Clinical Research Protocol MMTPRO114 Version 2.0

A Pilot Study Investigating
Apixaban and Dexamethasone InterAction in Multiple Myeloma (ADAM)

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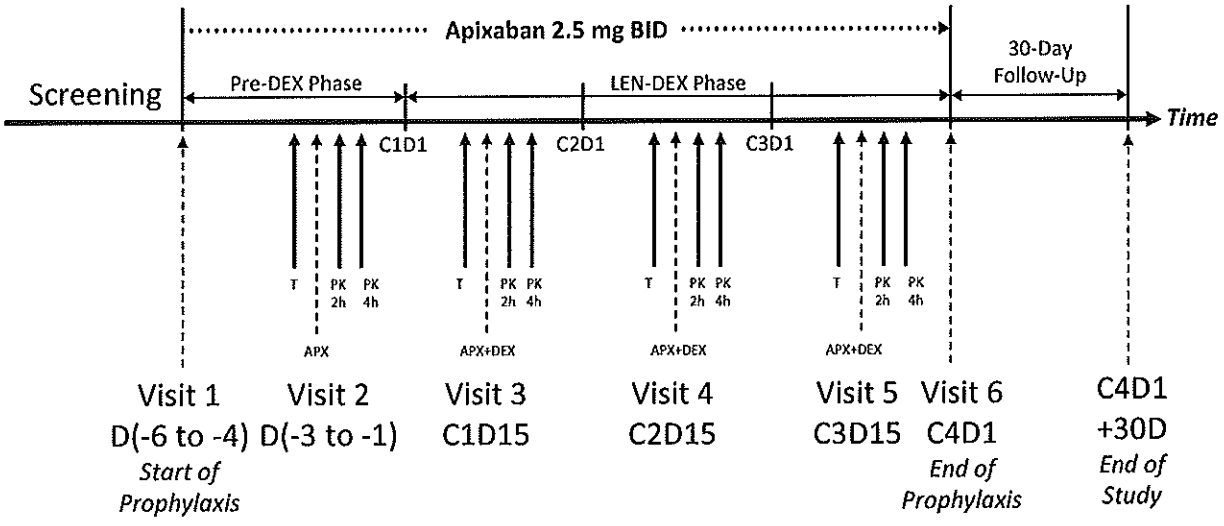
1. PROTOCOL SYNOPSIS

Prophylaxis for venous thromboembolism (VTE) with either low-molecular-weight-heparin (LMWH) or INR-adjusted warfarin is recommended in patients receiving lenalidomide (LEN) and dexamethasone (DEX)-based regimens for multiple myeloma. Oral Factor Xa inhibitors, such as APX (APX), are an attractive alternative to both LMWH and warfarin, and can potentially simplify and improve VTE prevention and treatment in myeloma patients with a high risk for VTE. However, co-administration with DEX, a potent inducer of the metabolic pathways critical for Factor Xa inhibitor clearance, may significantly reduce Factor Xa inhibitor plasma levels and result in inadequate prophylaxis. This study will investigate the impact of DEX on anti-Xa levels in subjects taking APX, a direct oral Factor Xa inhibitor. We propose a prospective, cohort study of 24 subjects with multiple myeloma who are starting a LEN-DEX-treatment regimen. Eligible subjects will initiate thromboprophylaxis with APX 4-6 days prior to starting their LEN-DEX regimen and continue until the end of cycle 3. Anti-Xa levels, D-Dimer and plasma drug concentration will be measured with exposure to APX alone and to APX plus DEX on day 15 of the first 3 cycles of LEN-DEX to evaluate relevant level changes. The sample size of 24 provides 90% power to detect a primary outcome of $\geq$ 50% reduction in peak anti-Xa levels from baseline. Secondary outcomes include changes in D-dimer, plasma APX levels and symptomatic VTE and bleeding during the 3-month treatment period.

2. SCHEDULE OF EVENTS

D = Day
C = Cycle LEN-DEX
APX = Apixaban administration
DEX = Dexamethasone administration
APX+DEX = Simultaneous apixaban + dexamethasone administration on D15 of each cycle of LEN-DEX
PK2h & PK4h = peak level measurement 2 hrs & 4 hrs (respectively) after administration of APX+DEX ⟶
T = Trough level measurement before admininstration of APX alone or APX+DEX on D15 ⟶



3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
APX	APX
ASA	Acetylsalicylic Acid
AST	Aspartate transaminase
ASCO	American Society of Clinical Oncology
BCCA	British Columbia Cancer Agency
BID	Bis in Die (twice daily)
BMS	Bristol-Myer Squibb
CAT	Cancer-Associated Thrombosis
CI	Confidence Interval
Cmax	Maximum Concentration (plasma)
Ctrough	Trough Concentration (plasma)
CrCl	Creatinine Clearance
CRNMB	Clinically Relevant Non-Major Bleeding
CTCAE	Common Terminology Criteria for Adverse Events (NCI)
CYP	Cytochrome P450
DEX	DEX
DVT	Deep Vein Thrombosis
EOS	End of Study
FXai	Factor Xa Inhibitor
GCP	Good Clinical Practice
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
INR	International Normalized Ratio
ISTH	International Society on Thrombosis and Haemostasis
LEN	Lenalidomide
LMWH	Low-Molecular-Weight Heparin
NCI	National Cancer Institute
NOAC	Novel Oral Anticoagulant
OD	Once Daily
PE	Pulmonary Embolism
P-gp	P-glycoprotein
PK	Pharmacokinetics
PO	Per Os (oral administration)
REB	Research Ethics Board
RR	Relative Risk
SAE	Serious Adverse Event
ULN	Upper limit of normal
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

5. BACKGROUND & SCIENTIFIC JUSTIFICATION - STUDY RATIONALE

5.1 Multiple Myeloma, Thrombosis Risk & Primary Thromboprophylaxis Indications

Multiple myeloma is a malignant plasma cell disorder associated with an increased incidence of venous thromboembolism (VTE). The most common presentations of VTE are deep venous thrombosis (DVT) and pulmonary embolism (PE). The incidence is especially high (up to 28%) in those myeloma patients receiving immunomodulatory therapy with thalidomide or lenalidomide (LEN) in combination with steroid or chemotherapy.[1-5] Consequently, primary thromboprophylaxis with anticoagulant agents is recommended by major clinical practice consensus guidelines.[2,6,7] The International Myeloma Working Group (IMWG) recommends a risk-stratification approach that uses acetylsalicylic acid (ASA) in patients with a low risk and low-molecular-weight heparin (LMWH) or International Normalized Ratio (INR)-adjusted warfarin in patients with a high risk for venous thrombosis (Table 1).[2] Other guidelines, such as the clinical practice guideline from the American Society of Clinical Oncology (ASCO), are less specific and recommend either LMWH or ASA for primary prophylaxis.[6] The British Columbia Cancer Agency (BCCA) recommends considering the use of ASA 81 mg daily in all patients and anticoagulation in those with higher thromboembolic risk.[8]

Table 1: Thromboprophylaxis Recommendations According to Risk Stratification by the International Myeloma Working Group[2]

Thrombosis Risk Factors	Action
Individual risk factors Obesity (BMI> 30kg/m2) Previous venous thromboembolism Central venous catheter or pacemaker Associated disease Cardiac disease Chronic renal disease Diabetes Acute infection Immobilization Surgery General surgery Any anesthesia Trauma Medications Erythropoietin Blood clotting disorders *Myeloma-related risk factors* Diagnosis of myeloma itself Hyperviscosity	If no risk factor or any one risk factor is present: Aspirin 81-325 mg once daily If two or more risk factors are present: LMWH (equivalent of enoxaparin 40 mg subcutaneous once daily) OR Full dose of warfarin (target INR 2-3)
Myeloma treatment High-dose dexamathasone (≥480 mg/month) Doxorubicin Multi-agent chemotherapy	LMWH (equivalent of enoxaparin 40 mg subcutaneous once daily) OR Full dose of warfarin (target INR 2-3)

5.2 Conventional Anticoagulant Limitations & Potential Benefits of Novel Oral Anticoagulants

Despite international guideline recommendations, prophylaxis with LMWH or warfarin is often avoided because of the discomfort and expense of daily subcutaneous injection with LMWH and the burden of frequent blood monitoring and dose adjustments required for warfarin therapy. In Canada, many patients are given ASA prophylaxis without regard to risk stratification largely because of these concerns. It is not surprising then that the novel oral anticoagulants (NOACs) are being considered as options for both primary thromboprophylaxis and treatment of cancer-associated thrombosis (CAT). These new drugs, which are orally administered at fixed doses and do not require monitoring of their anticoagulant effect, have now been approved for thromboprophylaxis in orthopedic surgery, stroke prevention in non-valvular atrial fibrillation and treatment of VTE in Canada.[9] In terms of efficacy and safety, the NOACs are at least non-inferior to traditional anticoagulant therapies in these settings, while having the important advantage of being easy to use.

