CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208383Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

Addendum

NDA	208383
Product (Generic Name)	Betrixaban
Product (Brand Name)	BevyxXa®
Dosage form	(b) (4)
Dosage strength	40 and 80 mg
Indication(s)	Extended prophylaxis of venous thromboembolism in acutely ill medical population with risk factors for VTE
Submission date	10/23/2016
Sponsor	Portola Pharmaceuticals
Reviewer	Lars Johannesen, PhD
Team leaders	Jeffry Florian, PhD Sudharshan Hariharan, PhD
OCP Division	DCP I / DPM
OND Division	DHP

Executive summary

Portola Pharmaceuticals (the Applicant) is seeking approval for betrixaban, a factor Xa inhibitor, for prophylaxis of venous thromboembolic events (VTE) in adult patients with acute medical illness who are at risk for VTE. The Office of Clinical Pharmacology (OCP) previously reviewed the NDA for betrixaban (DARRTs 4/3/2017) and recommended approval in the general population and a limitation of use in patients with severe renal impairment or on concomitant P-gp inhibitors (predefined subgroups) based on a less favorable benefit-risk profile compared to the comparator arm.

To further explore the less favorable benefit-risk profile in these patients, the OCP review team looked into patient factors and duration of P-gp inhibitor use (chronic vs acute). It was noted that there was a difference in the number of patients on P-gp inhibitors between the primary results in the study report for APEX (pivotal efficacy study for betrixaban) and the Applicant's midcycle communication (Seq 0022). Therefore, additional follow-up with the Applicant was required to reconcile these differences. In addition, the team further explored the definitions for clinically relevant non-major (CRNM) bleeds that were utilized in APEX and conducted sensitivity analyses to understand the impact of the included terms of the benefit-risk results. These two assessments are summarized below.

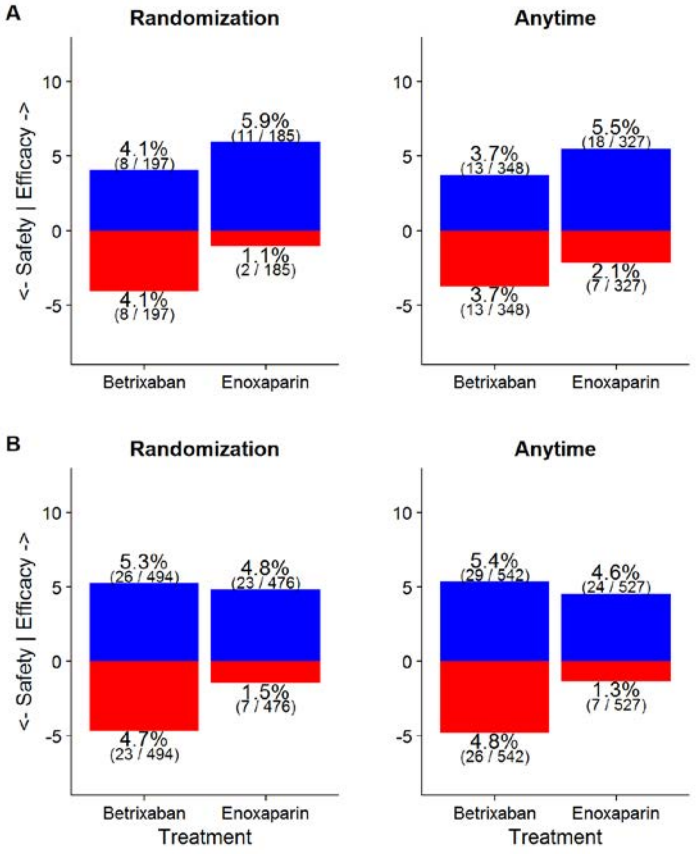
Based on these two analyses, the OCP review team still recommends a limitation of use for patients with severe renal impairment (CrCl < 30 mL/min) or patients receiving P-gp inhibitors. Alternatively, a strongly worded language under 'Warnings and Precautions' clearly describing the less favorable benefit-risk in these subgroups could be considered.

Sensitivity Analysis Based on P-gp Inhibitor Use Definitions

The Applicant clarified that the different definitions used were: i) P-gp inhibitor use at randomization; and ii) P-gp inhibitor use any point during the study. The latter definition was used in the recent communications, whereas the first definition was used in the primary presentation of results in APEX. The use of different definitions does not alter the interpretation

of the less favorable benefit-risk for patients receiving 40 mg betrixaban. However, for the patients administered 80 mg while on P-gp inhibitors at any time, the benefit risk compared to enoxaparin is more favorable when including patients who started on a P-gp inhibitor after randomization (in addition to at randomization) (Figure 1). This is likely because patients who started on P-gp inhibitors compared to patients on chronic P-gp inhibitors are two different patient populations, as was noted in the previous review (DARRTs 4/3/2017). The different definitions did not impact the assessment of 40 mg because the patients administered a reduced dose at randomization without a P-gp inhibitor use would likely have reduced renal function, a subgroup that had a less favorable benefit-risk profile by itself. Nevertheless, an underlying patient factor for identifying this population other than what is at best described by 'P-gp inhibitor use' could not be further identified.

Figure 1: Comparison of the different P-gp inhibitor definitions for 80 mg (A) and 40 mg (B) in the mITT population. *[Source: Reviewer's analysis]*



Sensitivity Analysis Based on CRNM Definitions

In the previous review, the OCP review team used a composite safety endpoint of major and CRNM bleeds (similar to Figure 1 above). The inclusion of CRNM bleeds was justified as the primary efficacy endpoint predominantly consisting of asymptomatic events and the sought indication being of a prophylactic nature. In APEX CRNM bleeds were defined as clinically overt bleeds that were not major and resulted in: 1) medical intervention; 2) unscheduled contact (telephone, emergency room, etc.); 3) cessation of study drug and/or 4) patient discomfort. Some of the elements of this definition are more subjective than others (e.g. patient discomfort or telephone contact). The definition is comparable to other trials in similar patient populations, e.g.

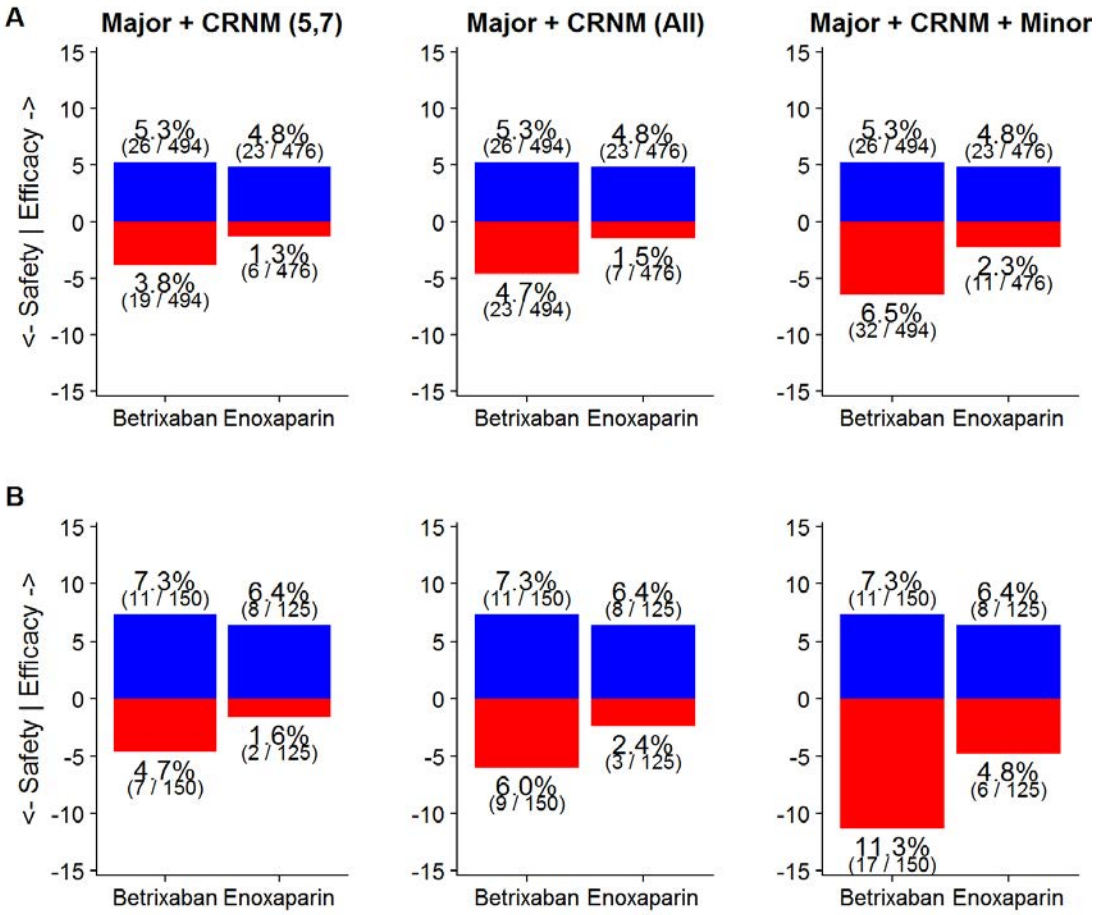
MAGELLAN or Hokusai VTE. However, a more limited definition for CRNM has been proposed in the literature focusing on medical intervention, cessation of study drug or unscheduled contact (excluding telephonic or electronic contact).[1]

The OCP review team conducted a sensitivity analysis to understand the potential impact of the CRNM definition on the less favorable-benefit risk profile for the P-gp and severe renal impairment subgroups. For this analysis the review team ordered the criteria for CRNM as follows: medical intervention, cessation of study drug, unscheduled contact (any) and patient discomfort. For example, if a CRNM bleed met both cessation of study drug and unscheduled contact it would be included when the CRNM definition was expanded to cessation of study drug, but not double counted when expanded to unscheduled contact. This sensitivity analysis is included in Figure 2. This figure shows that expanding the bleeding definition to include medical intervention and cessation of study drug has a less favorable benefit risk profile compared to enoxaparin. This is similar to an analysis based on the composite of major and CRNM bleeds used included in the previous review (DARRTs 4/3/2017). In addition, the relationship between benefit and the three bleeding definitions are included in Figure 3.

