



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: January 31, 2018

From: Jennifer L. Reed, Ph.D.; CBER/OTAT/DPPT/PDB
WO52-72 Room 4324; 240.402.8213

APPROVED

By Jennifer L. Reed, Ph.D. at 3:55 pm, Feb 20

To: File for 125586/0

Through: Dorothy Scott, M.D.; CBER/ OTAT/DPPT/PDB;

WO52-72 Room 4124; 240-402-8236

APPROVED

By Dorothy Scott at 10:14 pm, Feb 19, 2018

Cc: Jiahua Qian; CBER/OTAT/DRPM/RPMBI;
WO71 Room 4214; 240.402.8432

Subject: Review of Reply to Complete Response, Pharmacology / Toxicology
Product: Coagulation Factor Xa (Recombinant), Inactivated
Submission Date:
Manufacturer: Portola Pharmaceuticals

Recommendation: Approval.

- Pharmacology/toxicology data provided to support PRT064445 are acceptable.
- The firm has performed adequate risk-based extractables and leachables studies. Levels of extractable and leachable compounds are appropriately low, and identified compounds from product contact materials do not raise toxicity concerns.

Background Information

- The firm has submitted a BLA supporting PRT064445 (Andexanet alfa, ANDEXXA) a recombinant, genetically modified and inactive variant of human coagulation Factor Xa (FXa).
- PRT064445 binds anticoagulants which inhibit endogenous FXa, and may be used to promote coagulation under emergency situations when uncontrolled bleeding must be reversed, (b) (4)

- The proposed indication is single-use, for acute reversal of anticoagulation

Review Summary

Extractables and Leachables

(b) (4) drug product contact materials considered to have elevated risk for leachable components were subjected to appropriate extractables and leachables studies. These manufacturing materials included filters, (b) (4), silicone tubing, vial, and stopper. Known leachables in the (b) (4) analysis were at low levels, below the threshold of increased evaluation. The extractables and leachables from the vial and stopper were at acceptably low levels. The drug product sterile filter was evaluated using worst-case conditions and appropriate model solvents. Only (b) (4) exceeded the threshold of increased evaluation. The risk of toxicity associated with (b) (4) is considered low. The following list of compounds was considered as potential leachables, and will be monitored in stability studies: (b) (4)

(b) (4)

(b) (4)

Summary of Preclinical Data Supporting Efficacy of PRT064445: Multiple proof-of-concept studies presented by the firm demonstrate that PRT064445 rapidly reverses anticoagulant effects of a variety of direct and indirect fXa inhibitors. In experimental wounding models, administration of PRT064445 before or after treatment with fXa inhibitors reduced excess bleeding. This coincided with reduced anticoagulation effect demonstrated in whole blood via INR and prothrombin time measurements, and increased bound fXa inhibitor in plasma. Most of these studies presented by the firm were short term, carried out with research-grade material used at high dose.

Summary of Preclinical Data Supporting Safety of PRT064445: The firm used development lots of PRT064445 in 2 single dose toxicity studies in rats, and three multiple-dose toxicity studies in (b) (4) monkeys. These studies evaluated the test article alone, and also in the presence of fXa inhibitors. The drug was reported well tolerated in all study groups. In multi-dose studies, immunogenicity was observed in both rats and (b) (4) monkeys. The anti-drug antibodies were non-neutralizing and were not associated with specific toxicities, except for anaphylaxis in one (b) (4) monkey that received multiple high doses of a development lot of PRT064445. Extractables studies of (b) (4) drug product were appropriately performed, considering materials deemed to be higher risk. These included (b) (4) unit, sterile filter, container closure materials, silicone tubing, the (b) (4) (b) (4), and all filters. Extractions were performed using (b) (4) as solvents. Leachables studies of (b) (4) drug product evaluated product held in the intended container. Extractables and leachables (volatile, semi-volatile, non-volatile) were evaluated by (b) (4) techniques. These studies identified acceptably low levels of extractables and leachables, significantly lower than the maximally allowable daily exposure levels identified from clinical and non-clinical experience. A subset of compounds were monitored in stability studies, despite the fact that the levels detected were judged to be not toxic.