5.3 Novel Oral Anticoagulants in Cancer Patients

However, the role of NOACs in cancer patients has yet to be established because cancer patients represented only a small percentage of patients enrolled in clinical trials. Furthermore, the definition of active cancer is inconsistent across studies and those included were highly selected and likely do not represent the majority of oncology patients at risk for VTE [10]. In addition to the lack of clinical trial data, gastrointestinal problems, liver or renal impairment, potential drug interaction with chemotherapeutic or other cancer therapies are real concerns, especially when therapeutic levels and standardized methods of measuring these drugs' anticoagulant activity are not readily available. These agents are currently not recommended for use in cancer patients by clinical practice guidelines.[11]

5.4 Oral Factor Xa Inhibitors & Cancer Patients: Most Data for Apixaban

Among the NOACs currently available, apixaban (APX; Eliquis®) has a favourable safety profile in prophylaxis and treatment settings. Additionally, amongst NOACs, APX has the most cancer patient-specific data as summarized in Table 2. APX is a direct inhibitor of activated factor X (FXa_i) with an oral bioavailability of approximately 50%. It reaches peak plasma levels (Cmax) in 3 hours after oral administration and is metabolized largely through the hepatobiliary system with a half-life of approximately 12 hours in patients with normal renal and hepatic function.[12,13] Consequently, it is given in fixed doses twice daily (BID) at 2.5 mg BID in the prophylaxis setting and 5 mg BID in the stroke prevention and VTE treatment settings. It has no interaction with food but it has important drug interactions; potent inhibitors or inducers of the P-glycoprotein transport system and CYP3A4 cytochrome metabolic pathway can increase or decrease the plasma levels of APX, respectively. These drugs, including many chemotherapeutic agents, are either contraindicated or should be avoided in patients who are prescribed APX.

Clinical trials to date show that APX is an effective and safe anticoagulant compared with standard therapy in the treatment and prevention of VTE (Table 2). The AMPLIFY trial showed that APX 10 mg BID for 7 days followed by 5 mg BID is non-inferior to conventional VTE therapy with LMWH and warfarin but had a lower risk of bleeding.[14] In the 3-arm AMPLIFY-EXT study, in which patients were randomized to APX 5 mg BID, APX 2.5 mg BID or to

placebo for extended secondary prophylaxis of VTE, APX at either dose were superior to placebo, and major bleeding in the 2.5 mg BID APX arm was comparable to placebo.[15] The ADOPT trial studied thromboprophylaxis in hospitalized patients admitted for medical illnesses. In this study, 2.5 mg BID APX for 35 days was compared with enoxaparin 40 mg once daily for 7 days.[16] The risk of major bleeding was increased in the APX group but the risk of VTE was comparable. Finally, in the ADVANCE-1, -2 and -3 studies that evaluated APX for VTE prophylaxis after major hip and knee surgery, APX 2.5 mg BID is comparable to enoxaparin in efficacy and bleeding.[17-19] APX is also highly effective for stroke prevention in patients with non-valvular atrial fibrillation.[20,21] Although all of these studies only included a low proportion of or no patients cancer, the low bleeding rates comparable to ASA and placebo are reassuring.

The only cancer-specific study to date evaluating a NOAC is a safety, feasibility randomized phase II study in patients with advanced or metastatic cancer (ABLE study).[22] In this double-blind study, cancer patients receiving chemotherapy for advanced or metastatic solid tumours (including lung, breast, gastrointestinal, bladder, ovarian or prostate cancers, cancer of unknown origin, myeloma or selected lymphomas) were randomized to placebo or APX 5 mg, 10 mg or 20 mg once daily for 12 weeks. There were no major bleeding events reported in the 5 mg and 10 mg groups, whereas in the 20 mg and placebo groups, 2 and 1 major bleeds, respectively, were reported. There were no fatal bleeds. Overall, the rate of major bleeding in the 93 APX patients was 2.2% (95% confidence interval 0.26 to 7.5%). Of the patients receiving placebo, 3 of the 30 patients (10%) had symptomatic VTE, while none occurred in APX-treated patients.

An alternative FXa_i, rivaroxaban, is approved for prevention and treatment of VTE in Canada. Compared with APX, this FXa_i requires only once daily dosing but it has a similar CMax, half-life and slightly more dependence on renal clearance. Similar to APX, rivaroxaban is non-inferior to conventional anticoagulant therapy for stroke prevention in non-valvular atrial fibrillation (ROCKET-AF trial) and VTE treatment (EINSTEIN-DVT and EINSTEIN-PE trials) and is associated with a higher risk of bleeding for extended prophylaxis in hospitalized medical patients compared with standard in-patient prophylaxis with enoxaparin (MAGELLAN trial).[23-25] It is also associated with more bleeding compared with enoxaparin for primary prophylaxis in orthopedic surgery (RECORD 1-4 trials).[26] The only other available NOAC in Canada is dabigatran, a direct thrombin inhibitor. This twice daily oral drug is highly dependent on renal clearance.[12] Consequently, it is the least attractive candidate among the NOACs for use in patients with myeloma, who often have significant renal impairment. Overall, APX has the most comprehensive and reassuring data among NOACs in support of further investigation in the cancer patient population.

Table 2: Summary of Efficacy & Safety Outcomes of Apixaban

Study Name	Study Population	Agents, Dose & Comparison	Efficacy (New Agent vs Comparison)	Safety (New Agent vs Comparison)
AMPLIFY[14]	**Acute VTE treatment** (2.6% cancer patients)	APX 10 mg BID and 5 mg BID vs LMWH/VKA	**Non-inferior** VTE 59/2609 (2.3%) vs 71/2635 (2.7%), RR for APX 0.84 (95% CI, 0.60 to 1.18; P<0.001 for non-inferiority)	**Less (major) bleeding** MB 0.6% vs 1.8%, RR for APX, 0.31 (95% CI, 0.17 to 0.55; P<0.001 for superiority) MB+CRNMB 4.3% vs 9.7%, RR for APX, 0.44 (95% CI, 0.36 to 0.55)
AMPLIFY-EXT[15]	**Extended VTE prophylaxis** (2% cancer patients)	APX 2.5 mg vs APX 5 mg BID vs placebo	**Reduced the risk of recurrent VTE** Symptomatic VTE 1.7% for APX 2.5mg vs 1.7% for APX 5 mg vs 8.8% placebo; 95% CI 5.0 to 9.3 and 7.0 4.9 to 9.1, respectively (P<0.001 for both comparisons)	**Comparable** MB 0.2% for APX 2.5mg, 1% for APX 5mg and 0.5% in the placebo group (a difference of 0.2% (95% CI, −0.3 to 0.8) and 0.4% (95% CI, −0.2 to 0.9) respectively for APX 2.5mg and 5.0mg
ADOPT[16]	**Medically-ill** subjects (3% cancer patients)	APX 2.5 mg BID x 25 days vs ENX 40 mg OD x 7 days	**No added VTE reduction** VTE rate 2.7% vs 3.1%, RR with APX, 0.87 (95% CI, 0.62 to 1.23; P=0.44)	**APX showed significantly more bleeding** MB 15/3184 (0.47%) vs 6/3217 (0.19%), RR with APX, 2.58 (95% CI, 1.02 to 7.24; P=0.04)
ABLE[22]	**Primary thromboprophylaxis in advanced or metastatic cancer** patients (n=125)	APX 5 mg, 10 mg or 20 mg OD or placebo	**Underpowered** VTE: none with APX vs 3/33 with placebo	**No increased bleeding in 5mg and 10mg group of APX** MB 0/32, 0/30, 2/33 (6%) and 1/30 (2%) CRNMB were 1, 1, 2, and 0. No fatal bleeds.
ADVANCE 1[17]	**Total knee replacement**	APX 2.5 mg BID vs ENX 30 mg BID	**Non-inferior.** Primary efficacy outcome was a composite of asymptomatic and symptomatic DVT, nonfatal PE, and death from any cause during treatment. 9.0% with APX vs 8.8% with enoxaparin (RR, 1.02; 95% CI 0.78 to 1.32).	**Less bleeding:** MB+CRNMB 2.9% with APX and 4.3% with ENX (P=0.03).