Figure 2: Evaluation of impact of bleeding definition on assessment of benefit-risk between betrixaban and enoxaparin for patients on P-gp inhibitors at randomization (A) or patients with severe renal impairment (B) in the mITT population. *[Source: Reviewer's Analysis]*

[1] Kaatz S, et al. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13(11):2119-26

Figure 3: Evaluation of the benefit risk for patients on P-gp inhibitors at randomization (A) or with severe renal impairment (B) receiving 40 mg betrixaban or enoxaparin in the mITT population. Each column corresponds to different bleeding definitions, which were explored in Figure 2: Major and CRNM bleed (only cessation of medical intervention and cessation or study drug); Major and all CRNM bleeds and Major, CRNM and Minor combined. *[Source: Reviewer's Analysis]*



Based on the analyses described above which excluded more subjective components of CRNM bleeds, a greater risk for bleeding exists for betrixaban in these subgroups compared to short-term enoxaparin.

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/s/

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Office of Clinical Pharmacology Review

NDA or BLA Number	208383
Link to EDR	\\cdsesub1\evsprod\nda208383
Submission Date	10/23/2016
Submission Type	*Priority*
Brand Name	BevyxXa
Generic Name	Betrixaban
Proposed Dosage Form and Strength	40 and 80 mg capsules
Route of Administration	Oral
Proposed Indication	Extended prophylaxis of venous thromboembolism in acutely ill medical population with risk factors for VTE
Applicant	Portola Pharmaceuticals
Associated INDs	*IND 72679 (DHP)* (b) (4)
OCP Review Team	*Lars Johannesen, PhD* *Jeffry Florian, PhD* *Sudharshan Hariharan, PhD*
OCP Final Signatory	*Mehul Mehta, PhD*

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1. EXECUTIVE SUMMARY

The Applicant (Portola Pharmaceuticals) is seeking approval for betrixaban, a factor Xa inhibitor, for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and additional risk factors for VTE.

The proposed dosing regimen is based on the pivotal study APEX (Acute Medically Ill Prevention with Extended Duration Betrixaban Study), which compared an extended anti-coagulant dosing regimen of betrixaban (35 days) to the current standard of care (10 days treatment with enoxaparin). Patients receiving betrixaban in the study received a loading dose of 160 mg followed by 80 mg with food QD for 35 to 42 days. APEX included a prospective dose reduction i.e., loading dose of 80 mg followed by 40 mg with food QD, for patients with severe renal impairment (CrCl < 30 mL/min) or receiving concomitant P-gp inhibitors. The dose reduction was made to match betrixaban exposures to the general population and was based on dedicated PK studies as well as PK observations in patient studies.

The benefit-risk for the proposed regimen in the general population is considered acceptable. However, the OCP review team's assessment of the benefit-risk for patients receiving 40 mg (either based on severe renal impairment [CrCl < 30 mL/min] or concomitant use of a P-gp inhibitor) suggests an increased risk for bleeding (major or clinically relevant non-major [CRNM] bleeding; betrixaban: 4.8% vs enoxaparin: 1.4%) without an efficacy benefit (symptomatic and asymptomatic VTE events; betrixaban 7.0% vs enoxaparin: 6.7%) compared to enoxaparin. The available data does not support that an improvement in the benefit-risk could be achieved by altering the dose for patients who prospectively received 40 mg.

Therefore, the OCP review team proposes to label betrixaban as it was studied in APEX for the general population. However, since the benefit-risk is unfavorable in the prospectively dose-reduced subgroup, i.e., significant higher risk for bleeding with no apparent efficacy benefit, the OCP review team recommends limiting the use of betrixaban in patients with severe renal impairment or who require concomitant use with P-gp inhibitors.

1.1 Recommendations

The Office of Clinical Pharmacology reviewed NDA 208383 and recommends approval. The essential review focus with specific recommendations and comments are summarized below.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness is derived from a single phase 3 study (APEX), which showed a significant reduction in symptomatic and asymptomatic VTE events for betrixaban compared to a shorter treatment regimen of enoxaparin. Additionally, a PK/PD study of betrixaban showed that betrixaban inhibits thrombin generation at clinically relevant concentrations.

General dosing instructions	The recommended dosage regimen is a 160 mg loading dose on day 1 followed by 80 mg QD with food for a total treatment duration of 35 to 42 days.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Prospective dose reductions of 80 mg on day 1 followed by 40 mg QD for the treatment duration were studied in APEX for patients with severe renal impairment or on concomitant P-gp inhibitors. Due to an unfavorable benefit-risk in this prospectively dose-reduced subgroup, the OCP review team proposes limiting the use of betrixaban in patients with severe renal impairment or who require concomitant use with P-gp inhibitors.
Labeling	Labeling language concerning limitations of use based on analysis of benefit-risk by the OCP review team has been proposed. The review team has specific content and formatting recommendations to section 12 to conform with the clinical pharmacology labeling guidance.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable, since the to-be-marketed formulation was studied in the pivotal clinical study.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Betrixaban is an oral factor Xa inhibitor.

Absorption: Absolute oral bioavailability of betrixaban is 32%, and the median time to attain maximum concentration is 2 h. Betrixaban is also a P-gp substrate and food reduces the C_{max} and AUC by approximately 60%.

Distribution: Betrixaban has a volume of distribution of 32 L/kg and a plasma protein binding of 60%. No difference in protein binding was observed between healthy volunteers and patients with renal impairment.

Metabolism: The predominant metabolic pathway of betrixaban is amide hydrolysis with minor CYP-based metabolism. Two primary metabolites (PRT062802 and PRT063069) have been identified with approximately 18% molar-corrected AUC ratio to parent. None of the identified metabolites have been shown to be active for factor Xa or to interact with the hERG potassium channel.

Elimination: Following intravenous administration approximately 20% of the administered dose is excreted in urine (19% as unchanged betrixaban). The clearance of betrixaban is 677 mL/min and the terminal half-life is 40 h.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The general dosing is based on how betrixaban was studied in the pivotal phase 3 study (APEX): 160 mg loading dose on day 1 followed by 80 mg QD with food for a total treatment duration of 35 to 42 days.

2.2.2 Therapeutic individualization

Based on an unfavorable benefit-risk assessment [Efficacy (symptomatic and asymptomatic VTE events): 7.0 vs 6.7%, Safety (major or CRNM bleeds): 4.8% vs 1.4%] in patients prospectively dose-reduced to 40 mg (patients with severe renal impairment [CrCl < 30 mL/min] or who require concomitant use of P-gp inhibitors), the OCP review team proposes limiting the use of betrixaban in patients with severe renal impairment or who require concomitant use with P-gp inhibitors.

2.3 Outstanding Issues

Review of the efficacy and safety information from the pivotal phase 3 study revealed an unfavorable benefit-risk for the 40 mg subgroup, which included patients on concomitant P-gp inhibitors. As described in section 3.3.4 of the review, the unfavorable benefit-risk in these patients might be related to an unidentified underlying patient factor(s) that is currently, at best, identified by concomitant P-gp inhibitor use. To potentially identify the underlying patient factor, the OCP review team conducted additional analysis to assess whether the benefit-risk in this subgroup is altered based on duration (chronic versus acute) and timing (at randomization versus after start of trial) of P-gp inhibitor use. During this evaluation, the OCP review team identified inconsistencies in how P-gp inhibitor use was documented across APEX data sets (i.e., different number of patients reported on P-gp inhibitors in the CSR compared to the Applicant's midcycle communication). Additional follow-up with the Applicant is required to reconcile these differences and will be documented in a subsequent addendum review.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology agrees with the Applicant that the dose is to be labeled as it was studied in APEX for the general population. However, the OCP review team has proposed the following labeling recommendations for the final package insert:

- Indications and Usage: Limitation of use for patients with severe renal impairment or who require concomitant use of P-gp inhibitors based on an unfavorable benefit-risk in this prospectively defined subgroup.

- Pharmacodynamics: This section was revised to include description of clinical pharmacodynamics, e.g. inhibition of thrombin generation or the relative timing / relationship to plasma concentration.

- QTc effects: The proposed language was not consistent with the OCP labeling guidance. Moreover, since the true supratherapeutic dosing scenario is not consistent with the supratherapeutic dose studied in the TQT study, this section was updated.

- Pharmacokinetics: The section as proposed by the Applicant was not consistent with the clinical pharmacology labeling guidance, resulting in several revisions from the OCP review team.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Betrixaban is a fourth in class oral factor Xa inhibitor, and the clinical development program includes 15 clinical pharmacology studies, 3 patient studies (two dose ranging phase 2 studies and a patient PK study) and one pivotal phase 3 study (APEX).

During the development of betrixaban there were numerous interactions between the Applicant and the Agency. Key interactions between the Agency and the Applicant were focused on the observed QTc signal in the SAD and MAD study and design and analysis of APEX. Concerning the latter, the Agency communicated the following concerns to the Applicant:

1. The Agency noted concerns with the rational for the doses selected for APEX, (b) (4) [redacted]. The Applicant noted that they believed they had collected adequate data to inform dosing in APEX (DARRTs 11/07/2011).

2. It was noted that (b) (4) [redacted] and it was suggested that the Applicant should establish superiority over enoxaparin at day 10 in addition to day 35 (DARRTs 11/07/2011, 12/02/2011). The Applicant explained (b) (4) [redacted] The Agency responded that the lack of a day 10 assessment could limit interpretation of the APEX study results and impact approvability, which the Applicant acknowledged (DARRTs 02/17/2012).

