission 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 (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Serious Adverse Event Collecting and Reporting

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

days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Fax Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E 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.

Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, provide details of the following:

- Any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening

event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.

- BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:

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

Non-Serious Adverse Events

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

Non-Serious Event Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Nonserious adverse event 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.

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 study drug, or those that are present at the end of study treatment as appropriate.

Nonserious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

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

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

Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

Pregnancy

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 (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also 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 (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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 SAEs.

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 as a nonserious or serious adverse event, as appropriate, and reported accordingly.

c. Legal risks such as the risks that would be associated with breach of confidentiality.

There is the risk that information about you may become known to people outside this study.

d. Financial risks to the participants.

The study does not have funding to pay for any medical complications of study participation. The participants would therefore assume the potential financial risk of unanticipated medical care costs.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There may be no benefit to the participant. Potential benefits to society include improved knowledge about prophylaxis with oral anticoagulation medications during bariatric surgery and following surgery when treating a prior bariatric surgical patient with an oral anticoagulation medication for a medical condition such as stroke or atrial fibrillation.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

To compensate patients for their time and participation - $250.00 plus a parking pass will be given per visit completed:
Visit 1: **Pre-op**: 24 hours inpatient/48 hour blood draw outpatient/72 hour blood draw outpatient $250.00 completed visit
Visit 2: **1 month**: 24 hours inpatient/48 hour blood draw outpatient/72 hour blood draw outpatient $250.00 completed visit
Visit 3: **6 month**: 24 hours inpatient/48 hour blood draw outpatient/72 hour blood draw outpatient $250.00 completed visit
Visit 4: **12 month**: 24 hours inpatient/48 hour blood draw outpatient/72 hour blood draw outpatient $250.00 completed visit

Final Exit Interview by telephone (two weeks following visit #4): Review any adverse events that may have occurred. No compensation at this time.
The total amount of compensation possible is $1,000.00 plus parking.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

No costs to the participants.

Table 3. Timeline for Study

TASK	Year 1				Year 2			
	July 2016	Oct. 2016	Jan. 2017	April 2017	July 2017	Oct. 2016	Jan. 2018	April 2018
Submission of Grant to BMS								

and Organization of Study								
Materials and supplies								
Database creation/testing								
JHU IRB approval								
Recruitment and enrollment								
Data collection								
Enter and clean data								
Data quality review								
Analyze data								
Abstract submissions								
Manuscript preparation								
Preparation of other grants								

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