ADVANCE-2 [19]	**Total knee replacement**	**APX** 2·5 mg BID vs ENX 40 mg OD	Primary outcome: asymptomatic and symptomatic DVT, non-fatal PE, and all-cause death during treatment. 15% with APX vs 24% with ENX (RR 0·62 (95% CI 0·51 to 0·74; p<0·0001).	**Comparable bleeding rates.** MB+CRNMB occurred in 53 (4%) of 1501 patients receiving APX and 72 (5%) of 1508 treated with ENX (p=0·09).
ADVANCE-3[18]	**Total hip replacement**	APX 2.5 mg BID vs ENX 40 mg OD	**Lower rates of VTE** VTE 1.4% vs 3.9%, RR with APX, 0.36; (95%CI 0.22 to 0.54; P<0.001 for both non-inferiority and superiority)	**Comparable** MB+CRNMB 4.8% vs 5.0%, absolute difference in risk, −0.2%; 95% CI −1.4 to 1.0)
AVERROES[20]	**Non-valvular atrial fibrillation** subjects unsuitable for vitamin K antagonist (cancer patients not specified)	APX 5 mg BID vs ASA	**Reduced the risk of stroke or systemic embolism** Stroke or systemic embolism 1.6%/yr vs 3.7%/yr; HR with APX 0.45 (95% CI, 0.32 to 0.62; P<0.001).	**No significant increase of major bleeding** MB 1.4%/yr vs 1.2%/yr, HR with APX, 1.13 (95% CI, 0.74 to 1.75; P=0.57). Intracranial bleeding 11 cases with APX vs 13 with ASA.
ARISTOTLE[21]	**Atrial fibrillation** (cancer patients not specified)	APX 5 mg BID vs warfarin	**Better at preventing stroke** Ischemic or hemorrhagic stroke or systemic embolism 1.27% vs 1.60% per year, HR with APX 0.79; 95%CI, 0.66 to 0.95; P<0.001 for non-inferiority; P=0.01 for superiority).	**Less major bleeding** MB 2.1% vs 3.1%, HR for APX, 0.69 (95% CI, 0.60 to 0.80; P<0.001. Hemorrhagic stroke 0.24% vs 0.47% per year, HR for APX, 0.51; (95% CI, 0.35 to 0.75; P<0.001)

APX, Apixaban; ENX, enoxaparin; MB, major bleed; CRNMB, clinically relevant non-major bleed; HR, hazard ratio; RR, relative risk; DVT, deep vein thrombosis; PE, pulmonary embolism.

5.5 Pharmacokinetics of Apixaban & Potential Drugs Interactions of the New Anticoagulants

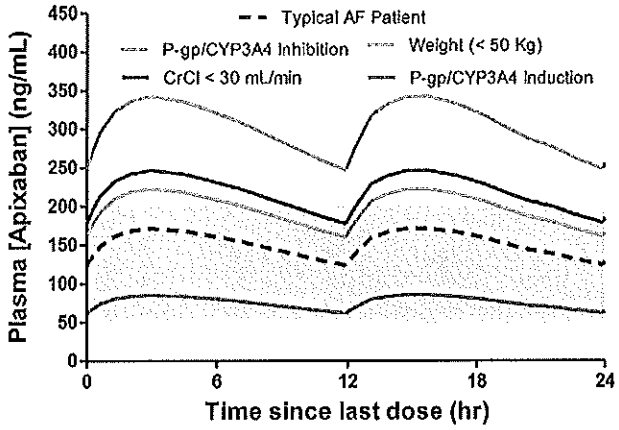
The maximum concentrations (Cmax) of APX appears 3 to 4 hours after tablet intake, and has a half-life of approximately 12 hours.[12] APX can be taken with or without food, and this does not affect the Cmax or area under the curve. APX is cleared via both renal and biliary mechanisms in addition to direct intestinal elimination. The anticoagulant activity of APX can be measured using anti-Xa activity assays. Studies have shown that anti-Xa activity correlates well with APX drug levels.[27] Overall, there is a linear relation between dose and drug level.[28]

However, like other NOACs, APX has potential drug interactions. Because APX is a substrate of the p-glycoprotein transport mechanism and is metabolized by the CYP3A4 pathway, its plasma level is influenced by drugs that are moderate or strong inhibitors or inducers of these pathways (**Figure 1**). Dexamethasone (DEX) is both a CYP3A4 and p-glycoprotein inducer, and thereby can potentially lower APX plasma levels. The clinical significance and duration of this effect has

not been examined. Although the half-life of DEX is 3–6 hours, it has a biological half-life of 36-72 hours. The onset of induction might also be delayed for days or weeks after the introduction of DEX. Moreover, DEX may change long-term CYP3A4 expression, possibly leading to even more profound effects in patients taking this drug long-term.[29,30] Therefore, co-administration of APX and DEX may have clinically important impact on APX levels.

These theoretical pharmacokinetic (PK) effects, however, have not been studied in patients. Currently, there is no recommendation against the co-administration of DEX and APX. Furthermore, because DEX is not given on a daily or continuous basis in myeloma or other anti-cancer or anti-emetic regimens, it is possible that intermittent exposure would not result in any measurable, sustained or physiologically important induction of p-glycoprotein and CYP3A4 pathways. Clearly, there is sufficient clinical and pharmacological equipoise to support formal investigation of the interaction.

Figure 1



Predicted mean steady-state APX plasma concentrations after 5 mg twice-daily administration is represented by the dashed black line (digitized from Leil et al.[31] Coloured solid lines represent the predicted effect of various clinical variables on APX concentration based on known AUC change. The shaded area represents the population PK model predicted 5%-95% confidence interval of Ctrough in atrial fibrillation patients. The effect of P-gp/CYP3A4 inhibition or induction on APX plasma concentration curves shown here was in the presence of the P-gp/CYP3A4 inhibitor ketoconazole (top straw-coloured line) and P-gp/CYP3A4 inducer rifampicin (bottom purple line).

Abbreviations: AF: atrial fibrillation; CrCl, creatinine clearance; Ctrough, trough plasma concentration; CYP, cytochrome P450; P-gp, P-glycoprotein;From Gong et al, Canadian Journal of Cardiology 2013.[28]

5.6 Treatment of Multiple Myeloma with LEN-DEX

Currently, LEN-DEX is recommended for treatment of myeloma in patients who have received at least one prior therapy.[32] Emerging evidence suggests that it is also effective as first-line treatment but this has not been adopted widely as standard of care. At our centre, LEN is given at 25 mg once daily for the first 21 days of a 28-day cycle, while DEX is given as a single dose of 40 mg or 20 mg once weekly (days 1, 8, 15, 22 of the 28-day cycle). Higher-dose DEX regimens are also used, such as once-daily dosing on days 1-4, 9-12, 17-20 of each cycle. The exact DEX dose regimen is selected and adjusted based on disease severity, expected toxicity and patient tolerance. For most patients with myeloma who are elderly, the more intensive DEX regimens are difficult to tolerate and the low-dose, once-weekly regimen is associated with lower toxicity (especially VTE) and better short-term overall survival.[33] For the purpose of this pilot study, we will study the impact of the 2 most commonly used DEX regimens: 20 mg once weekly and 40 mg once weekly. These regimens are associated with a lower risk of thrombosis and potentially a lower risk of clinically significant APX-DEX interaction.

6. PURPOSE OF THIS STUDY

Our pilot study will assess whether APX plasma levels are significantly lowered when APX is combined with DEX in patients being treated with LEN-DEX regimen for myeloma. To focus on measuring the impact on the anticoagulant activity of APX, we will examine the anti-Xa levels as well as D-dimer plasma concentrations over the first 3 cycles of therapy. If we demonstrate that APX levels remain unchanged and stable over time, APX could be an attractive alternative for thromboprophylaxis in myeloma patients requiring prophylaxis. Results of this study will provide critical information regarding drug interaction for the further development of APX and other NOACs in the oncology population.

7. RESEARCH HYPOTHESIS

Co-administration of APX, a Factor Xa inhibitor, with DEX in patients being treated with a LEN-DEX regimen for multiple myeloma does not produce a 50% or more reduction in peak anti-Xa activity levels for APX over a 3-month treatment period during the first 3 cycles of LEN-DEX therapy.

7.1 Primary Objective

To determine the interaction between DEX and APX by measuring peak anti-Xa levels achieved with a prophylactic dose of APX (2.5 mg PO BID) over the course of the first 3 cycles of LEN-DEX treatment regimens (approximately 3 months) in patients with multiple myeloma.