3. The definition of the population for the evaluation of efficacy in APEX, specifically the Applicant's proposal (b) (4) [redacted] as proposed by the Agency (DARRTs 01/06/2016). The OCP review team has used the mITT population for their analysis, which is the population used in the clinical and statistical review for the efficacy evaluation (DARRTs 03/29/2017). For a more detailed discussion of this issue please refer to the clinical and statistical review.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Inhibitor of factor Xa (FXa) that selectively blocks the active site of FXa and does not require a cofactor such as anti-thrombin III for activity. By directly inhibiting FXa, betrixaban decreases thrombin generation.
Active Moieties	Betrixaban

QT Prolongation	In a study that evaluated the effect of betrixaban on the QT interval, a concentration-dependent increase in the QTc interval was observed. Based on the observed concentration-QTc relationship a mean (upper 95% CI) QTc prolongation of 4 ms (5 ms) is predicted for 80 mg betrixaban and 13 ms (16 ms) for a 4.7-fold increase in exposure. [Study 07-013, Reviewer's analysis]
General Information	
Molecular weight	451.9 g/mol
Bioanalysis	Betrixaban and its metabolites in plasma and urine were measured using validated LC-MS/MS methods (Appendix 4.1).
Healthy Volunteers vs Patients	No formal comparison of PK between healthy volunteers and the proposed patient population due to limited PK collection, however, a comparable trough concentration was observed following 80 mg QD for 7 days in a digoxin DDI study (21.8 ng/mL) compared to the average concentration in the 20 - 24 h post-dose window in APEX for the 80 mg group (23.3 ng/mL). [Study 08-014, Reviewer's analysis]
Dose Proportionality	Slightly greater than dose-proportional change in AUC and C_{max} were observed over a dose-range of 40 to 140 mg, though there is some uncertainty about this observation. [Reviewer's analysis]
Accumulation	2.3-fold and 1.6 accumulation for AUC and C_{max} respectively. [Study 08-016]
Variability	Moderate to high inter-subject variability: 44.5% and low intra-subject variability 16.6% for $AUC_{0\text{-}inf}$ [Study 15-020, Reviewer's analysis].
Absorption	
Bioavailability	32% absolute bioavailability [Study 07-012]
Tmax	2h [0.5 to 6h] [Study 15-020]
Food effect	Food (high fat and low fat) decreases AUC and C_{max} by approximately 60% [Studies 05-002, 09-018, and pn001]. Because of the food effect, betrixaban was administered under fed conditions in APEX.
Substrate transporter systems	Betrixaban is a substrate of P-gp. [Study NC-16-0735] The potential for betrixaban to inhibit P-gp, MRP2, BCRP, BSEP, OAT1, OATP1B1 and OATP1B3 has also been evaluated and suggested a potential for inhibition of P-gp (IC_{50}: 11.6 µM) and BCRP (IC_{50}: 11.6 µM). [Study NC-09-0282] A clinical DDI study, however, showed no impact of betrixaban on digoxin PK, suggesting betrixaban is not an inhibitor of P-gp in vivo [08-014]. Based on this finding, betrixaban might also not be a clinically significant BCRP inhibitor ($[I]/IC_{50}$ <0.1) based on a similar in vitro IC_{50} value as that for P-gp.
Distribution	
Volume of Distribution	32 L/kg [Study 07-012]
Plasma Protein Binding	60% protein binding based on micro-equilibrium dialysis [Study NC-10-0330]. Similar protein binding was observed in renal impairment study with no difference between healthy volunteers and patients with renal impairment [Study 08-016].
Blood to Plasma Ratio	1.4 [Study NC-10-0331]
Elimination	
Mean Terminal Elimination half-life	40 h [Study 07-012]

Metabolism	
Primary metabolic pathway(s)	Amide hydrolysis is the primary metabolic pathway and two predominant inactive metabolites are observed PRT06802 and PRT063069 with molar-corrected AUC of ~18%. (section 4.2.4) [Response to IR request dated March 3rd]
Inhibitor/Inducer	Betrixaban was not observed to inhibit CYP1A2, 2C9, 2C19, 2D6, 3A4/5 [Study NC-07-0107] or to induce CYP1A2, 2B6 or 3A4 [Study NC-08-0173].
Excretion	
Primary excretion pathways	Urinary elimination: 20% (19% unchanged) of dose administered IV [Study 07-012, addendum] Presumably the main pathway of elimination is biliary excretion, however the radioactivity observed in feces is only reported in the mass balance study which was following oral dosing.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Primary evidence of effectiveness for betrixaban in the indicated population was provided by the pivotal Phase 3 study (APEX). Additional supportive evidence was provided from pharmacodynamic relationships (described below) between betrixaban exposure and biomarkers of anticoagulation, as well as two Phase 2 studies in patients with total knee replacement (EXPERT) and atrial fibrillation (Explore-Xa).

Betrixaban is the fourth in class factor Xa inhibitor, a class with understood impact on biomarkers of coagulation such as activated partial thromboplastin time (aPTT), prothrombin time (PT) and endogenous thrombin potential (ETP), which was also studied clinically for betrixaban (**Figure 1**). The maximum change in endogenous thrombin generation appears to coincide with time of peak betrixaban concentration, supporting a direct effect of betrixaban on this coagulation biomarker. Of note, the translation from these biomarkers to clinical outcomes is not known.

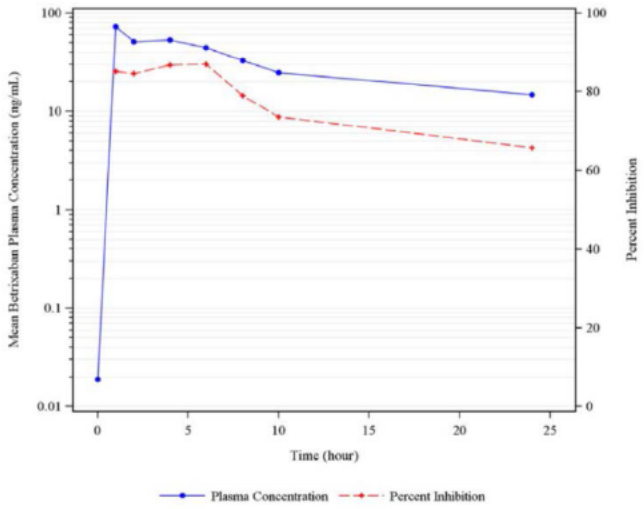

Figure 1: Relationship between betrixaban concentration and change in endogenous thrombin generation. *[Source: PN002 CSR, Figure 3, Page 45]*

As noted above, the sponsor also conducted two phase 2 studies in patients with total knee replacement (EXPERT) or atrial fibrillation (EXPLORE), which are different populations than for the proposed indication. EXPERT included two dose levels 15 and 40 mg BID and enoxaparin. The primary endpoint in the EXPERT study was the prevention of VTE after total knee replacement. The study showed a 20% and 15.4% VTE rate for 15 and 40 mg BID betrixaban compared to 10% with enoxaparin. In addition to EXPERT, the Applicant also conducted a phase 2 study in atrial fibrillation patients (EXPLORE) with major or CRNM bleeds as the primary endpoint comparing 40, 60 and 80 mg QD betrixaban to warfarin. In EXPLORE, for the primary endpoint of bleeding, an event rate of 2.02%, 10.1% and 10.5% were observed for 40, 60 and 80 mg betrixaban respectively and 14.6% for warfarin. While, EXPERT and EXPLORE provide supporting evidence of the anti-coagulant properties of betrixaban, both studies were conducted in two different study populations compared to the APEX study population (see section 3.1).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the general dosing regimen proposed for betrixaban (160 mg loading dose followed by 80 mg QD) is supported by the pivotal phase 3 study (APEX), which showed a reduction of VTE events (symptomatic and asymptomatic) for a 35-day betrixaban treatment regimen compared to a 10-day enoxaparin treatment regimen with a modest increase (betrixaban: 2.7%, enoxaparin: 1.6%) in major or CRNM bleeds (**Figure 2A**). The Applicant defined symptomatic and asymptomatic VTE as the primary efficacy endpoint and major bleeding as the primary safety endpoint. The OCP review team used the same primary efficacy endpoint, but evaluated major and CRNM bleeds as the primary safety endpoint, and considers the inclusion of CRNM bleeds in the safety endpoint relevant because the primary efficacy component is primarily comprised of asymptomatic events (~80%) and CRNM bleeds are still clinically meaningful.

An evaluation of symptomatic VTE events and major and CRNM bleeds by time suggests a clear separation between betrixaban and enoxaparin starting around day 10 for efficacy, which coincides with the switch from enoxaparin to placebo in the enoxaparin arm (**Figure 2B**). This seems to indicate that the superiority in efficacy is attributable to the longer duration of anticoagulation associated with the betrixaban arm as opposed to betrixaban being a superior anticoagulant compared to enoxaparin. On the contrary, an apparent earlier separation for major and CRNM bleeds was noted suggesting an increased risk for bleeding with betrixaban compared to enoxaparin. As asymptomatic events were recorded on the last visit, the time-to-event analysis for efficacy was carried out using symptomatic events.

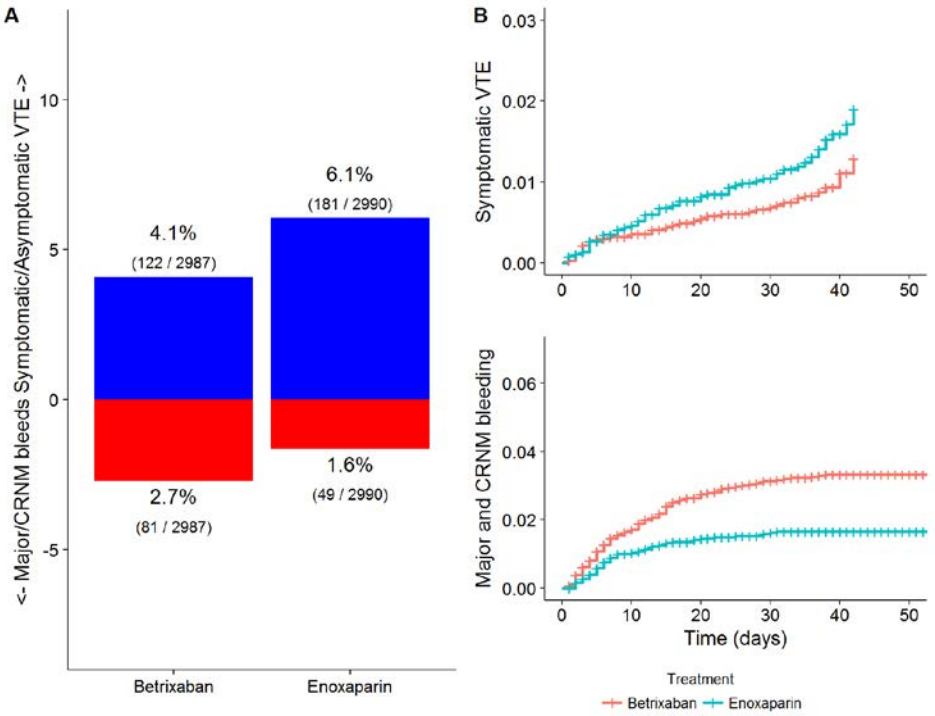

Figure 2: **(A)** Analysis of the primary efficacy events (blue: symptomatic and asymptomatic VTE) and safety events (red: major and clinically relevant non-major [CRNM] bleeds) for 80 mg for betrixaban (left) and enoxaparin (right). **(B)** Symptomatic VTE (top) and major and CRNM bleeding (bottom) for betrixaban (red) and enoxaparin (blue) in patients receiving the 80 mg dose. Both analyses are based on the modified ITT population. *[Source: Reviewer's Analysis]*

In addition, the Applicant collected sparse PK at a single time point from patients in APEX with the intent of using this information to explore the exposure-efficacy and -safety relationships for patients in this study. However, the OCP review team does not agree with the performed population PK analysis in part due to the limited data and nature of data collection in APEX (one sample per subject, at a non-standard time-point). As such, no exposure-response analyses for either efficacy or safety could be conducted based upon the provided information, and the evaluation of efficacy and safety is instead based on summary of event rates and time-to-event analysis.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, the OCP review team recommends limiting the use of betrixaban in patients with severe renal impairment (CrCl < 30 mL/min) due to an unfavorable benefit-risk.