Linking to Phase 1 - Confirmation of D-Dimer, TAT Markers: Phase 1 studies in normal volunteers demonstrated elevations in thrombotic factors D-dimer, F1+2, TFPI, and TAT after PRT064445 administration. These markers were not observed in previous animal studies. To address the issue, a very small non-GMP study in (b) (4) monkeys, NC-12-0472, evaluated these markers of pro-thrombotic properties after administration of Phase 1 clinical trial material. Use of more sensitive kits confirmed elevations of D-Dimer and TAT after PRT064445 administration; levels subsequently returned to baseline conditions over days. The firm stated that the data supported the use of (b) (4)

monkeys as relevant efficacy and safety models. No comparison with research-grade material was pursued.

End of Phase 2 Meeting August 2013

At an End of Phase 2 (EOP2) meeting held on August 14, 2013, the firm discussed additional preclinical pharmacology / toxicology studies with FDA. FDA agreed that subchronic and chronic nonclinical tox studies were not required based on the indication sought. FDA stated, “**The need for additional toxicology studies to support continued development of PRT064445 will depend on the comparability of the product pre- and post-manufacturing changes.**” FDA agreed that standard 2-year rodent carcinogenicity bioassays were not required, but the firm should include a carcinogenicity risk assessment with the BLA.

Minimal Bridging to GEN2 Product

Comparability of Drug Presentation: Beginning in 2013, the firm took a minimal bridging approach to demonstrate comparability of GEN 1 (Phase 1) and GEN 2 (Phase 3) clinical trial materials, with the original research / development lots. There were few differences reported. The small, non-GMP study NC-12-0472 performed in 2 (b) (4) monkeys did reveal skin reactivity in animals receiving the Phase 1 clinical trial material that had not been previously reported in animals receiving research-grade PRT064445. Petechiae and ecchymoses were not reported in subsequent studies. Later, GMP (b) (4) study NC-12-0469 identified no statistically significant differences in 96-hour pharmacokinetic profiles of 2 clinical lots and a single development lot of PRT06445 tested in (b) (4) monkeys. Study NC-13-0545 evaluated potential toxicities of Phase 1 versus lyophilized PRT06445, administered twice over 4 hours with a 3 day follow-up. These short-term studies did not identify major differences in safety endpoints among the different lots and presentations of the test article. The studies were not geared to evaluate or compare immunogenicity.

Immunogenicity of PRT064445

Regarding immunogenicity observed in safety studies, the firm has stated:

“The **transient presence** of anti-drug antibodies that do not cross react with any endogenous similar proteins poses (based on the lack of antibodies against fX and fXa in clinical studies) no significant toxicity risk.”

Unfortunately the persistence of ADAs generated in animals receiving PRT064445 was never evaluated, as ADAs remained to the end of study. Therefore there is no preclinical evidence for transience of ADAs from the preclinical data set. The possible distribution of antibody:drug complexes in tissue has not been evaluated. Long-term risks could include the development of neutralizing antibodies against PRT064445 that target endogenous coagulation-relevant factors or complexes.

In November 2016, the firm acknowledged that the rate of non-neutralizing anti-drug antibody responses was higher in the Phase 3 trial (lyophilized GEN2 material) compared with the rate observed in the Phase 1 trial (b) (4) GEN1 material, lower concentration). “The initial (b) (4) formulation had a very low rate of confirmed low titer non-neutralizing antibodies against andexanet (2%) while the rate observed for the lyophilized formulation was higher (20%). The overall rate of confirmed anti-andexanet antibodies was 12.1%” The firm has stated that anti-PRT064445 antibodies do not appear to pose a risk to patients, due to intended single, acute administration of the drug. There is insufficient preclinical information presented to support this conclusion.

Submitted Materials

Preclinical Models

The following studies establish the rat and the rabbit as appropriate models for evaluation of acute PRT064445 blockade of direct and indirect fXa inhibition. Activity of PRT064445 was repeatedly shown in prophylaxis and treatment studies.

Reversing Anticoagulation Mediated by Direct fXa Inhibitors

The firm supplied reports of 6 models demonstrating PRT064445 reverses anticoagulation mediated by different fXa inhibitors. These studies mostly utilized non-GMP manufactured test article. The last study utilized both a non-GMP development lot 11-16, and a GMP clinical study lot J7101A1.