7.2 Secondary Objectives

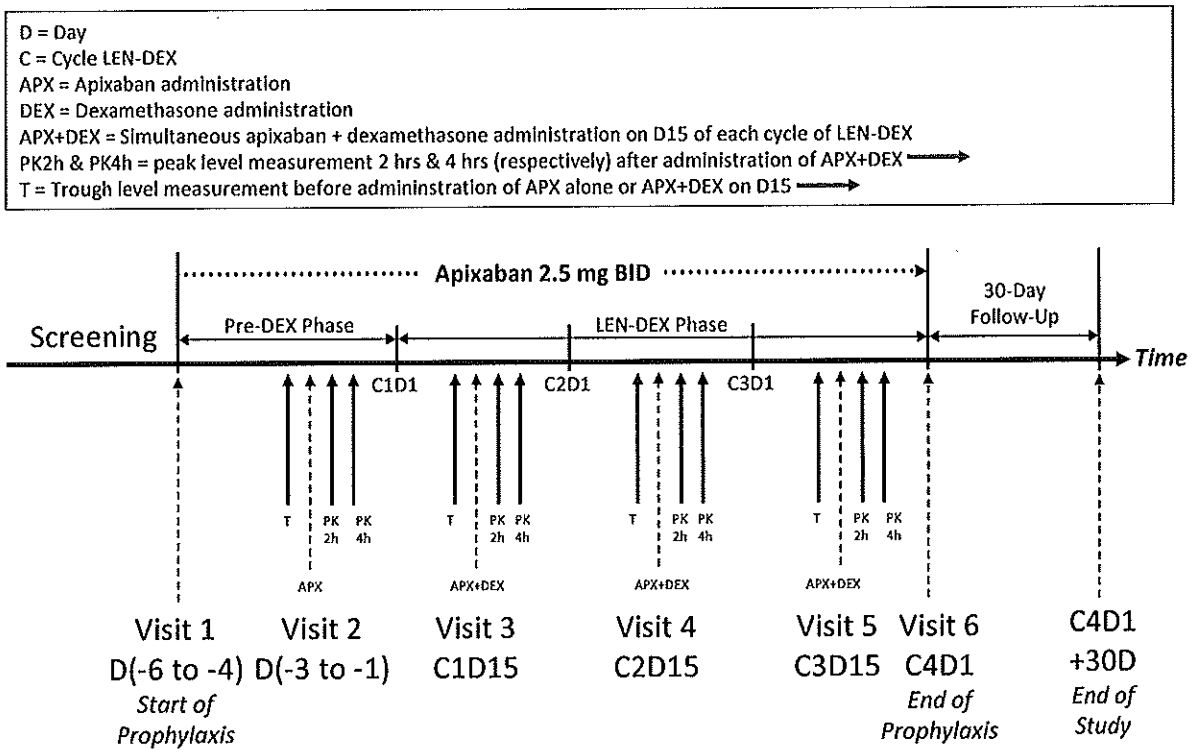
1. To follow the serial D-dimer levels and APX plasma concentrations in patients receiving APX 2.5 mg PO BID for primary thromboprophylaxis during the first 3 cycles of LEN-DEX therapy for myeloma.
2. To determine the feasibility and safety of 3 months of APX 2.5 mg PO BID for primary thromboprophylaxis, by following patients for clinical events, including all bleeding events, thromboembolic events, serious adverse events and death.

8. STUDY DESIGN

This is a prospective, open-label, single centre cohort study (Fig 2). Eligible and consenting subjects will start APX at a dose of 2.5 mg PO BID approximately 4-6 days (Day -4 to -6) prior to the start of LEN-DEX treatment (Pre-DEX phase). This will ensure that steady state has been achieved (minimum of 5 doses of APX) for establishing baseline peak and trough APX levels. The first blood samples will be taken on day -1 to -3 of cycle 1 before the morning dose of APX (trough level) and at 2 hours and 4 hours after APX administration (peak levels). Subsequently, blood samples will be collected prior to the morning dose of APX and DEX and at 2 hours and 4 hours after APX and DEX on day 15 of cycles 1, 2 and 3 of LEN-DEX. Timing of APX and DEX administration in relation to the blood sampling will be standardized and recorded in all

subjects. Subject compliance with study drug will be monitored. APX will be continued daily for approximately 3 months, corresponding with the first 3 complete cycles of LEN-DEX (28 days per cycle). Study outcomes include anti-Xa, d-dimer and APX levels, symptomatic VTE, bleeding, death and adverse events. A 30-day post-APX assessment will be done to complete the study.

Figure 2 - SCHEDULE OF EVENTS



9. STUDY DRUG AND TREATMENT DURATION

Subjects will be given a study supply of APX 2.5 mg tablets for the duration of the 3-month study treatment period. The number of tablets dispensed at each visit will be sufficient for administration until the next visit. All unused APX will be counted and recorded at each visit. Subjects will keep records of their APX dosing in a study diary. All dispensation and return of APX will be logged by the investigative team. Subjects will be informed that APX must be stored at room temperature (15-30˚C) and in a secured location.

The total duration of study drug exposure will be approximately 3 months, corresponding to the 4 – 6 days of APX taken before the first day of DEX administration plus the first three 28-day cycles of LEN-DEX therapy. The exact duration will vary from subject to subject depending on the start date of APX and the end date of the 3rd cycle of LEN-DEX, which will be determined by the subject's primary hematologist according to patient characteristics, response to LEN-DEX and potential cycle delays for cytopenia or adverse effects associated with LEN-DEX treatment.

The 3-month duration was chosen for a number of reasons. First, the risk of thrombosis is highest during the initial few months after cancer diagnosis and treatment and therefore warrants consideration of thromboprophylaxis.[1,9] Second, a shorter duration of exposure to APX and DEX might not detect clinically significant drug interaction and 3-month exposure should provide evidence of increasing induction with prolonged co-administration, if that indeed occurs. Third, disease response is usually assessed after 3 cycles and those patients who do not respond to LEN-DEX therapy will be switched to salvage therapy. Fourth, a previous phase II study demonstrated acceptable safety and feasibility of 12 weeks of APX use in patients with advanced or metastatic cancers, including 29 patients with myeloma.[22] Finally, exposing patients to APX beyond 3 months may be potentially harmful if there is no efficacy associated with APX use. After the 3-month study treatment period, subjects may switch to another form of thromboprophylaxis per discretion of their primary hematologist.

10. STUDY OUTCOMES

10.1 Primary Outcome

Peak anti-Xa levels of APX over first 3 cycles of LEN-DEX treatment.

10.2 Secondary Outcomes

1. Trough anti-Xa APX levels during first 3 cycles of LEN-DEX
2. APX drug levels over during first 3 cycles of LEN-DEX
3. D-dimer levels during first 3 cycles of LEN-DEX
4. Correlation of anti-Xa levels to APX drug levels
5. Venous thromboembolic events during the 3-month study period
6. All bleeding events (major, clinically relevant non-major and minor bleeding) up to 7 days after the last dose of APX
7. All-cause death during the study period
8. Drug adherence to schedule

Venous thromboembolic events must be objectively documented using standardized radiological imaging, such as computer tomography pulmonary angiogram for PE and venous compression ultrasonography for DVT. Site of involvement will be recorded. APX will be discontinued at the time of a confirmed venous thromboembolic event and treatment will be initiated per discretion of the most responsible physician..

Bleeding events will be classified according to the International Society on Thrombosis and Hemostasis (ISTH) guidelines.[34] APX may be interrupted or discontinued per discretion of the most responsible physician and investigator. Management of the bleeding event will be per discretion of the most responsible physician.

All-cause death will be documented. The specific cause of death will recorded according to the stated cause on the death certificate. Efforts will be made to clarify if the death could be attributable to venous thromboembolic event or bleeding or an adverse effect of APX.

Good adherence will be defined as 80% or more of the study drug was taken as scheduled based on patient diary and pill count.

11. STUDY POPULATION

For consideration as a subject for this study, the patient must meet all of the following criteria:

11.1 Inclusion Criteria

1. Diagnosis of multiple myeloma according to criteria of the International Myeloma Working Group
2. LEN-DEX treatment regimen is indicated (20 mg or 40 mg DEX once weekly per week) for a minimum of three 28-day cycles (i.e., DEX taken on Days 1, 8, 15, 22 of cycles 1, 2, 3)
3. Adult patients ≥ 19 years of age who are able to freely provide informed consent

The patient is excluded if the patient meets any of the following criteria:

11.2. Exclusion Criteria

1. Concomitant antiplatelet or anticoagulant use
2. Calculated creatinine clearance < 30 mL/min by Cockcroft-Gault formula
3. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times upper limit of normal (ULN)
4. Total bilirubin > 2 x ULN
5. Thrombocytopenia < 50 x 10^9/L
6. High bleeding risk, known bleeding disorder or spontaneously prolonged prothrombin time or activated partial thromboplastin time > 1.5 x ULN
7. Body weight <50 or >120 kg
8. DEX use within last 2 weeks
9. Concomitant use of CYP3A4 or P-glycoprotein inducers or inhibitors (see Appendix)
10. Use of Ginkgo biloba or St. John's Wort within 14 days before first dose of study drug
11. Sexually active men or women of childbearing potential not using highly effective contraceptive measures (see Section 11.3)
12. Women who are pregnant or breast feeding
13. Life expectancy less than 3 months
14. Inability to swallow or issues with malabsorption of the study drug
15. Any other medical, social, logistical, geographical or psychological factors, which in the opinion of the investigator, would prohibit follow-up, compliance and study completion

11.3. Reproductive Definition and Contraception Requirements

A women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

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

All 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.

WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug APX plus 5 half-lives of study drug APX (3 days) plus 30 days (duration of ovulatory cycle) for a total of 33 days post-treatment completion.

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug APX plus 5 half-lives of the study drug (3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion.

Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However WOCBP must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

12. STUDY PROCEDURES

12.1 Subject Consent, Screening & Eligibility

Potential subjects will be identified by their primary hematologist, and those expressing interest will be invited to review and consider study participation. These potential subjects will have as much time as they need to review an informed consent form and provide written informed consent. Subjects providing informed consent will be evaluated for inclusion and exclusion criteria for eligibility. Blood work will be done if needed to confirm eligibility, if not already available from the usual blood work done before starting LEN-DEX therapy.

12.2 Visit 1: Initiation of Apixaban / Pre-DEX Phase

Consenting subjects will come to the clinic a minimum of 4 days prior to the first day of their LEN-DEX treatment (Cycle 1 Day 1; C1D1). This can be the same day when eligibility and consent were assessed and confirmed. History and physical exam will be conducted. Subjects' demographics, medical history (including all concomitant medications and doses) and laboratory investigations will be documented. Study procedures will be reviewed with the subject. The start date of the subjects' first cycle of LEN-DEX treatment for myeloma (C1D1) will be reviewed and confirmed.

Subjects will be given an open-label study supply of 2.5 mg tablets of APX to take until the next visit. Subjects will be instructed to start APX on the evening starting 4 – 6 days before C1D1 and continue every morning and evening (approximately 12 hours apart) thereafter. This will ensure that a minimum of 5 doses of APX is taken prior to the first blood sample for anti-Xa levels, D-dimer and plasma drug levels.

Subjects will be given a study diary in which they will record the dates and time when APX was taken.

Subjects will be instructed to return to the clinic for Visit 2 in the morning 1-3 days (Day -1 to -3) prior to C1D1 of LEN-DEX treatment, and return their remaining APX supply and study diary to the clinic for compliance review. Subjects will be instructed to NOT take their morning dose of APX for Visit 2.

12.3 Visit 2: Day (-1 to-3) Trough and Peak Baseline Apixaban Level Sampling

Subjects will return to the clinic on the morning 1 – 3 days (Day -1 to -3) prior to C1D1 of LEN-DEX treatment. Assessment for drug compliance, diary entries, outcome events and adverse events, interval medical and medication history since the last visit will be done.

After confirmation that at least 5 doses of APX had been taken, a blood sample will be drawn before the morning dose of APX (trough level). The subjects will then take their morning dose of

APX and blood samples will be drawn at 2 hours and 4 hours after APX administration (peak levels). The times of blood sampling and APX doses (prior evening and morning) will be recorded. This will establish baseline levels prior to DEX exposure.

Subjects will be given a further supply of APX sufficient up to the next visit and instructed to continue their APX twice daily and return to the clinic in the morning of Day 15 of the first cycle (C1D15) of LEN-DEX treatment. Subjects will be instructed to NOT take their morning dose of APX and DEX before the clinic appointment. LEN-DEX will begin on C1D1 as scheduled by their hematologist.

12.4 Visit 3, 4, 5: Day 1 of the First 3 Cycles of LEN-DEX (LEN_DEX Phase)

Subjects will return to clinic with their study supply of APX and diary on the morning of Day 15 of the first 3 cycles of LEN-DEX treatment. Day 15 of the cycle has been chosen as patients would have taken 2 doses of DEX for that cycle, and induction of P-glycoprotein and CYP3A4 pathways should have occurred. This also provides more consistency in DEX exposure than collection of blood samples on Day 1 because the start of a cycle might be delayed in some patients due to LEN-DEX toxicity or other reasons. For patients with a delayed cycle start, the last dose of DEX before Day 1 would be 2 weeks prior, rather than the usual 1 week. Assessment for drug compliance, diary entries, outcome events and adverse events, interval medical and medication history since the last visit will be done.

Subjects will confirm the timing of their last dose of APX in the evening prior to the visit. A blood sample will be drawn for trough APX levels. The time of blood sampling and prior evening dose of APX will be recorded. The subjects will subsequently take their morning dose of APX and DEX as part of their myeloma treatment on Day 15 of each cycle of LEN-DEX. The time of APX and DEX dosing will the recorded. At 2 hours and 4 hours after the morning dose of APX and DEX, subjects will provide a second and third blood sample for peak APX levels. The times of blood sampling will be recorded.

Subjects will be given a further supply of APX sufficient up to the next visit and instructed to continue their APX twice daily and return to the clinic in the morning of Day 15 of cycles 2 and 3 of LEN-DEX treatment. They will bring their remaining APX supply and study diary for compliance review. Subjects will be instructed to NOT take their morning dose of APX and DEX on the morning of the study visit.

12.5 Visit 6: Day 1 Cycle 4 End of Apixaban Administration.

Subjects will take their last dose of APX on C3D28 as part of the study. Subjects will return to site with their remaining study supply of APX and diary on the morning of Day 1(+ 2) of cycle 4 (C4D1) of LEN-DEX treatment. Assessment for drug compliance, diary entries, outcome events and adverse events, interval medical and medication history since the last visit will be done.

The date of the last APX dose will be confirmed. All remaining unused study drug will be collected and counted. Study diaries will also be retrieved. Subjects will continue with their LEN-DEX treatment and follow-up as per discretion of their primary hematologist.

Subjects will be reminded that ongoing follow-up for the next 30 days will be necessary to ensure safety and capture any delayed adverse events after discontinuation of study drug.

12.6 30-Day Post-Apixaban Follow-Up: End of Study (EOS)

At the completion of 30 days follow-up post discontinuation of APX, subjects will be contacted to review any adverse or serious adverse events for the purposes of safety monitoring. Any interval medical history, such as hospitalization, physician office or emergency department visits, and medication changes will also be recorded.

12.7 Missed Doses of Apixaban

If a subject misses a scheduled dose of APX, the missed dose of APX should be taken immediately; however, a double-dose of APX should not be taken to make up for a missed dose. In such cases, the subject may skip the missed dose and take the next dose of APX as scheduled ensuring the missed dose is recorded in the study diary.

12.8 Unanticipated or Premature Discontinuation of Apixaban

Subjects may discontinue taking APX at any time over the course of study if:

1. Consent to thromboprophylaxis with APX is withdrawn (NOTE: subjects may continue to provide consent for follow-up and safety evaluation)
2. Any concurrent medical circumstance or adverse event in the opinion of an investigator that prohibits further thromboprophylaxis with APX
3. Pregnancy
4. Termination of the study by the investigative team

Subjects who prematurely discontinue APX over the course of the study will be encouraged to have final blood sampling as soon as possible after discontinuing APX (within approximately 12 hours of discontinuing APX if possible) so long as is reasonable in the opinion of the investigative team. The timing of last APX dose and of blood sample will be documented. Subjects will have ongoing safety assessment as outlined in the End of Study (EOS) follow-up for 30 days after the last dose of study drug.

Subjects who withdraw consent to further study participation will not be asked to provide further blood samples. The reason for study withdrawal will be documented. Data collected prior to withdrawal of consent must be retained for the purposes of the study in accordance with Health Canada's Food and Drug Regulations Part C Division 5. The subjects may request to have their blood samples destroyed.

12.9 Interruption of Apixaban for Invasive Procedures, Thrombocytopenia or Renal Impairment

In the event of unanticipated surgeries or procedures while receiving thromboprophylaxis with APX, investigators will manage thromboprophylaxis per their discretion in the perioperative setting. APX should be stopped prior to the procedure and restarted after the procedure according to standard recommendations based on renal function and bleeding risk.[35]Subjects will not be disqualified from participating in this study due to unanticipated surgeries except in rare situations at the discretion of investigators. Management details will be captured, including the last dose of APX prior to the procedure and the first dose of APX afterwards, and use of other

anticoagulants. Investigators will inform surgical and procedural teams that subjects are participating in a clinical trial involving APX.