A prospective dose reduction was implemented in APEX for patients with severe renal impairment (CrCl < 30 mL/min) based on PK information from EXPLORE and DEC. However, based upon the results from APEX in this subgroup of patients, there appears to be a lack of efficacy benefit in patients with severe renal impairment compared to a similar group of patients in the enoxaparin control arm (**Figure 3**). The Applicant asserts that the lower efficacy observed in the 40 mg subgroup is due to a lower exposure (based on Applicant's population PK analysis), and as a result the Applicant proposed that patients with severe renal impairment should receive the [redacted] (b) (4)

However, the OCP review team notes that major and CRNM bleeds in this subgroup are already significantly higher compared to enoxaparin than the general population without an apparent efficacy benefit, regardless of Applicant's assertion that these patients were under dosed. Clearly, the benefit-risk is unfavorable in this subgroup compared to general population, and bleeding would be expected to be even worse with dosing instructions to utilize a higher dose (**Figure 3A**). Moreover, there is a trend for an earlier separation between the betrixaban and the enoxaparin arm in terms of major and CRNM bleeds which suggests that these patients have a higher risk for bleeding with betrixaban (**Figure 3B**). Therefore, the OCP review team recommends a limitation of use for patients with severe renal impairment.

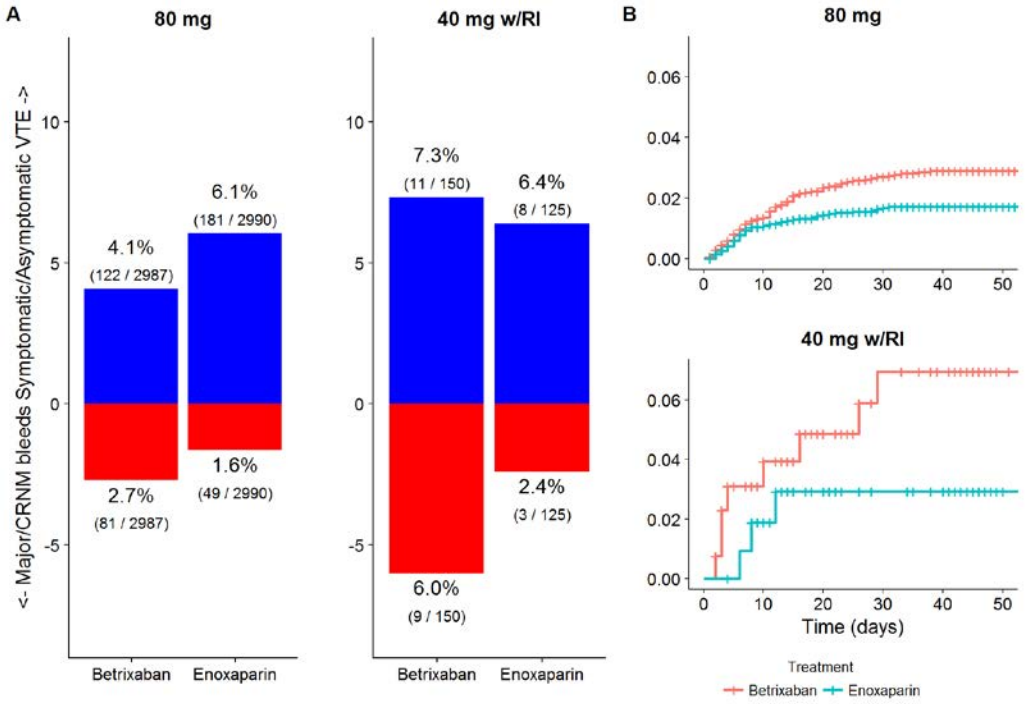

Figure 3: **(A)** Primary efficacy outcome (blue: symptomatic and asymptomatic VTE) and safety (red: major and clinically relevant non-major [CRNM] bleeds) for 80 mg (left) and patients with severe renal impairment (CrCl < 30 mL/min) (right). **(B)** Time-to-event analysis for major and CRNM bleeds for 80 mg (top) and 40 mg with severe renal impairment (bottom). The analysis is based on the modified ITT population. *[Source: Reviewer's analysis]*

The OCP review team's concerns about the results in the 40 mg group for patients with severe renal impairment were discussed at the midcycle meeting and subsequently communicated to the Applicant (DARRTs 02/09/2017). The Applicant submitted a response to the midcycle communication (Seq 0022, 02/24/2017), stating that the observed data for patients with severe renal impairment was "underpowered, confounded and not compelling" and considers (b) (4) mg to be the appropriate dose for patients with severe renal impairment based on population PK analysis of APEX.

The OCP review team does not agree with the Applicant's conclusion for this subgroup and as discussed in section 3.3.2, the OCP review team does not agree with the performed population PK analysis. The OCP review team has therefore conducted an independent analysis based on the observed PK data and the relationship to CrCl for PK samples collected between 20 and 24 h post-dose (approximately C_{trough}). This analysis is presented in **Figure 4A**, and shows a relationship between CrCl and betrixaban

concentrations, which supports that: i) betrixaban exposure is influenced by renal impairment; and ii) a dose reduction would be needed for patients with severe renal impairment so such patients would have exposures similar to patient without renal impairment. This analysis is further supported by evaluation of the PK data from the DEC study, where repeated PK samples were collected more systematically (**Figure 4B**). Therefore, the OCP review team believes that the dose-reduction was appropriate in this subgroup from a PK standpoint to match exposures to the general population receiving 80 mg. However, due to a lack of efficacy benefit together with an increased risk for bleeding (**Figure 3**), the OCP review team does not recommend the use of betrixaban in patients with severe renal impairment.

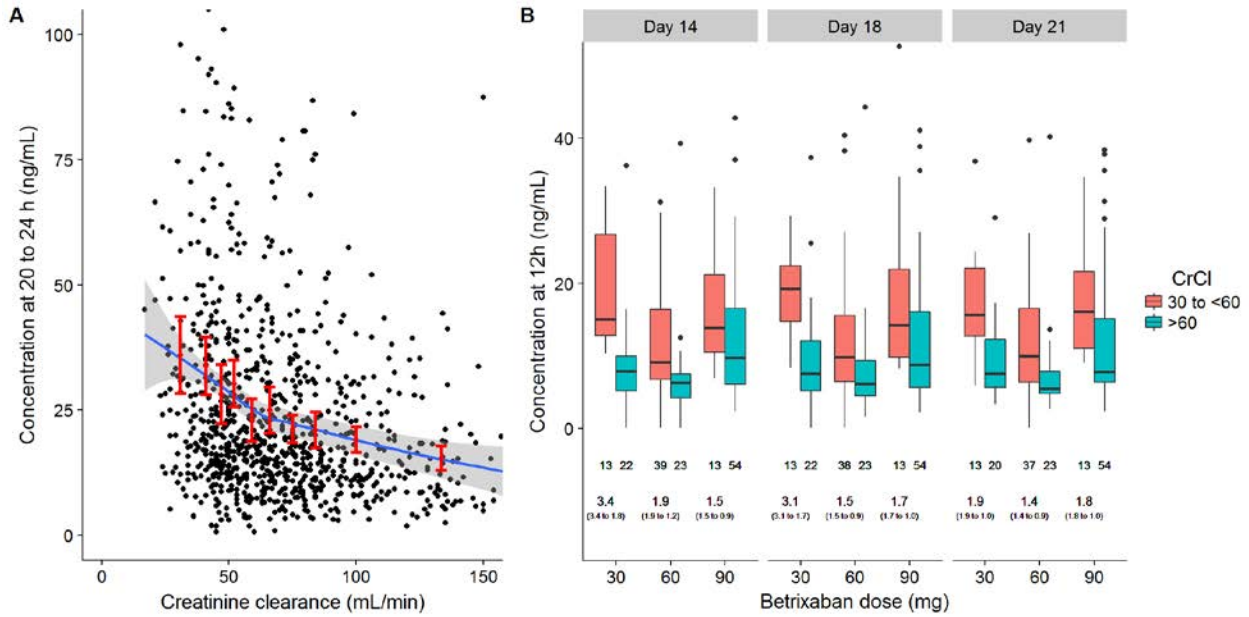

Figure 4: **(A)** Evaluation of the relationship between creatinine clearance (Cockcroft-Gault) and betrixaban concentration, windowed to 20 to 24 h, due to limited PK sample collection in APEX. The analysis only includes the 80 mg dose group. The red error bars correspond to mean and 95% CI for data binned into 10 bins and the blue line and shaded area correspond to a loess regression **(B)** Evaluation of the relationship between betrixaban concentrations 12 hours post-dose and renal function, by dose group and study day in the DEC study. *[Source: Reviewer's Analysis]*

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, clinically meaningful effects on betrixaban exposure were observed when given with a low or high fat meal, or when administered with a P-gp inhibitor. Therefore, betrixaban was administered with food in APEX and a dose reduction was implemented for patients on concomitant P-gp inhibitors. The Applicant observed lack of efficacy benefit in the 40 mg subgroup and asserts that this finding is due to under dosing, [redacted] (b) (4) (based on their population PK analysis). However, because of an unfavorable benefit-risk relationship in this subgroup of patients, the OCP review team recommends a limitation of use for patients on concomitant P-gp inhibitors. Lastly, based on the observed food effect and conduct of APEX, the Applicant is proposing to label betrixaban to be taken with food, a recommendation with which the OCP review team concurs.

Food Effect

There is a reduction in the AUC and C_{max} of betrixaban when given with a low or high fat meal (**Figure 5**). This effect appears to be present when betrixaban is taken up to 6 h after the administration of a meal. Because of the observed food effect, the Applicant proposes betrixaban to be taken with food, which is how it was studied in APEX. The OCP review team concurs with this recommendation.