Study NC-12-0457 dated April 19, 2012, is titled "Reversal of Rivaroxaban Anticoagulation with PRT0-64445 Reduces Blood Loss in Mice Co-Administered Aspirin". (b) (4) mice received aspirin for 7 days in drinking water prior to the blood loss experiment. Mice received 50 mg/kg fXa inhibitor rivaroxaban by oral gavage, then two hours later were anesthetized. Anesthetized mice received a 40 mg/kg dose of PRT064445 by tail vein injection prior to tail transection. The test article was a research lot of PRT064445. Blood loss from the tail transection was evaluated for 15 minutes prior to terminal exsanguination for coagulation measures in blood and test article measurement in plasma. Mice that received rivaroxaban demonstrated lower fXa and increased bleeding in the transection model, compared with mice that received vehicle alone. Mice that received rivaroxaban followed by PRT064445 prior to transection demonstrated reduced anti-coagulation effects in whole blood and reduction of blood loss.

Study NC-12-0449 dated April 18, 2012, is titled "PRT064445 Acts as a Universal Reversal Agent for Direct Factor Xa Inhibitors". In this study, rats received either vehicle or one of two different fXa inhibitors apixaban or betrixaban a 1 mg/kg/hr. PRT064445 or control vehicle was then administered by IV route. PRT064445 was an engineering lot. Free fXa inhibitor concentration in plasma decreased in rats that received PRT064445, demonstrating anti-coagulative effects of PRT064445.

Study NC-12-0453 dated April 18, 2012, is titled "Sustained Reversal of Rivaroxaban-Induced Anticoagulation with PRT064445 Correlates to Decrease in Plasma Unbound Fraction." In this study, (b) (4) rats received vehicle or fXa inhibitor Rivaroxaban by intravenous route for 30 minutes. Then PRT064445 (research lot) or vehicle was administered by intravenous route to anesthetized animals for 30 to 90 minutes. Femoral blood was sampled via catheter from 30 to 90 minutes after initiating PRT064445 dosing. Reduced anti-coagulation in PRT064445 recipients was demonstrated by whole blood INR and prothrombin time measurements, plus increased concentration of bound rivaroxaban in plasma. Reduction in rivaroxaban anti-coagulation was observed over the full course of the 90 minute intravenous injection.

Study NC-13-0567 dated April 18, 2012, is titled "Andexanet Reverses Edoxaban-Induced Anticoagulation Administered Prior to Injury as Measured by Reduction in Blood Loss in a Rabbit Liver Laceration Model." Deeply anesthetized male (b) (4) rabbits were administered the fXa inhibitor edoxaban, or vehicle control, via ear vein injection. Laparotomy was performed 15 minutes later, and lower lobes of liver were isolated with pre-weighed gauze to capture blood loss. PRT064445 (Development Lot DEV 11-16) or vehicle was administered by ear vein over 5 minutes prior to liver laceration. Bleeding from liver laceration was evaluated over 15 minutes. The rabbits were then euthanized. fXa inhibitor increased blood loss from the laceration, and that increase was blocked approximately 80% by administering PRT064445 prior to the laceration. Reduced anti-coagulation in

PRT064445 recipients was demonstrated by whole blood INR and prothrombin time measurements, plus increased concentration of bound edoxaban in plasma.

Study NC-13-0573 dated September 22, 2015, is titled “Reversal of Rivaroxaban-Induced Bleeding and Coagulation Markers with Adnexanet in a Rabbit Liver Laceration Model: Comparison with Four-Factor Prothrombin Concentrates.” The same liver laceration model in (b) (4) rabbits was used as described in NC-13-0567. Administration of the fXa inhibitor rivaroxaban prior to laceration increased blood recovery from the lacerated liver 2 fold over the course of 50 minutes. Administration of PRT064445 (Development Lot DEV 11-16) at 25-50 mg/kg reduced blood loss from the lacerations by approximately 50%, more effectively than Four-Factor Prothrombin Concentrate. Reduced anti-coagulation in PRT064445 recipients was demonstrated by whole blood INR and prothrombin time measurements, plus increased concentration of bound rivaroxaban in plasma.