In the event of severe thrombocytopenia (platelet count < 50 x 10^9/L), which can occur with LEN-DEX therapy in up to 13% of patients,[36] APX should be withheld until recovery of the platelet count above 50 x 10^9/L. Duration of APX interruption will be captured. If platelet count recovery is not expected, then APX should be permanently discontinued (see section 12.8).

In the event of severe renal impairment (CrCl < 30 mL/min), which can occur in patients with multiple myeloma, APX should be withheld until improvement of the renal function (CrCl > 30 mL/min). Duration of APX interruption will be captured. If renal function recovery is not expected, then APX should be permanently discontinued (see section 12.8).

12.10 Delays in LEN-DEX Treatment

In the event of unanticipated delays to cycles of LEN-DEX treatment, subjects are to continue thromboprophylaxis with APX per protocol, provided that this does not pose any safety concerns. Subjects will continue with follow-up blood sampling and safety assessments at their C1D15, C2D15, C3D15 and C4D1 visits so long as is reasonable in the opinion of the investigative team. Subjects will contact the investigative team if their cycle initiation is delayed and obtain further supplies of APX, if necessary.

13. BLOOD SAMPLE STORAGE AND ANALYSIS

Following phlebotomy, citrated venous blood samples will be processed immediately in the Hematology Laboratory of the Vancouver General Hospital, where they will be centrifuged to generate platelet poor plasma for storage at -70°C on site in a secured research freezer. When accrual of all samples from all subjects is complete, plasma samples will be thawed and batch-analyzed by trained laboratory personnel on automated coagulation analyzers (ACL Top 700, Instrumentation Laboratory, Lexington, MA, USA). Plasma anticoagulant activity will be quantified using the HemosIL® Liquid Anti-Xa assay, using separate calibration curves created using commercial plasma samples containing known quantities of APX.[37] Plasma D-dimer levels will be assessed using the HemosIL® D-Dimer HS 500 latex particle immunoassay. APX plasma levels will be performed.All samples will be analyzed by personnel blinded to the timing of the samples.

14. MANAGEMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

The investigational medicinal product in this study is APX in the form of 2.5 mg tablets. It will be provided by Bristol-Myer Squibb. Packaging and labelling of the investigational medicinal product will be done in accordance with Health Canada's Food and Drug Regulations. APX will be stored on site as per its Canadian Product Monograph at 15 – 30°C in a secure, temperature-controlled location. A full accountability will be documented at site. Accountability will include:

- APX expiration date
- APX bottle lot assignment to subjects

- APX dispensation date including number of tablets dispensed
- APX return date including number of tablets
- Final disposition of APX (including all unused bottle and tablets of APX)

APX will be dispensed to subjects upon receipt of reviewed and signed orders from investigators. Subjects will be counseled by the investigative team on correct dosage and use of APX. Subjects will be counseled to return all APX bottles and tablets to the site for objective compliance assessment and accountability.

15. ADVERSE EVENTS

All subjects who have provided written consent will be followed for adverse events (AEs) until 30 days after the last dose of apixaban. An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. Therefore, an AE can be any abnormal laboratory finding, symptom or disease temporally associated with the use of an investigational product, whether or not considered related to that product. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

In this study, AEs will be graded (severity) and their attribution (causality) to APX will be assessed by a qualified investigator who is also a licensed physician.

The investigative team will inform subjects and all treating physicians regarding the reporting requirement of adverse events for this protocol.

15.1 Severity and Causality of Adverse Events

The severity or intensity of AEs will graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The following guidelines regarding grading are applicable:

Mild	Grade 1	• Tolerated & no intervention is indicated
Moderate	Grade 2	• Interferes with usual activities of daily living (ADLs); intervention is indicated
Severe	Grade 3	• Renders subject unable to carry out ADLs; urgent intervention indicated
Very Severe	Grade 4	• Incapacitates subject despite medical/surgical interventions
Causing death	Grade 5	• Causes death as a result of the event

Also, AEs will be assessed as being *unrelated* or *related* to the study drug APX:

Unrelated	• There is not a reasonable causal relationship between APX and the AE
Related	• There is a reasonable causal relationship between APX and the AE; i.e., there is evidence to suggest a causal relationship

AEs will also be classified as *unexpected* if the event or the severity or frequency of the event is not previously identified in the current protocol, product monograph (or Investigator's Brochure) for the study drug.

15.2 Serious Adverse Events (SAE)

Each AE is to be classified by the investigator as *serious* or *nonserious*. A SAE is any event (including VTE, bleeding and chemotherapy-related events) over the course of a subject's participation in a study that:

1. Results in death
2. Is life-threatening
3. Requires or prolongs inpatient hospitalization or incapacity
4. Causes a congenital defect
5. Is an important medical event in the opinion of an investigator that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes

Although pregnancy, transmission of infectious agent via study drug, medication error, misuse, abuse or overdose and a new cancer do no always meet these criteria, they should be handled as SAEs.

Any SAE occurring beyond the 30-day post-APX discontinuation period should be reported if it is related to APX or protocol-specified procedures.

All SAEs must be reported by the Principal Investigator or appropriate delegate to Bristol-Meyers Squibb within 24 hours of awareness. The Principal Investigator or delegate must:

1. Communicate the SAE using the Council for International Organizations of Medical Sciences (CIOMS) Report Form (or Pregnancy Surveillance Form if appropriate) by fax or email within 24 hours to Bristol-Meyers Squibb:
   Bristol-Myers Squibb Global Pharmacovigilance & Epidemiology
   Fax Number: 609 818 3804
   Email: worldwide.safety@bms.com
2. Notify Health Canada if the SAE is unexpected and related to APX
3. Report within 7 days to the REB if the SAE is both unexpected and possibly related or related to APX

If new information about the SAE becomes available, a follow-up report using the same procedures as above is required. All SAEs should be followed to resolution or stabilization.

Unusual failures in efficacy must be reported to BMS with 24 hours of becoming aware of the event. Unusual failures in efficacy must also be reported to Canadian Health Authorities in an expedited manner in order to comply with Health Canada Regulations.

If the SAE is felt to be <u>related</u> and <u>unexpected</u>, the Qualified Investigator must be notified immediately who will then report the SAE to Health Canada Office of Clinical Trials, using:

1. Adverse Drug Reactions (ADRs) for Clinical Trials Expedited Reporting Summary Form and;
2. Council for International Organizations of Medical Sciences (CIOMS) form within the following time frames:
   - Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
   - Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days of becoming aware of the information; and

Within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings.

15.3 Exception to Adverse Events Reporting

For this study, study outcomes (anti-Xa levels, D-dimer levels, APX levels, VTE, bleeding events and death) will not be recorded as AEs. However, they must be reported as a SAE if they meet SAE criteria (see above).

In addition, adverse drug reactions that are related to the chemotherapy (LEN-DEX) will not be recorded as an AE. However, they must be reported as a SAE if they meet SAE criteria (see above). AEs well documented to be related to LEN-DEX include:[36]

Adverse Event	CTCAE Grade 1 – 4 AE, %*	CTCAE Grade 3-4 AE, %*
Fatigue	45.6	6.5
Insomnia	36.5	< 2%
Confusion	9.3	2.3
Depression	12.7	2.8
Constipation	42.2	2.3
Diarrhea	38.8	3.1
Nausea	26.1	2.0
Pneumonia	13.9	9.1
Skin rash	21.5	< 2%
Muscle cramp	34.3	< 2%
Back pain	25.8	< 2%
Headache	26.6	< 2%
Paresthesia	14.4	< 2%
Hyperglycemia	16.1	7.6
Neutropenia	43.1	35.4
Anemia	33.7	10.8
Thrombocytopenia	22.7	13.0
DVT/PE	9.1/<5%	7.9/2.0

**From Revlimid® product monograph, revised May 1, 2015[36]*

15.4 Adverse Events of Special Interest

In this study, the following adverse events are to be reported to Bristol-Myers Squibb (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.

16. STATISTICAL ANALYSIS

As this is a small pilot study and we have no prior information on the quantitative impact of DEX on plasma levels of APX, the focus of our analysis is to generate descriptive data that will be informative for further definitive investigation.

We will report on the number and proportion of patients showing a drop of ≥50% in peak anti-Xa levels at any time during follow up, which we consider as clinically relevant. A paired sample t-test or Wilcoxon test, depending on the distribution, will be used to assess the difference between the baseline peak anti-Xa level and the lowest peak anti-Xa level during the 3-month treatment period.

Plasma anti-Xa levels over time for each patient will be plotted to illustrate temporal changes following exposure to DEX. The patterns of change will be summarized, if possible. We will also describe if changes in plasma anti-Xa levels differ between the 2 doses of DEX.