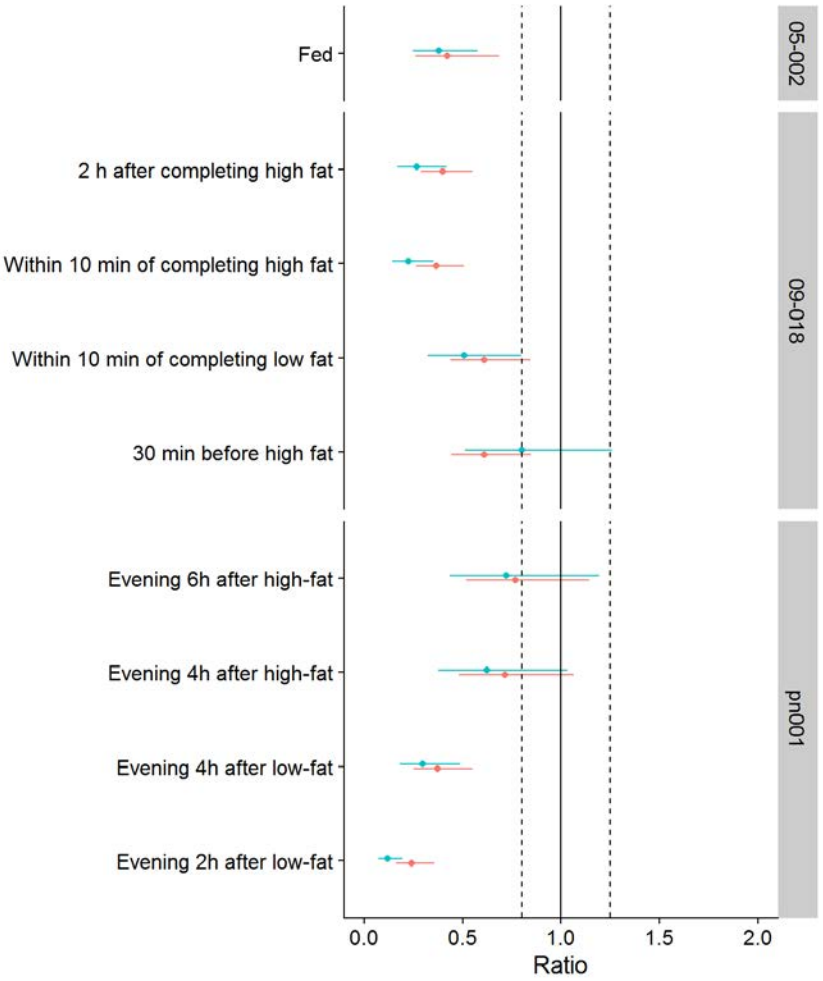

Figure 5: Evaluation of the impact of food (high and low-fat) and timing of food on betrixaban PK, where red is $AUC_{0\text{-}inf}$ and blue is C_{max}. The solid and vertical lines are located at 1 and 0.8/1.25 respectively, and represent the bioequivalence limits. *[Source: Reviewer's analysis]*

P-gp Inhibitors

A prospective dose reduction was included in APEX for patients on concomitant P-gp inhibitors, similarly to the dose reduction for patients with severe renal impairment. In this subgroup the Applicant noted a decreased efficacy (**Figure 6**), which the Applicant asserts is due to under dosing. The Applicant is basing this conclusion on their population PK analysis and suggests that the dose (b) (4)

The OCP review team analyzed the major and CRNM bleeds in this subgroup and observed a lack of efficacy (symptomatic and asymptomatic VTE events; betrixaban: 5.3%; enoxaparin: 4.8%), as noted by

the Applicant, as well as an increase in bleeding risk (major or CRNM bleeds; betrixaban: 4.6%; enoxaparin: 1.5%) (**Figure 6A**). The OCP review team's concern with this observation was included in the midcycle communication letter, and the Applicant did not provide any meaningful explanation for the findings in the 40 mg P-gp subgroup. The Applicant asserted that the (b) (4)

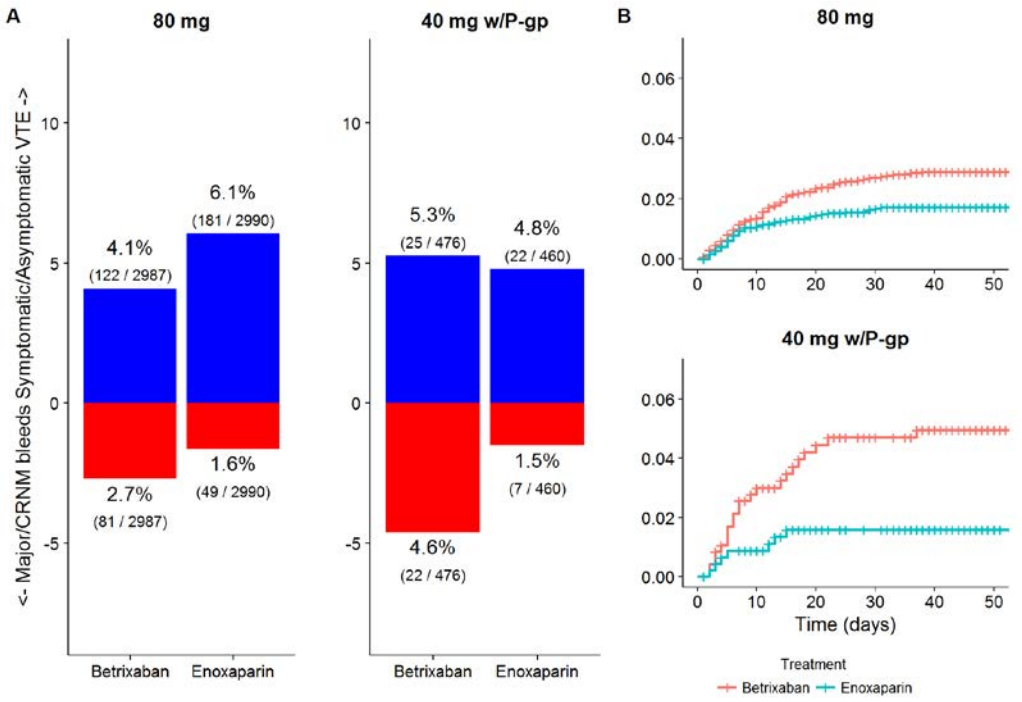

Figure 6: **(A)** Primary efficacy outcome (blue: symptomatic and asymptomatic VTE) and safety (red: major and clinically relevant non-major [CRNM] bleeds) for 80 mg (left) and patients receiving concomitant P-gp inhibitors (right). **(B)** Time-to-event analysis for major and CRNM bleeds for 80 mg (top) and 40 mg with concomitant P-gp inhibitor use (bottom). The analysis is based on the modified ITT population. *[Source: Reviewer's analysis]*

The OCP review team has concerns about the population PK analysis performed by the Applicant (see section 3.3.2, and conducted an independent analysis similar to the analysis for patients with severe renal impairment described in Section 3.3.3 (**Figure 7**). As can be seen from two examples below – amiodarone and carvedilol (which represent the most commonly used P-gp inhibitors) – dose adjustment seems to be appropriate for amiodarone but an over-correction for carvedilol. However, the over correction is not conclusive. It is possible that carvedilol is a weak P-gp inhibitor (although a classification system doesn't exist) or the magnitude of interaction is not captured due to time of administration of the P-gp inhibitor relative to betrixaban.

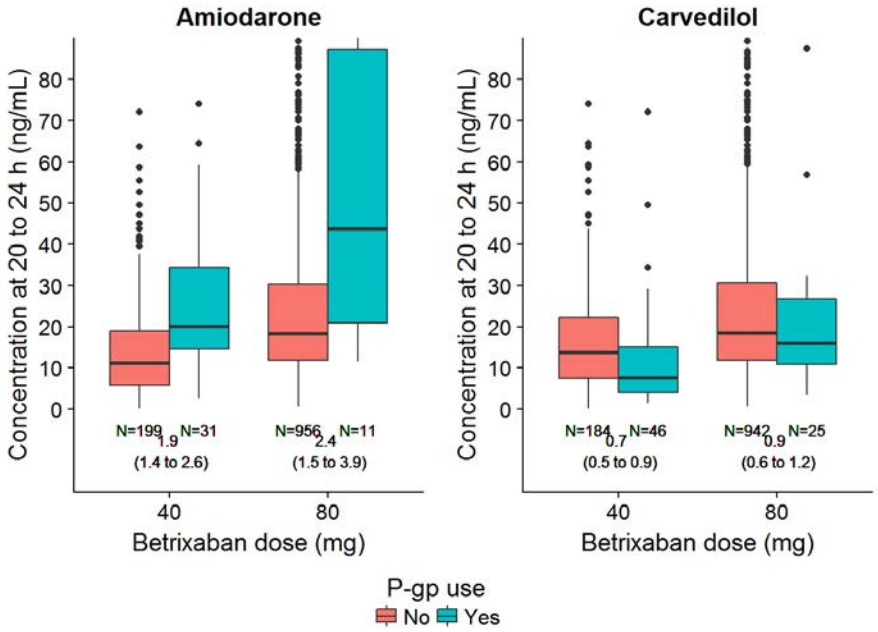

Figure 7: Comparison of windowed betrixaban concentrations (20 to 24 h) for the 40 and 80 mg dose between patients on amiodarone (left) or carvedilol (right). *[Source: Reviewer's analysis]*

Despite the dose reduction for the patients in the 40 mg subgroup, an increase in major and CRNM bleeding was observed without an efficacy benefit compared to the enoxaparin group. Therefore, the OCP review team proposes limiting the use of betrixaban in patients who require concomitant use with P-gp inhibitors, as the observed unfavorable benefit-risk cannot be explained by exposure.

In addition, a comparable increase in major and CRNM bleeding between the overall 80 mg group and 80 mg subgroup on P-gp inhibitors who were not dose reduced was observed (relative risk 80 mg: 1.63 [1.12 to 2.39]; 80 mg + P-gp: 1.75 [0.7 to 4.32]) (**Table 1**). While, the latter observation is in a comparably smaller subgroup it supports the notion that the unfavorable benefit-risk in the 40 mg subgroup is unlikely to be explained by exposure or the concomitant use of P-gp inhibitors. This suggests, that the unfavorable benefit-risk is related to an unidentified underlying patient factor(s) that is preferentially present in the patients who received 40 mg. However, at present these patients can only be identified, at best, on the basis of concomitant P-gp inhibitor use (refer 2.3).

Table 1: Summary of major and clinically relevant non-major bleeding in the safety population. *[Source: Response to midcycle communication dated 2/9/2017]*

	80 mg		80 mg w/P-gp	
	Betrixaban (n=2622)	Enoxaparin (n=2643)	Betrixaban (n=348)	Enoxaparin (n=327)
Major bleed and CRNM	2.6% (68)	1.6% (42)	3.7% (13)	2.1% (7)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical method validation summarized by the Applicant (Table 2) meets the requirements of the FDA guidance for "*Bioanalytical Method Validation*" and is acceptable. However, the bioanalytical assay utilized in the mass balance study did not have adequate sensitivity, i.e. the LLOQ was 14.2 ng /mL, and as a result the mass balance study has a reduced interpretability. The reduced interpretability of the mass balance study is mitigated by the collection of metabolite information in other clinical pharmacology studies utilizing more sensitive assays.