Study NC-14-0575 dated June 3, 2015, is titled “Andexanet Reverses Rivaroxaban-Induced Anticoagulation as Measured by Reduction in Blood Loss and Reversal of Pharmacodynamic markers in a Rabbit Liver Laceration Treatment Model.” The liver laceration model in (b) (4) rabbits was similar to the one described in NC-13-0567. The fXa inhibitor rivaroxaban was administered by ear vein to deeply anesthetized animals, prior to laparotomy and liver laceration. Bleeding from lacerations was evaluated for 30-40 minutes prior to administration of PRT064445 (Development Lot (b) (4)), or GMP clinical study lot J7101A1). Bleeding from lacerations was evaluated for an additional 40 to 75 minutes, then the animals were euthanized. fXa inhibitor increased bleeding from the liver lacerations by 2 fold in the first 10 minutes, compared with lacerated animals that received vehicle control. Differences in blood recovery from lacerations in fXa anticoagulated animals versus control animals was less pronounced and more variable at later time points. Administration of 35 or 75 mg/kg PRT064445 by intravenous route, 40 minutes post-laceration, reduced blood recovery from the laceration, compared to anti-coagulated and lacerated rabbits that received vehicle control treatment. Reduced anti-coagulation in PRT064445 recipients was demonstrated by whole blood INR and prothrombin time measurements, plus increased concentration of bound rivaroxaban in plasma.

Reversing Anticoagulation Mediated by Indirect fXa Inhibitors

The firm provides an additional 4 studies showing Andexanet-mediated reduction in blood loss and anticoagulation activity in rats, when rats were coadministered an indirect fXa inhibitor (enoxaparin or (b) (4) plus Andexanet prior to tail transection. For test article, all four of these studies used non-GMP research lots.

Study NC-12-0432 is titled “Reduction in Blood Loss in Enoxaparin Anticoagulated Rats with Bolus Only Administration of PRT064445”. The study is dated April 18, 2012. Deeply anesthetized male (b) (4) rats were administered enoxaparin followed by PRT064445 or vehicle, by intravenous route. The test article was a research lot of PRT064445. A straight cut through the tail was made, and the tail laceration was permitted to bleed for a total of 45 minutes prior to terminal exsanguination. Rats that received enoxaparin demonstrated increased bleeding in the transection model, and reduced fXa activity. Rats that received enoxaparin followed by PRT064445 prior to transection demonstrated 80% reduction in anti-coagulation activity early. However, anti-fXa activity of enoxaparin became increasingly detectable in whole blood 30 and 45 minutes after a bolus dose of PRT064445. Anti-coagulation activity in the blood late after transection did not translate to increased bleeding at those later time points.

Study NC-12-0437 is titled “PRT064445 Can Reduce Blood Loss in a Setting of Active Bleeding with Only Partial and Transient Reversal of Enoxaparin Anticoagulation”. The study report is dated April 18, 2012.

The study uses a model very similar to NC-12-0432, except PRT064445 was administered 10 minutes after the tail transection in rats that received enoxaparin anticoagulant. Reduced cumulative blood loss was observed in anticoagulated, transected rats treated with PRT064445, compared with vehicle control recipients. The reduction in blood loss coincided with reversal of anti-fXa activity in the blood, which was dose-dependent and lasted approximately 45 minutes after PRT064445 administration.

Study NC-12-0454 is titled "Reversal of Enoxaparin-Induced Anticoagulation Reduces Blood Loss in the Rat Tail Transection Model". The study report is dated April 18, 2012. This study sought to demonstrate that reversal of enoxaparin-mediated anticoagulation in the blood leads to reduction of blood loss in the transection model. The model is similar to the one described in NC-12-0432. Deeply anesthetized (b) (4) rats received a bolus IV injection of enoxaparin, followed 5 minutes later by bolus IV injection then continuous infusion of PRT064445 (or vehicle control). Tail transection was performed and blood recovery was measured over 15 minutes. Blood recovery from transection was increased 7-fold in rats that received enoxaparin, and the increased blood recovery was blocked by prophylactic administration of PRT064445. Reversal of anticoagulation was confirmed by decreased plasma anti-fXa activity.