Similar analyses will be performed for D-dimer and APX plasma levels. Correlation between these parameters with anti-Xa levels will be performed.

Incidence of thrombotic events, bleeding events, death, and adverse events will be reported with 95% confidence intervals.

Assuming a mean value of 0.5 anti-Xa units/mL for peak baseline values and a standard deviation of 5 – 20 % for anti-Xa assays reported in the literature,[29, 31] we will need 4 – 13 subjects to exclude a 50% drop in peak anti-Xa levels with a two-sided alpha of 0.01 (significance) and a beta of 90% (power). To detect a smaller effect size of 20% decrease, 8 – 63 patients would be required. As we expect a low drop-out rate, we will aim for a total sample size of 24 (12 patients receiving DEX 20 mg once weekly and 12 patients receiving DEX 40 mg once weekly),, which is feasible to enroll over a 1-2 year period based on our current patient referral pattern.

17. ETHICAL CONSIDERATIONS

17.1 Good Clinical Practice & Applicable Regulations

The investigative team will adhere to Good Clinical Practice as outlined by the International Conference on Harmonisation (ICH) in its Efficacy Guidelines E6: Good Clinical Practice (GCP): ICH HARMONISED TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) Current Step 4 version dated 10Jun1996; and by Health Canada in its GUIDANCE FOR

INDUSTRY Good Clinical Practice: Consolidated Guideline ICH Topic E6 published by authority of the Minister of Health in 1997. Additionally, this study fulfills the regulatory definition of a clinical trial and is governed by regulations as outlined by Health Canada's Food and Drug Regulations Part C Division 5. The study will be conducted as per the controlled, ethics and regulatory-approved protocol, and the investigative team will demonstrate qualification to undertake their respective tasks as delegated.

17.2 Research Ethics Board

The investigative team will obtain ethics approval from the appropriate research ethics board (REB) prior to conducting this study. The investigative team will ensure the study's protocol, informed consent form and all other materials distributed to subjects are reviewed and approved for use by the REB. Annual renewal will be sought on an ongoing basis for the complete duration of this study. The REB will be updated as to the study status and informed upon study closure.

17.3 Informed Consent

Subjects will be provided with sufficient time to review the study and consider participation. Subjects who participate in this study must agree to freely provide informed consent prior to participating in this study. Subjects are to be routinely updated about the study status and any issues that may affect their willingness to provide ongoing consent to participation.

17.4 Privacy & Confidentiality of Subjects

Subjects will be only contacted by the investigative team after explicit permission in order to preserve confidentiality. Subjects participating in this study will be identified by a unique anonymised study identifier. The data will be gathered and analyzed using only this unique study identifier. The personal identifiable information linked to this unique study identifier will not be allowed to leave the custody of the investigator or investigative site. Subjects may withdraw from the study at any time for any reason and will be discontinued from the study should the subject fail to comply with study procedures over the course of the study period, or if continuation in the study is deemed to expose the subject to excessive harm. Questions about the treatment decisions will be addressed by the subjects' treating physicians. The Principal Investigator and delegates will be available for questions throughout the study.

17.5. Statement of Risks and Benefits

APX has been proven safe and effective as an agent for thromboprophylaxis in previous studies as summarized in the background. It is more convenient than daily subcutaneous injections of LMWH and INR-adjusted warfarin therapy, the only other regimens that are available and approved for thromboprophylaxis. Although ASA is inexpensive and convenient, and it is often used in myeloma patients for thromboprophylaxis, its efficacy has not been proven in robust clinical trials and it is not recommended in patients with a high risk of thrombosis. Consequently, APX or other NOACs are attractive alternatives. However, the effect of DEX on APX levels and anticoagulant activity is uncertain, and therefore, there is a risk that and the standard prophylaxis dose of APX 2.5 mg BID may be ineffective in reducing the risk of thrombosis. Overall, we feel there is potential benefit with minimal harm to study subjects based on the available information. Data from this pilot study will also provide important information

and help to advance knowledge that can ultimately lead to clinical practice changes in thromboprophylaxis in all patients with myeloma.

18. COMPOSITION OF INVESTIGATIVE TEAM

Agnes Lee, Principal Investigator: overall governance of the project, supervisor, design, analysis of data. Geerte van Sluis, sub-investigator: design, data collection, analysis of data. Adam Ludlow, sub-investigator: design, data collection, analysis of data. Erica Peterson, sub-investigator: design, data collection, analysis of data. Tyler Smith, sub-investigator: laboratory testing, analysis of data. Kevin Song, sub-investigator: design, data collection, analysis of data. Members of the Division of Hematology, Vancouver General Hospital, will be active site investigators, participating in subject enrollment and follow-up.

19. TIMELINE OF STUDY

We expect to enroll 1-2 subjects per month; therefore, we expect that it will take approximately 1-2 years to complete enrollment. Allowing for completion of follow-up and the time required for laboratory testing, data clean up and analysis, we anticipate we will be able to report the results of the study 2-3 years from the start date.

20. LIMITATIONS OF THE STUDY

This pilot study has limitations. Due to the exploratory nature of the study and the small sample size, it will not be able to reliably inform the impact of APX on relevant clinical outcomes, such as thromboembolic and bleeding events. The study design of collecting only peak and trough blood levels is also not typical of PK and pharmacodynamics studies designed to examine drug interactions. However, it would be very difficult to justify exposing patients with myeloma to multiple and serial blood sampling over several cycles of chemotherapy, especially many of them are elderly, have bone pain and rely on others for transportation. The study is also unable to determine if different doses or schedules of LEN-DEX therapy will have differential impact on APX levels.

21. EXPECTED RESULTS & IMPACT STATEMENT

We expect that the effect of DEX on the anti-Xa levels is limited (i.e.: < 50%). If we confirm this, we will conduct a phase III randomized study to compare APX with the conventional thromboprophylaxis or standard of care. This is of major interest to myeloma patients requiring thromboprophylaxis as APX is a much more patient-friendly drug. If the levels decrease more than 50%, we may consider proceeding with a new pilot study to see if a higher dose of APX (e.g., 5 mg BID) results in an adequate dose of APX in myeloma patients receiving LEN-DEX treatment.

22. REFERENCES

1. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293:715-722.

2. Palumbo A, Rajkumar SV, Dimopoulos MA et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22:414-423.

3. Zangari M, Anaissie E, Barlogie B et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood. 2001;98:1614-1615.

4. Zangari M, Tricot G, Polavaram L et al. Survival effect of venous thromboembolism in patients with multiple myeloma treated with lenalidomide and high-dose DEX. J Clin Oncol. 2010;28:132-135.

5. Zamagni E, Brioli A, Tacchetti P et al. Multiple myeloma, venous thromboembolism, and treatment-related risk of thrombosis. Semin Thromb Hemost. 2011;37:209-219.

6. Lyman GH, Khorana AA, Kuderer NM et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:2189-2204.

7. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Venous Thromboembolic Disease Version 2.2011. Accessed November 26, 2013. National Comprehensive Cancer Network , http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive. 26-11-2013.

8. British Columbia Cancer Agency LEN DEX protocol: http://www.bccancer.bc.ca/health-professionals/professional-resources/chemotherapy-protocols/lymphoma-myeloma#Myeloma. Accessed 25 May 2015.

9. Cove CL, Hylek EM. An updated review of target-specific oral anticoagulants used in stroke prevention in atrial fibrillation, venous thromboembolic disease, and acute coronary syndromes. J Am Heart Assoc. 2013;2:e000136.

10. Lee AY, Carrier M. Treatment of cancer-associated thrombosis: perspectives on the use of novel oral anticoagulants. Thromb Res. 2014;133 Suppl 2:S167-S171.

11. Lyman GH, Bohlke K, Khorana AA et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014. J Clin Oncol. 2015;33:654-656.

12. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and APX in preclinical and clinical development. Thromb Haemost. 2010;103:572-585.

13. Nutescu E. APX: a novel oral inhibitor of factor Xa. Am J Health Syst Pharm. 2012;69:1113-1126.

14. Agnelli G, Buller HR, Cohen A et al. Oral APX for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808.

15. Agnelli G, Buller HR, Cohen A et al. APX for extended treatment of venous thromboembolism. N Engl J Med. 2013;368:699-708.

16. Goldhaber SZ, Leizorovicz A, Kakkar AK et al. APX versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365:2167-2177.

17. Lassen MR, Raskob GE, Gallus A et al. APX or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009;361:594-604.

18. Lassen MR, Gallus A, Raskob GE et al. APX versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med. 2010;363:2487-2498.