Table 2: Summary of validation reports for betrixaban and the major metabolites PRT062802 and PRT063069 *[Source: Summary of Biopharmaceutic Studies & Associated Analytical Methods, Table 2.7.1-1, Page 7]*

Validation Study Number	(b) (4) Report Number	Matrix	Analyte	Range (ng/mL)	Accuracy (%)	Precision (%)	Clinical Studies
NC-15-0686	DCN 11-526, (2 amendments)	K_2-EDTA Plasma	Betrixaban (MLN1021)	0.50-500	1.0–8.2 from nominal	0.84-3.9	02-401 04-001 05-002
TR03-0016	(b) (4) 11-526-V1	Urine	Betrixaban (MLN1021)	0.50-500	96.0-102 of actual	4.61-9.45	02-401
NC-15-0696	(b) (4) DCN 1000051, (2 amendments)	K_2-EDTA Plasma	Betrixaban (PRT054021)	0.100-50.0	-4.6 to 4.8	1.9-7.8	06--004 07-008 07-009 07-011 07-012 07-013 08-014 05-003 PN006
NC-09-0240	(b) (4) DCN 1003250, (3 amendments)	K_2-EDTA Plasma	Betrixaban (PRT054021)	0.100-50.0	-6.7 to -1.5	4.5-9.8	08-015 08-016 09-018
NC-09-0240	(b) (4) DCN 1003250, (3 amendments)	K_2-EDTA Plasma	PRT062802	0.100-50.0	-7.0 to -0.0	3.2-6.5	08-015 08-016 09-018
NC-15-0692	(b) (4) DCN 1001853	Urine	Betrixaban (PRT054021)	0.50-250	1.5-3.3	2.0-2.9	07-012 08-014
NC-16-0742	(b) (4) DCN 1004201 (5 amendments)	K_2-EDTA Plasma	Betrixaban (PRT054021)	0.100-50.0	-2.5 to 5.0	2.0-4.9	11-019
NC-16-0742	(b) (4) DCN 1004201	K_2-EDTA Plasma	PRT062802	0.100-50.0	-7.6 to 8.2	3.4-6.0	11-019
NC-10-0312	(b) (4) DCN 1003817, (1 amendment)	Urine	Betrixaban (PRT054021)	1.00-500	-9.8 to -5.3	1.9-3.7	08-016
NC-10-0312	(b) (4) DCN 1003817, (1 amendment)	Urine	PRT062802	2.00-200	-5.6 to -2.3	2.0-3.8	08-016
NC-08-0226	Not done at (b) (4)	K_2-EDTA Plasma	PRT063069	0.50-100	90.9-119 of actual	3.94-11.7	07-013 08-014

4.2 Clinical PK and/or PD Assessments

This section provides PK information from the individual studies in terms of single-dose and multiple-dose PK, absolute bioavailability, metabolism, excretion, impact of covariates such as weight and sex on betrixaban PK, drug-drug interaction studies and QT.

4.2.1 Single-dose

There are two single ascending dose studies in healthy volunteers: 02-401 and 04-001. In study 02-401 a (b) (4) formulation was studied, which was not used any longer in the development program. Therefore the PK results from study 02-401 are not described here and the description of single-dose pharmacokinetics will focus on the second part of study 04-001. In study 04-001 the subjects were dosed twice for 10 days (except day 10) with 40, 80 and 120 mg. The morning dose was after an overnight fast and followed by a 3-hour fast, however, the second dose in the day was 2 h after a meal.

A greater than proportional change in C_{max} and AUC_{0-12h} was observed on day 1 (**Table 3**), resulting in a ~3-fold increase in C_{max} and AUC_{0-12h} for a doubling of the dose (C_{max}: 2.99 [1.99 to 4.48], AUC_{0-12h}: 3.25 [1.99 to 5.31], based on Table P, page 70).

Table 3: Pharmacokinetic summary from study 04-001. *[Source: 04-001 CSR, Table N, page 68]*

Dose (mg)	C_{max} (ng/mL)	t_{max} [+] (h)	AUC_{0-12h} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)
40	9.37	1.55	53.5	83.1 [6]
	(68.6)	(1.00 - 4.00)	(54.5)	(76.8)
80	38.0	3.50	174	393 [4]
	(64.6)	(1.00 - 4.05)	(61.1)	(33.0)
120	58.2	2.00	298	600 [5]
	(44.9)	(1.00 - 4.00)	(41.3)	(9.24)

[+] = Median (range) for t_{max}, n = 8 unless otherwise indicated [ ]

The confidence interval around the point estimate for a doubling in dose includes 2 in most cases likely due to the small number of subjects included and the inter-subject variability in betrixaban pharmacokinetics (CV ~50%). Therefore, the reviewer conducted a pooled analysis of data from single-dose studies under fasting conditions, which supported the greater than dose-proportional increase (AUC: 2.6 [2.5 to 2.8]; C_{max}: 2.8 [2.6 to 3.4]) and it appears to be most pronounced between 40 and 80 mg (**Figure 8**). Of note, the independent analysis by the reviewer is based on a pool of all single dose studies. No mechanism for the apparent and not entirely consistent observation of greater than dose proportional pharmacokinetics has been identified and it is plausible that it is a chance finding.

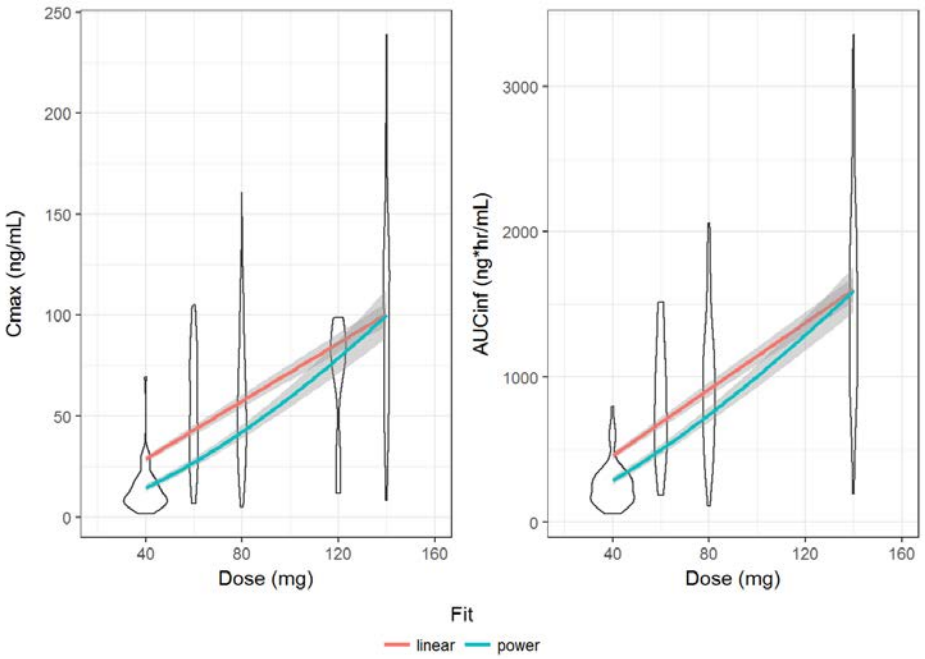

Figure 8: Pooled dose proportionality assessment across studies 04-001, 05-002, 09-018, pn001, 08-016, 15-020, 07-009, pn010, 07-008 and 07-013. Only data from single dose 80 mg fasting were included for the assessment C_{max} (left) and AUC (right). The red line represents a linear fit through the original (with confidence area) and the blue line represents a fitted power model (with confidence interval). The distribution of data at each dose group is visualized using a violin plot. *[Source: Reviewer's analysis of pooled data]*

4.2.2 Multiple-dose

Multiple dose pharmacokinetics were evaluated in part B of study 04-001, where betrixaban was administered twice daily under fasting conditions for 10 days, where a ~2.8-3.8-fold increase in $AUC_{0\text{-}12h}$ (**Table 4**), corresponding to an effective half-life of 18.8 – 27.2 h and expected time to steady state of 5 days. A similar effective half-life is also estimated from study 08-016, where 80 mg betrixaban was once daily administered for 8 days (R_{AUC}: 2.3, $T_{1/2,eff}$: 29.2 h).

Table 4: PK parameters for betrixaban on day 10 in study 04-001 *[Source: 04-001 CSR, Table O, Page 68]*

Dose (mg)	C_{max} (ng/mL)	C_{min} (ng/mL)	$C_{max}/C_{min\ ss}$*	t_{max} + (h)	$AUC_{0\text{-}12h}$ (ng.h/mL)	$AUC_{0\text{-}t}$ (ng.h/mL)	λ_z (/h)	$t_{1/2}$ (h)	R_O
40	23.2	9.09	2.60	4.00	179	674	0.0174	39.7	3.76
	(29.3)	(27.9)	(24.6)	(1.00 - 4.00)	(28.4)	(26.7)	(12.6)	(11.6)	(56.7)
80	73.1	22.4	3.06	4.00	488	1583	0.0186 [6]	37.3 [6]	2.91
	(48.8)	(52.6)	(15.4)	(1.00 - 4.02)	(46.2)	(46.1)	(6.24)	(6.29)	(55.6)
120	122 [8]	39.7[8]	3.00 [8]	3.00[8]	821[8]	2565[8]	0.0193[8]	35.9[8]	2.75[8]
	(48.9)	(40.2)	(38.7)	(1.02 - 4.00)	(43.2)	(40.2)	(21.7)	(26.6)	(60.2)

+ = Median (range) for t_{max}, n = 7 unless otherwise indicated [ ];

*$C_{min\ ss}$ derived from the average of C_{trough} on Day 8, Day 9 and Day 10.

Source: Pharmacokinetic/Pharmacodynamic Report included in Appendix 12.1

4.2.3 Absolute bioavailability

The absolute bioavailability of betrixaban was evaluated in eight healthy male volunteers in study 07-012, who received a single dose of 2 x 40 mg capsules of betrixaban or an IV dose of 80 µg of [^{14}C]-betrixaban. The oral dose was administered following an overnight fast and the IV dose was

administered two hours after the oral administration over 15 minutes. The overall results from the study are:

- Absolute oral bioavailability of 32.4% with moderate variability (CV: 49.4%, range: 7 to 53.8%, table 14.2.2)
- Volume of distribution of 32 L/kg (CV: 28.5%, range: 19.5 to 45.5 L/kg)
- Betrixaban clearance: 677.2 mL/min (CV: 20.4%, range: 461.4 to 920.2 mL/min)

4.2.4 Metabolites

The extent of metabolism of betrixaban has been evaluated in multiple studies either as a primary objective or a subsequent analysis of collected samples, and the proposed metabolic pathways are shown in **Figure 9**, which shows CYP and non-CYP mediated metabolism.