Study NC-12-0456 is titled "Reversal of (b) (4) -Induced Anticoagulation Reduces Blood Loss in the Rat Tail Transection Model." The final report is dated April 18, 2012. Deeply anesthetized male (b) (4) rats were administered fXa inhibitor (b) (4), followed 5 minutes later by PRT064445 or vehicle, via intravenous route. A straight cut through the tail was made, and the tail laceration was permitted to bleed for a total of 15 minutes prior to terminal exsanguination. Rats that received (b) (4) demonstrated a 4.6-fold increase in bleeding in the transection model, compared to transected mice that received no anti-coagulant. Rats that received (b) (4) followed by PRT064445 prior to transection blood loss similar to transected animals that received no anti-coagulant. (b) (4)-mediated anti-fXa activity in blood was reduced 94-97% out to 30 minutes after administration of PRT064445, and coincided with reduction in blood recovery in transected rats.

Comparison of Anticoagulation Blocking Agents in Rabbit Model of Liver Laceration

The firm provides two additional studies, NC-14-0561 and NC-13-0564, which evaluate alternative blockers of fXa inhibitor rivaroxaban in the rabbit model of liver laceration. PRT064445 was used as a concurrent positive control in these two studies. The source of PRT064445 was GMP clinical lot JV101A1, and demonstrated similar anticoagulant blocking activity as described in **Study NC-13-0573**.

Pharmacokinetics studies **NC-12-0442**, **NC-12-0441**, **NC-12-0470**, and **NC-12-0469** evaluated pharmacokinetic parameters of a single dose of PRT064445 administered by intravenous route to rats or monkeys. These small studies did demonstrate dose-dependent increase in C_{max} and AUC in both species evaluated. The volume of distribution was short in both species, and elimination half-life was longer. In the rat study, PRT064445 reduced the plasma concentration of unbound direct fXa inhibitor. This activity is linked to PRT064445 mechanism of action.

Study NC-12-0469 is a Covance report titled "Collection of Samples for Determination of the Pharmacokinetics and Pharmacodynamics of PRT064445 After a Single Intravenous Dose to Monkeys." The final study report is dated June 7, 2013. A total of 15 (b) (4) monkeys received a single IV dose of vehicle control, or 10 mg/kg PRT064445 representing an engineering lot ((b) (4)), or a GMP lot intended for clinical study, with or without in-line filtration. Blood was collected for pharmacokinetic analyses and clinical pathology evaluation from the end of infusion through 96 hours. Cageside observations, performed once daily through study end, revealed no test article associated changes.

Plasma values were similar for all animals receiving test article. There were no statistically significant differences in pharmacokinetic values associated with the presence of an in line filter.

Safety Pharmacology and Toxicology Studies

Study NC-11-0395 is titled "Respiratory Safety Pharmacology Evaluation Using Head-Out Plethysmography of PRT064445 following Intravenous Administration to Male Rats." The final report is dated November 17, 2011. The test article was Development lot (Lot (b) (4)). Eight (b) (4) rats per group received either vehicle control, or 3, 10, or 30 mg/kg test article by intravenous infusion into the femoral vein (10 ml/kg set volume). Respiratory function was assessed using head-out plethysmography for 30 minutes at baseline. Average lung function measurements were taken over 15 minute intervals for 3.75 hours post infusion start, and a 30 minute reading was performed 24 hours post-dose. Assessments of mortality and clinical observations were also taken. **Results:** All rats survived to scheduled euthanasia on day 2. No test article-related effects on lung function were observed. No test article-related mortality or morbidity was observed.

Study NC-11-0396 is titled "Central Nervous System Safety Pharmacology Evaluation of PRT064445 following Intravenous Injections Administration to Male Rats." The final report is dated November 17, 2011. The test article was a non-GMP Development lot (Lot (b) (4)). Six (b) (4) rats per group received either vehicle control, or 3, 10, or 30 mg/kg test article by intravenous infusion into the femoral vein (10 ml/kg set volume). A modified Irwin battery of neurological tests (e.g. home cage, hand-held, open-field, and elicited response observations) were evaluated predose after randomization, and postdose at 5 minutes, 1 hour, 2 hours, 4 hours, and 24 hours. Overall health of the rats was evaluated based on viability, clinical signs, and body temperature. **Results:** All rats survived to scheduled euthanasia on day 2. There were no effects of the test article on mortality or clinical signs. No abnormal observations noted at any time point were related to the test article.