19. Lassen MR, Raskob GE, Gallus A et al. APX versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375:807-815.

20. Connolly SJ, Eikelboom J, Joyner C et al. APX in patients with atrial fibrillation. N Engl J Med. 2011;364:806-817.

21. Granger CB, Alexander JH, McMurray JJ et al. APX versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-992.

22. Levine MN, Gu C, Liebman HA et al. A randomized phase II trial of APX for the prevention of thromboembolism in patients with metastatic cancer. J Thromb Haemost. 2012;10:807-814.

23. Bauersachs R, Berkowitz SD, Brenner B et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-2510.

24. Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-1297.

25. Cohen AT, Spiro TE, Spyropoulos AC. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368:1945-1946.

26. Turpie AG, Haas S, Kreutz R et al. A non-interventional comparison of rivaroxaban with standard of care for thromboprophylaxis after major orthopaedic surgery in 17,701 patients with propensity score adjustment. Thromb Haemost. 2014;111:94-102.

27. Barrett YC, Wang Z, Frost C, Shenker A. Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay. Thromb Haemost. 2010;104:1263-1271.

28. Gong IY, Kim RB. Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and APX. Can J Cardiol. 2013;29:S24-S33.

29. Pascussi JM, Drocourt L, Gerbal-Chaloin S et al. Dual effect of DEX on CYP3A4 gene expression in human hepatocytes. Sequential role of glucocorticoid receptor and pregnane X receptor. Eur J Biochem. 2001;268:6346-6358.

30. Fardel O, Lecureur V, Guillouzo A. Regulation by DEX of P-glycoprotein expression in cultured rat hepatocytes. FEBS Lett. 1993;327:189-193.

31. Leil TA, Feng Y, Zhang L et al. Quantification of APX's therapeutic utility in prevention of venous thromboembolism: selection of phase III trial dose. Clin Pharmacol Ther. 2010;88:375-382.

32. Chen C, Baldassarre F, Kanjeekal S et al. Lenalidomide in multiple myeloma-a practice guideline. Curr Oncol. 2013;20:e136-e149.

33.Rajkumar SV, Jacobus S, Callander NS et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010;11:29-37.

34. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692-694.

35. Thrombosis Canada clinical guides. http://thrombosiscanada.ca/wp-content/uploads/2015/01/NOACs-Peri-Operative-Management-2015Jan22-FINAL.pdf. Accessed 25 May 2015.

36.Revlimid (lenalidomide) Product Monograph (date of revision May 1, 2015). http://www.celgenecanada.net/pdfs/Revlimid%20Product_Monograph_-_English_Version.pdf Accessed 25 May 2015

37. Gouin-Thibault I, Flaujac C, Delavenne X et al. Assessment of APX plasma levels by laboratory tests: suitability of three anti-Xa assays. A multicentre French GEHT study. Thromb Haemost. 2014;111:240-248.

23. APPENDIX

The following is a guide and not an exhaustive list. Investigators should exercise clinical judgment in managing concomitant medication use. The following medications are known CYP3A4 or P-glycoprotein inducers and/or inhibitors:

Drug	Interaction	Reference
amiodarone	Weak-moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
aprepitant	Moderate inhibitor of CYP3A	[5]
armodafinil	Weak inducer of CYP3A	[1]
atazanavir	Moderate-strong inhibitor of CYP3A	[1], [2]
avasimibe	Strong inducer of CYP3A & inducer of P-gp	[1]
azithromycin	Weak-moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
boceprevir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
bosentan	Moderate-strong inducer of CYP3A	[1], [2]
captopril	Inhibitor of P-gp	[1]
carbamazepine	Strong inducer of CYP3A & inducer of P-gp	[1], [2]
carvedilol	Inhibitor of P-gp	[1]
chloramphenicol	Moderate-strong CYP3A inhibitor & inhibitor of P-gp	[2], [3]
cimetidine	Weak-moderate CYP3A inhibitor & inhibitor of P-gp	[1], [2], [5]
ciprofloxacin	Weak to moderate inhibitor of CYP3A	[1]
clarithromycin	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [5]
cobicistat	Strong inhibitor of CYP3A & inhibitor of P-gp	[2]
conivaptan	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
cyclosporine	Weak-moderate CYP3A inhibitor & inhibitor of P-gp	[1], [2]
darunavir	Moderate-strong inhibitor of CYP3A	[1], [2]
delavirdine	Strong inhibitor of CYP3A & inhibitor of P-gp	[2]
dexamethasone	Strong inducer of CYP3A4 & inducer of P-gp	[1]
diltiazem	Moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
doxorubicin	Inducer of P-gp	[2]
dronedarone	Moderate inhibitor of CYP3A4 & inhibitor of P-gp	[1], [2]
Echinacea	Weak inducer of CYP3A	[1]
efavirenz	Moderate-strong inducer of CYP3A	[1], [2]
erythromycin	Moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
etravirine	Moderate-strong inducer of CYP3A	[1], [2]
felodipine	Weak-moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
fluconazole	Moderate inhibitor of CYP3A	[1]
fosamprenavir	Moderate-strong inhibitor of CYP3A	[1], [2]
fosphenytoin	Strong inducer of CYP3A	[2]
Ginkgo biloba	Strong inhibitor of CYP3A	[4]
grapefruit	Moderate-strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2], [5]
imatinib	Moderate-strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
indinavir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1]
itraconazole	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
ketoconazole	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
lapatinib	Moderate inhibitor of CYP3A & inhibitor of P-gp	[2]
lopinavir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1]
mibefradil	Strong inhibitor of CYP3A	[1]
mifepristone	Moderate inhibitor of CYP3A & inhibitor of P-gp	[2]

modafinil	Moderate inducer of CYP3A	[1]
nafcillin	Moderate-strong inducer of CYP3A	[1], [2]
nefazodone	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
nelfinavir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1]
nevirapine	Strong inducer of CYP3A	[2]
nicardipine	Moderate inhibitor of CYP3A & inhibitor of P-gp	[2]
oxcarbazapine	Strong inducer of CYP3A	[2]
phenobarbital	Strong inducer of CYP3A	[2]
phenytoin	Strong inducer of CYP3A & inducer of P-gp	[1], [2]
pioglitazone	Weak inducer of CYP3A	[1]
posaconazole	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
prazocin	Inducer of P-gp	[2]
prednisone	Weak inducer of CYP3A	[1]
primidone	Strong inducer of CYP3A	[2]
quercetin	Inhibitor of P-gp	[1]
quinidine	Weak-moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
ranolazine	Weak-moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
rifabutin	Strong inducer of CYP3A	[2]
rifampin	Strong inducer of CYP3A & inducer of P-gp	[1], [2]
rifapentine	Strong inducer of CYP3A	[2]
ritonavir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
rulfinamide	Weak inducer of CYP3A	[1]
saquinavir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1]
St. John's Wort	Strong inducer of CYP3A & inducer of P-gp	[1], [2]
tacrolimus	Inhibitor of P-gp	[1]
tamoxifen	Moderate inhibitor of CYP3A & inhibitor of P-gp	[2]
telaprevir	Strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
telithromycin	Moderate-strong inhibitor of CYP3A & inhibitor of P-gp	[1], [2], [5]
ticagrelor	Moderate inhibitor of CYP3A & inhibitor of P-gp	[2]
tipranavir	Inducer of P-gp	[1], [2]
trazodone	Inducer of P-gp	[2]
verapamil	Moderate inhibitor of CYP3A & inhibitor of P-gp	[1], [2]
vinblastine	Inducer of P-gp	[2]
voriconazole	Strong inhibitor of CYP3A	[1]

References:

[1] US FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [Internet]. 2011 Sep 16 [cited 2014 May 26]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

[2] University of Washington. Apixaban Drug Interaction Potential [Internet]. 2013 [cited 2014 May 26]. Available from: http://depts.washington.edu/anticoag/home/content/apixaban-drug-interaction-potential

[3] Park, J. Y.; Kim, K. A.; Kim, S. L. Chloramphenicol Is a Potent Inhibitor of Cytochrome P450 Isoforms CYP2C19 and CYP3A4 in Human Liver Microsomes. Antimicrobial Agents and Chemotherapy 2003;47 (11): 3464–3469.

[4] Kimura, Y; Ito, H; Ohnishi, R; Hatano, T. Inhibitory effects of polyphenols on human cytochrome P450 3A4 and 2C9 activity. *Food Chemistry Toxicology* 2010;48 (1): 429–35.

[5] Indiana University. P450 Drug Interaction Table [Internet]. 2011 [cited 2014 May 27]/ Available from: http://medicine.iupui.edu/clinpharm/ddis/main-table/