An *in vitro* study using human CYP isoforms suggested that the O-desmethyl (PRT058326) and N-desmethyl (PRT054156) metabolites are formed by multiple CYP enzymes, with CYP3A4 and CYP2D6 likely to be involved in the formation of either metabolite (NC-10-0337). Pharmacokinetic samples from a multiple dose study were analyzed to determine the presence of these metabolites *in vivo*. This analysis showed that the plasma concentrations observed after 10 days of 120 mg BID dosing were <BLQ on day 10 for all subjects but one (C_{max}: 0.6 ng/mL) for PRT058326 and that the C_{max} ranged from 0.7 to 1.7 ng/mL for PRT054156 (BLQ for 3/8).

The Applicant also carried out a mass balance study in humans, which suggested that the predominant moiety in human plasma was unchanged betrixaban. As noted previously (section 4.1) the assay utilized for the plasma analysis had sensitivity issues, however, the presence of the main metabolite identified in the mass balance study (PRT06802) was evaluated in other clinical pharmacology studies showing an approximately 18% molar-corrected AUC ratio for this metabolite. In addition, to the PRT06802 metabolite identified in the mass balance study another metabolite (PRT063069) has been identified, which has a molar-corrected AUC ratio of approximately 15%. However, none of the identified metabolites are active in terms of FXa inhibition (Response to IR, Seq 0028) and neither of the major metabolites (AUC>10%) inhibit the hERG potassium channel.

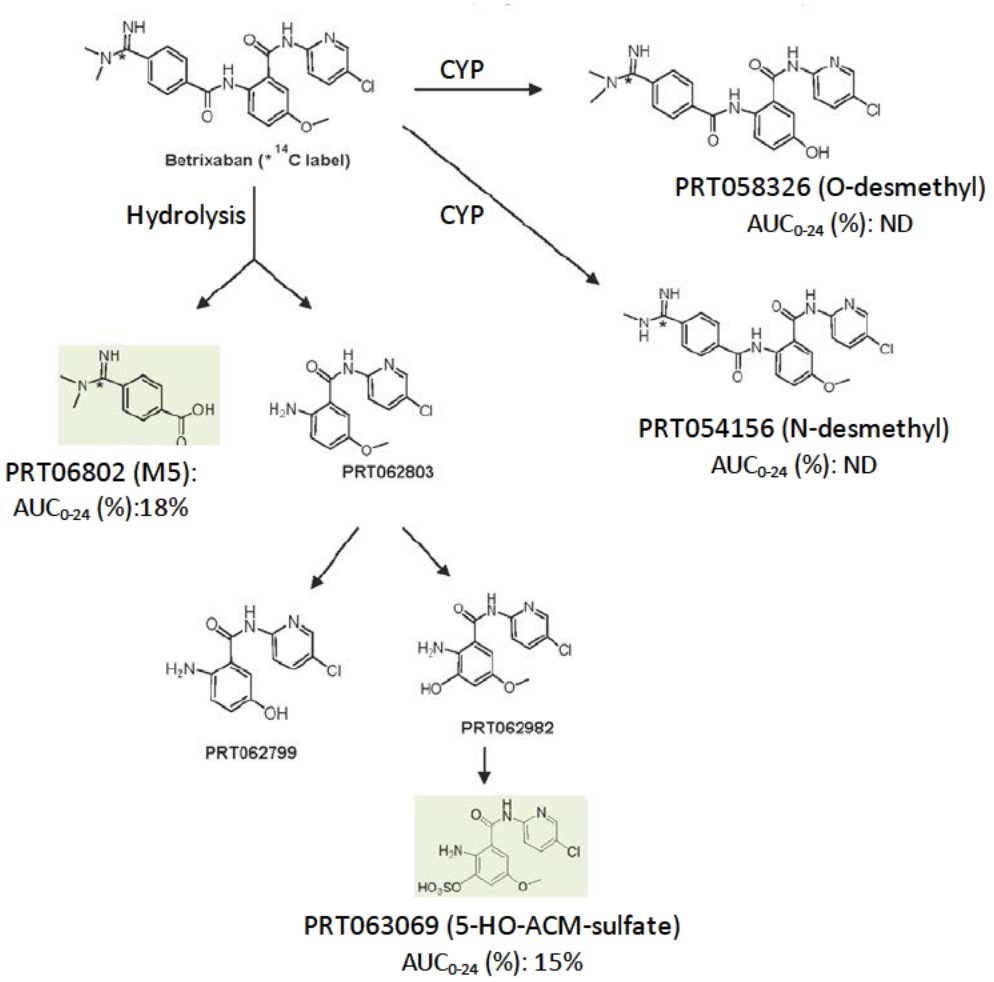

Figure 9: Overview of proposed pathway of betrixaban metabolism *[Source: Summary of Clinical Pharmacology Studies, page 28, Figure 2.7.2-4 and Seq 0028/Response to information request dated 03/03/02017]*

4.2.5 Urinary excretion

The fraction of unchanged betrixaban in urine was assessed in multiple studies, and the Applicant summarized the fraction excreted relative to the observed absolute bioavailability. Due to the variability in betrixaban PK this approach is not ideal. However, the Applicant also assessed the urinary excretion of betrixaban in the absolute bioavailability study and determined the fraction of unchanged betrixaban in urine represented: 18.7% (CV: 27.8%, range: 10.2 to 26.7%) and represented the majority of the drug excreted in urine.

The Applicant conducted a renal impairment study (Table 5), which showed an increase in C_{max} and AUC with declining renal function, however, the Applicant asserts that the apparent increase in C_{max} and AUC can be attributed to a lower than expected AUC in the healthy group and that the results of the study is a spurious finding. The reviewer has conducted additional analysis of PK data from patient studies, which is summarized in the main body of the review (section 3.3.3) that supports a difference in betrixaban PK based on renal function.

Table 5: Comparison of geometric means for C_{max} and AUC for different categories of renal function. The Applicant used the 186 multiplier in the MDRD equation for initial classification (top) and performed sensitivity analysis to using a 175 multiplier (bottom). *[Source: 08-016 CSR, page 62, Table 11-2]*

Parameter	Day	Mild Renal Impairment versus Healthy Subjects Ratio (90% CI)	Moderate Renal Impairment versus Healthy Subjects Ratio (90% CI)	Severe Renal Impairment versus Healthy Subjects Ratio (90% CI)	Severe Renal Impairment versus Mild Renal Impairment Subjects Ratio (90% CI)
Subjects grouped using 186 as multiplier in the MDRD equation:					
AUC_{0-24}	1	1.54 (0.963, 2.47)	1.90 (1.20, 3.01)	2.46 (1.60, 3.80)	1.60 (1.02, 2.50)
AUC_{0-24}	8	1.89 (1.18, 3.03)	2.27 (1.43, 3.59)	2.63 (1.71, 4.06)	1.39 (0.888, 2.18)
C_{max}	1	1.70 (0.952, 3.02)	2.27 (1.29, 3.99)	2.54 (1.49, 4.33)	1.50 (0.863, 2.60)
C_{max}	8	1.88 (1.05, 3.35)	2.32 (1.32, 4.07)	2.52 (1.48, 4.29)	1.34 (0.772, 2.32)
Subjects grouped using 175 as multiplier in the MDRD equation:					
AUC_{0-24}	1	1.90 (1.11, 3.25)	1.85 (1.07, 3.20)	2.69 (1.63, 4.41)	1.41 (0.903, 2.20)
AUC_{0-24}	8	1.94 (1.14, 3.31)	2.44 (1.41, 4.22)	2.86 (1.74, 4.70)	1.47 (0.944, 2.30)
C_{max}	1	2.09 (1.08, 4.03)	2.24 (1.14, 4.39)	2.82 (1.53, 5.20)	1.35 (0.781, 2.34)
C_{max}	8	1.96 (1.01, 3.78)	2.38 (1.21, 4.67)	2.69 (1.46, 4.96)	1.37 (0.793, 2.38)
Geometric least squares mean ratios (90% CI)					

4.2.6 Impact of weight and sex

The Applicant evaluated the impact of weight and sex in their population PK analysis of APEX, and concluded on the basis of this analysis a 20% difference between the genders and a 30% difference between the 10th and 90th percentile for weight for the projected concentration at 20 h post-dose. However, the review team does not agree that the Applicant's PK data collected from APEX included sufficient sampling to reliably inform patient PK parameters or exposures (section 3.3.2). Therefore, the reviewer utilized data from the bioequivalence study (15-020) and the thorough QT study (07-013) for the 80 mg dose to assess the impact of weight and gender. This data pool contains the largest number of subjects and is relatively balanced with regards to gender. Using the pooled data the relationship between apparent oral clearance and weight and gender was conducted, which confirmed the Applicant's conclusions of no clinically relevant impact of either weight (5th percentile vs median: 0.76 [0.65 to 0.88], 95th percentile vs median: 1.27 [1.11 to 1.46]) or sex (male vs female: 1.43 [1.2 to 1.72]) on betrixaban exposure.

4.2.7 Drug-drug interaction

Four dedicated drug-drug interaction studies were conducted, which are described below in full.

4.2.7.1 Ketoconazole

Study 07-009 evaluated the impact of ketoconazole on the pharmacokinetics of betrixaban. Participants in the study received a single dose of 40 mg of betrixaban on two separate occasions, once alone or following a 5 day regimen of ketoconazole 200 mg BID. The last two doses of ketoconazole were administered 1 hour prior to betrixaban and 12 hours afterwards. Drugs were dosed under fasting conditions. The study showed an increase in C_{max} and AUC of ~2.3-fold (**Table 6**).

Table 6: Summary of effect of ketoconazole on betrixaban PK. *[Source: 07-009 CSR, Page 9, Panel 2.1]*

Parameter (unit)	Treatment	n	Geometric LS Mean	Pairwise Comparisons			
				Pair	Ratio (%)	90% CI	p-value
C_{max} (ng/mL)	A	11	9.996	B/A	233.8	(183.1, 298.4)	0.0001
	B	12	23.37				
$AUC_{(0-\infty)}$ (ng*h/mL)	A	11	171.1	B/A	211.9	(179.8, 249.6)	<0.0001
	B	12	362.5				
$AUC_{(0-tlast)}$ (ng*h/mL)	A	11	147.3	B/A	228.5	(191.3, 272.9)	<0.0001
	B	12	366.5				
T_{max} (hr)	A	11	1.00 [a]			(0.50, 6.00) [b]	
	B	12	1.00 [a]			(0.50, 6.02) [b]	

Treatment A: 40 mg of PRT054021 alone; Treatment B: 40 mg of PRT054021 following 5 days of ketoconazole 200 mg orally every 12 hours.