Study NC-11-0397 is titled "2-Week Intravenous Twice-Daily Bolus Injection Toxicity and Toxicokinetic Study with PRT064445 in Rats with a 4-Week Recovery Phase". The final report is dated July 18, 2012. The test article was a non-GMP Development lot (Lot Dev-(b) (4)). Male and female (b) (4) rats were assigned to four toxicity (n=15M, 15F) and recovery (n=3M, 3F) groups. The groups received vehicle control, or 3, 10, or 30 mg/kg test article as a slow bolus injection vial tail vein, twice per day. Assessment of toxicity was based on mortality, clinical observations, ophthalmic exams, body weights, food consumption, and clinical / anatomic pathology. Blood samples were collected for toxicokinetic and anti-drug antibody analyses. Four rats in different groups died immediately after dosing; the deaths were attributed to air emboli from loose intravenous connections, and were not attributed to test article. A fifth rat died accidentally during the blood collection procedure. During dosing and recovery phases, no test article related effects were observed on body weight, food consumption, ophthalmic exam, or anatomic pathology. Rats that received test article demonstrated a slightly prolonged prothrombin time, compared with vehicle treated animals. The effect was reversible and dose-related. All rats that received the test article developed drug-directed antibodies. No impact of anti-drug antibodies on body weight, food consumption, ophthalmic exam, or anatomic pathology was reported. Relationship of anti-drug antibodies to prolonged prothrombin time was not specifically evaluated. Anti-drug antibodies were dose dependent, but persisted in highest dose group through recovery phase, after prolonged prothrombin time reverted to normal.

Study NC-11-0394 is titled "2-Week Intravenous Injection Toxicity and Toxicokinetic Study with PRT064445 Alone and After Dosing Rivaroxaban or Enoxaparin in (b) (4) Monkeys with a 4-Week

Recovery Phase. The final study report is dated May 11, 2012. Ten (b) (4) monkeys per group (5M, 5F) received 2 intravenous doses of the test article, 4 hours apart. The test article was non-GMP development lot Dev11-16, which was delivered at 3, 10, or 30 mg/kg/dose. Separate groups of (b) (4) monkeys were pre-treated with fXa inhibitors 4 hours prior dosing the test article twice at the 30 mg/kg dose. This regimen was continued every 3 day over 2 weeks. Assessments of toxicity continued through the dosing phase and a 4-week recovery period. All animals survived to the scheduled study end. The firm notes that no coagulation (PT or aPTT) changes were observed at any time after dosing with the test article alone. One male that received the highest dose of test article alone demonstrated hypoactivity, clear oral discharge, and anaphylaxis on day 13. The symptoms were reversed with epinephrine and diphenhydramine. The test article was immunogenic whether administered alone or in the presence of anticoagulant. There is a suggestion that the test article may be more immunogenic in (b) (4) monkeys when co-administered with anticoagulant. Dose-dependent anti-drug antibody development was observed through the recovery period. Test article reversed markers of anticoagulation in blood despite the presence of anti-test article antibodies, suggesting the antibodies were not neutralizing in vivo. No impact of the test article was observed on mean body weight, weight gain, body temperature, ophthalmic examination, ECG measurements, mean blood pressure, clinical pathology results, organ weights, or macroscopic / microscopic examinations. The NOAEL was found to be 60 mg/kg/day, which corresponds to the maximal feasible dose in (b) (4) monkeys.

Study NC-12-0417 is titled “2-Week Intravenous Injection Toxicity and Toxicokinetic Study with PRT064445 in (b) (4) Monkeys After Administration of Apixaban or Betrixaban with a 4-Week Recovery.” The final study report is dated November 2, 2012. The study setup was similar to study NC-11-0394, except that only the highest dose of PRT064445 was evaluated, together with anticoagulant challenge 2 hours (not 4 hours) before PRT064445. The test article was again non-GMP development lot (b) (4). PRT064445 administration in combination with apixaban or betrixaban, had no effect on body weight, body temperature, ophthalmic examinations, EEG, clinical pathology test results, organ weights, or macroscopic and microscopic examinations when compared with monkeys dosed apixaban or betrixaban and PRT064445 vehicle. Nonadverse, low food consumption was observed at slightly higher occurrence in animals given PRT064445 in combination with apixaban or betrixaban. These differences were not present during the recovery phase and had no correlation to body weight change; therefore, no toxicological importance was ascribed to this change. Females given PRT064445 in combination with apixaban or betrixaban had a slightly higher incidence of nonformed feces during the first week of the dosing phase. Almost all animals developed anti-PRT06445 antibodies which persisted through the recovery phase, without apparent toxicity. The NOAEL was found to be 60 mg/kg/day, which corresponds to the maximal feasible dose in (b) (4) monkeys.