Note: Based on fitting a linear mixed model with fixed effects for sequence, period, and treatment and a random effect for subject within a sequence to the log-transformed values.

n=number of subjects; LS=Least-squares; CI=confidence interval

[a] T_{max} presented as median

[b] T_{max} interval presented as range

4.2.7.2 Verapamil

The impact of verapamil on the pharmacokinetics of betrixaban was assessed in study PN010, which was an open-label study of a single dose of betrixaban or a single-dose of betrixaban on day 1 or day 14 of a 14 day QD regimen of verapamil sustained release to study the effects after a single dose and at steady-state. Both betrixaban and verapamil were co-administered in a fasting state. The results of the study are shown in **Table 7**, which showed a ~4.7-fold increase in C_{max} and a ~3-fold increase in AUC, which was comparable for day 1 and 14.

Table 7: Summary of the effect of verapamil on betrixaban PK *[Source: PN010 CSR, page 48, table 9]*

Treatment	N	C_{max} [a] (ng/mL)	AUC_{last} [a] (ng·hr/mL)
Betrixaban Alone	20	13.09 (9.59, 17.87)	241.14 (188.34, 308.75)
Betrixaban + Verapamil [Day 1]	20	59.63 (45.77, 77.67)	754.78 (646.58, 881.08)
Betrixaban + Verapamil [Day 14]	18	61.75 (49.45, 77.10)	796.80 (678.69, 935.46)

Comparison	C_{max} [b] (ng/mL)	AUC_{last} [b] (ng·hr/mL)
Betrixaban + Verapamil [Day 1] / Betrixaban Alone	4.55 (3.57, 5.80)	3.13 (2.71, 3.62)
Betrixaban + Verapamil [Day 14] / Betrixaban Alone	4.74 (3.69, 6.09)	3.32 (2.85, 3.86)

GM = Geometric mean; GLSMR = Geometric least-squares mean ratio between treatments; CI = Confidence interval;
Source: Tables 14.2.1.1, 14.2.1.2, and 14.2.1.3

[a] GM back transformed from log scale (95% CI)

[b] GLSMR (90% CI)

[c] Median (Minimum, Maximum)

[d] harmonic mean ± jackknife SD

$AUC_{0-\infty}$ [a] (ng·hr/mL)	T_{max} [c] (hr)	$t_{1/2}$ [d] (hr)
269.23 (209.11, 346.64)	1.0 (0.5, 8.0)	41.7 ± 7.0
780.45 (668.39, 911.30)	2.0 (1.0, 5.0)	28.5 ± 4.5
823.21 (700.88, 966.88)	2.5 (0.5, 5.0)	30.4 ± 6.4

$AUC_{0-\infty}$ [b] (ng·hr/mL)	NA	NA
2.90 (2.50, 3.36)	NA	NA
3.07 (2.64, 3.57)	NA	NA

NA = Not applicable.

4.2.7.3 Digoxin

The effects of betrixaban (80 mg) on the pharmacokinetics of digoxin was studied in study 08-014, which is a cross-over study with digoxin alone, betrixaban alone or together for 7 days. All drugs were taken under fasting conditions, which showed no impact of betrixaban on digoxin PK and no effect of digoxin on betrixaban PK.

4.2.7.4 PPI and antacid

The effect of a PPI or antacid on the pharmacokinetics of betrixaban (40 mg) was studied in study 07-008, which was a cross-over study of betrixaban alone or following dosing of a PPI (esomeprazole) for 5 days or an antacid (Maalox) (**Table 8**). While, not meeting formal criteria for bioequivalence the Applicant asserts that the increase (PPI) and decrease (antacid) are unlikely to be clinically significant. The OCP review team concurs with the conclusion of the Applicant, as the direction of change observed was different between esomeprazole and the antacid and the change was less than the observed inter-subject variability (~50%).

Table 8: Comparison of betrixaban alone (treatment A) and betrixaban with a PPI (esomeprazole, treatment B) or an antacid (Maalox, treatment C). *[Source: 07-008 CSR, Synopsis, Table 9]*

Parameter (unit)	Treatment	n	Geometric LS Mean	Pairwise Comparisons			
				Pair	Ratio (%)	90% CI	p-value
Cmax	A	12	12.77				
(ng/mL)	B	12	14.40	B/A	112.8	(75.3, 169.0)	0.6132
	C	12	10.99	C/A	86.0	(57.4, 128.9)	0.5287
AUC(0-∞)	A	12	267.4				
(ng*h/mL)	B	12	308.3	B/A	115.3	(91.3, 145.7)	0.3060
	C	12	247.2	C/A	92.4	(73.2, 116.8)	0.5675
AUC(0-Tlast)	A	12	222.4				
(ng*h/mL)	B	12	257.9	B/A	115.9	(89.8, 149.6)	0.3294
	C	12	205.7	C/A	92.5	(71.7, 119.3)	0.6015

Note(s): LS=Least-squares; CI=confidence interval.
Treatment A = 40-mg PRT054021 alone.
Treatment B = 40-mg PRT054021 with esomeprazole.
Treatment C = 40-mg PRT054021 with antacid.
Analysis of variance with fixed effects for treatment, period, sequence, and a random effect for subject within treatment.

4.2.8 QT

The relationship between betrixaban concentrations and QTc prolongation was noted early on and a pooled analysis of data from studies 02-001, 04-001 and 05-003 were conducted showing ~10 ms per 100 ng/mL. In addition, a TQT study was conducted that was reviewed by the QT-IRT (IND 72679 (b) (4) 10/29/2008 by Dr. Madabushi) that showed a similar concentration-QTc relationship (**Figure 10**).

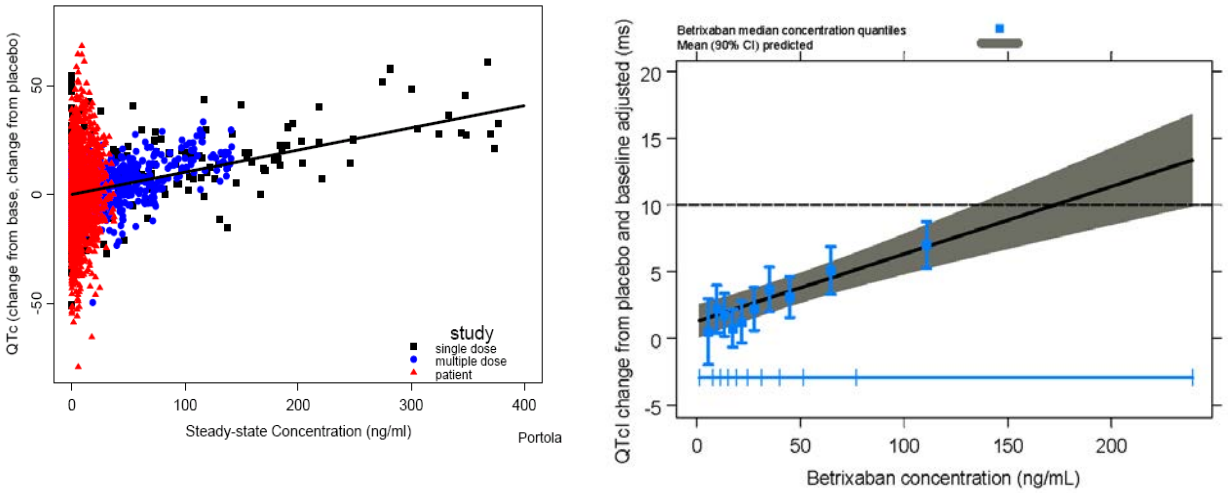

Figure 10: Analysis of QTcF from previous studies is shown to the left and to the right is the C-QT analysis for the TQT study by Dr. Madabushi. A similar concentration-QTc relationship was observed (pooled analysis: 10 ms per 100 ng/mL (90% CI: 8 – 12 ms per 100 ng/mL; TQT: 6 ms per 100 ng/mL (90% CI: 4 to 7 ms per 100 ng/mL)). *[Source: QT-IRT review, IND (b) (4) 72679 (b) (4) 10/29/2008 by Dr. Madabushi]*

However, at the time the supra-therapeutic dose was defined as a single dose of 140 mg betrixaban fasted based on results from the ketoconazole DDI study, which can no longer be considered the supra-therapeutic dose as a greater impact on betrixaban exposures were observed with verapamil (~2.3 fold increase in C_{max} following ketoconazole compared to ~4.7-fold with verapamil). Because of the change in definition of the supratherapeutic exposure the reviewer has used the proposed model in the QT-IRT review to predict the exposure for the new supratherapeutic exposure scenario.

This analysis extends outside the observed exposure range, on a mean level, of the TQT study but data from other studies such as the pooled analysis by the Applicant (**Figure 10**) suggests a linear C-QTc relationship for betrixaban in this range. The linear relationship is consistent with predominant blockade of the hERG potassium channel being the driver of the observed QTc prolongation. The provided predictions were at the observed geometric C_{max} following 80 mg (across studies) under fasting conditions (as food is expected to decrease the C_{max} by approximately 60% and there is an expected accumulation of ~2.3-fold) representing the therapeutic C_{max} and 4.7-fold increase in the therapeutic C_{max} to represent the new supratherapeutic dose (**Table 9**).

Table 9: Predicted ΔΔQTcI effect at therapeutic and supratherapeutic exposures *[Source: Reviewer's analysis]*

Exposure scenario	Geometric C_{max} [ng/mL]	ΔΔQTcI mean±90% CI (ms)	ΔΔQTcI mean±90% CI (ms) *
Therapeutic	49.1 ng/mL	3.7 (2.6 to 4.8)	3.9 (2.8 to 5.0)
Supratherapeutic (verapamil)	230.8 ng/mL	12.9 (9.5 to 16.2)	13.9 (11.5 to 16.4)

* - Using's sponsor's model (ΔΔQTcI ~ CONC + (1|USUBJID)

The OCP review team has proposed changes to the betrixaban label to reflect the predicted QTc at the new therapeutic and supratherapeutic dose. However, the OCP review team does not consider it to be necessary to describe the QTc observations outside section 12, as the margin between supratherapeutic and therapeutic was approximately 4.7-fold and the betrixaban is not recommended to be given to patients on concomitant P-gp inhibitors (the supratherapeutic scenario).

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