Study NC-12-0472 is a non-GLP study titled “TAT and D-Dimer Levels in Monkeys Following PRT064445 Administration-UC Davis Study”. The final study report is dated October 25, 2012. The study was undertaken to understand why IND-enabling studies of PRT064445 NC-12-0417 and NC-11-0394 did not demonstrate changes in coagulation markers in blood, when such changes were observed in normal volunteers receiving PRT064445 during the Phase I study. Two monkeys were administered 10 mg/kg PRT064445. Test article was the clinical lot J7101, rather than the development lot used previously. An in-line filter was not used during the administration. Evaluation of D-Dimer and TAT was performed in (b) (4) blood sample using more sensitive kits than had been used during previous studies. Both TAT and D-Dimer markers of pro-coagulant state were elevated early after administration of the test

article, and resolved to baseline within 24-48 hours. Both monkeys demonstrated skin petechiae and ecchymosis 4-8 hours post drug administration, which resolved in about 5 days. No evidence of illness or thrombotic / bleeding events were noted in the two monkeys over the 5 day observation period. Evaluation of anti-drug antibodies was not performed.

Study NC-13-0545 is titled "Two Dose Toxicokinetic and Clinical Pathology Intravenous Injection Study with PRT064445 in (b) (4) Monkeys." The final report is dated December 4, 2013. This small study evaluated potential differences between two preparations of test article, PRT064445, assessed over 3 days. Groups of 10 (b) (4) monkeys (5M, 5F) were administered 30 mg/kg by intravenous route two times over 4 hours. Group 1 was administered Phase 1 clinical trial material (lot J710A1), while group 2 received the new lyophilized preparation ((b) (4)) intended for pivotal Phase 3 studies. The test article was in-line filtered during administration. Exposure to test article was judged to be similar in both groups. Both groups demonstrated increases in TAT and D-Dimer. TAT increased in the first 2 hours after each dose and reduced to baseline again at 4 hours after each dose. D-Dimer concentrations increased from 0.5 hours postdose to a peak at 6 hours. D-Dimer reduced to baseline over 48-72 hours after the study start. The groups were not different from each other in mean body weights, food consumption, or clinical pathology. Neither preparation of test article had a discernible effect on hematology test results or clinical chemistry measures. Both preparations of test article were judged to be equally well tolerated.

Genotoxicity

At the EOP2 meeting held with CBER, the firm presented a case that PRT064445 constitutes a low genotoxicity risk, and that genotoxicity studies were not considered appropriate in accordance with ICH S6. The firm reached agreement with the Agency that andexanet is a standard biotechnology-derived protein without any organic linkers that would be a cause for concern.

Carcinogenicity Risk Assessment

At the EOP2 meeting held with CBER, the firm presented a case that PRT064445 poses a low carcinogenic risk, and nonclinical evaluation of carcinogenicity potential is considered unnecessary (ICH Guideline S1A and S6 (R1)). Agreement was reached with the Agency that carcinogenicity studies were not essential, based on the following points:

1. PRT064445 is intended to be used as a single use therapeutic to reverse uncontrolled bleeding that may occur in patients taking fXa inhibitors. The molecule is a protein therapeutic, similar, but not identical to, human fXa.
2. The fXa-derived protein therapeutic is not a DNA-reactive molecule nor is it expected to have any epigenetic effect that might be expected to change cellular growth patterns.
3. PRT064445 structure is similar to fXa and is unlikely to have any immunomodulatory or immunosuppressive activity that would result in increased cancer risk, as has been reported with some immunomodulatory biologic molecules.
4. Safety evaluations of PRT064445 included assessments typical for protein therapeutics, as well as safety measures associated with the coagulation pathway. No data set collected to date has raised concern that the single use therapeutic would increase the risk of cancer development in the patient.

Extractables and Leachables Information

3.2.S.2.5.8

This section documents extraction studies to evaluate potential leachables from sterile filtration. (b) (4) sterile filters are used in more than one step. The (b) (4) sterile filter has a (b) (4) surface area ((b) (4)); therefore the (b) (4) was evaluated as worst case in the extractables study. (b) (4) solvents were used: (b) (4) were identified in all (b) (4) extraction solvents at levels approaching the (b) (4) level, the level designated as supporting additional analysis. The levels of (b) (4) reported are orders of magnitude below reported toxic levels in animals and people. Volatile and semi-volatile organic carbon results identified (b) (4) . Levels of these substances were (b) (4) per batch. These reported levels are orders of magnitude below levels associated with toxicity in vivo. The firm reports that the extractables levels associated with (b) (4) steps are far below their respective safety thresholds of concern. The data support the firm's assertion that sterile filters are not a source of extractables of concern.

3.2.S.5.14

This section provides a summary risk assessment of extractables and leachables from materials used in the drug substance manufacturing process. These materials included the (b) (4) (b) (4) were used as extraction solvents, and semi-quantitative assessments of non-volatile, semi-volatile and volatile extractable compounds were performed. Extracted compounds are presented in Table 3.2.S.2.5-123. All impurities identified fell below (b) (4) , the designated threshold level for additional analysis. The firm presents results from a leachables evaluation of (b) (4) lot of (b) (4) held at (b) (4) in a representative (b) (4) for (b) (4) . One non-volatile compound was identified as arising from the (b) (4) , when (b) (4) was stored inverted. The firm indicates that the unknown compound will continue to be followed through stability for potential identification. Leachables identified in analysis of (b) (4) lot (b) (4) were separately listed in Table 3.2.S.2.5-125. (b) (4) potential volatile leachables were identified as (b) (4) . These are common extractables from consumer plastics. The potential leachables will be tracked through stability studies, although these (b) (4) leachables do not raise particular toxicity concerns. In addition, (b) (4) unknown non-volatile leachables were detected at a level that exceeded the threshold level at which further analysis is triggered. The firm indicates that unknown compounds will continue to be followed through stability for potential identification.

3.2.P.2.3.1.7.2

This section summarizes the risk assessment of the drug product manufacturing process. Product contact components considered high risk for leachables were the sterilizing filter, the (b) (4) used to store intermediate, the (b) (4) silicone tubing, and the vial and rubber stopper used in container closure. Extractables were assessed using (b) (4) as extraction solvents. Table 3.2.P.2.3-7 lists extractable compounds found above the (b) (4) limit for additional analysis. Compounds not previously identified in the (b) (4) extractables studies included (b) (4) . Both are typical extractables from consumer packaging materials. A (b) (4) study was performed with high-risk drug product contact components using (b) (4) and worst-case exposure times. The (b) (4) study yielded only (b) (4) and an unknown, nonvolatile compound as potential leachables. The unknown compound was not observed in the extractables study. For leachables, (b) (4) drug product lots were evaluated. Lot (b) (4) was held at 5°C for (b) (4)

months, and lot (b) (4) was held at 5°C for 5 months. The studies identified the following potential leachables into drug product: (b) (4)

These (b) (4) leachables will be evaluated during stability studies.

The firm notes that elemental impurities were evaluated from high-risk product contact materials via extraction with (b) (4). Metals detected by (b) (4) were within allowable limits.

The firm provides "Extractables Test Validation Report: Andexanet Alfa (PRT064445) and (b) (4) Filter Device, Catalog Numbers (b) (4) and (b) (4)", a study performed in October 2015 by (b) (4) (manufacturer of the drug product sterile filter) on behalf of the firm. (b) (4) uses a model solvent system for extractables testing, as a practical alternative to extractables testing with actual drug product. The solvents evaluated by (b) (4) were (b) (4). The (b) (4) filter was subjected to worst case sterilization condition. A (b) (4) of the system yielded the majority of extractable substances. The filter was (b) (4) case time and temperature conditions. Under these conditions, only (b) (4) was found to exceed the (b) (4) threshold for additional analysis. (b) (4) notes that (b) (4) is a low toxicity risk. The other compounds identified were similar in kind and amount to those found in the firm's own filter studies.