



Department of Health and Human Services
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United States Food and Drug Administration
Center for Biologics Evaluation and Research



Pharmacology / Toxicology Primary Discipline Review

To: File (Original BLA 125574/0)

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Subject: STN 125574/0 – Bayer’s KOVALTRY™, Antihemophilic Factor (Recombinant) Formulated with Sucrose, with Modified Bulk Drug Substance Manufacturing process

Indication: On-demand treatment and control of bleeding episodes, peri-operative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes, in adults and adolescents (12 to less than 18 years) Hemophilia A patients

This memorandum is the final primary pharmacology/toxicology review of the nonclinical program submitted in the Original Biological License Application (BLA) for Bayer’s Healthcare Incorporated KOVALTRY™, Antihemophilic Factor (Recombinant). KOVALTRY is indicated for on-demand treatment and control of bleeding episodes, peri-operative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes in adult and adolescent (12 to less than 18 years) patients with Hemophilia A. From the toxicology/pharmacology reviewer perspective, this original biological application STN 125574/0 is recommended for approval.

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I. Recommendations

Nonclinical studies to evaluate the general pharmacologic activity, pharmacokinetics, safety and toxicity of KOVALTRY™ for the proposed indications were included in the BLA submission. Based on review of the submitted pharmacology/toxicology data, this original biological application STN 125574/0 is recommended for approval. The clinical trials completed with KOVALTRY™ further support the intended use of this product. There were no nonclinical deficiencies identified in this submission, and there are no requests for further nonclinical evaluations at this time. There are no outstanding issues from the nonclinical standpoint that would prevent approval of this BLA.

II. Summary Basis for Regulatory Action (SBRA) for Nonclinical Kovaltry Data

Official Summary Basis for Regulatory Action (SBRA)

4. Non-clinical Pharmacology/Toxicology

General Considerations

The safety and effectiveness of KOVALTRY were characterized in a nonclinical program that included in vivo comparison of its effectiveness in hemostasis and induction of thrombogenesis with the Applicant's predecessor recombinant Factor VIII (FVIII) product KOGENATE, as well as in vivo pharmacokinetics, local tolerability, and single and repeat-dose toxicity studies in FVIII-deficient (hemophilic) mice, and in FVIII replete (i.e., wild-type) dogs, rats and rabbits. Studies were Good Laboratory Practices (GLP) compliant or non-compliant. A risk assessment of the potential extractable and leachable components present in the KOVALTRY drug substance, as per the ISO 10993 standards, was also completed.

Previous experience with similar recombinant and plasma-derived FVIII products has demonstrated that the toxicities of exogenously administered FVIII are extensions of its pharmacologic activity, i.e. hypercoagulability of blood, thrombosis, and thromboembolus formation in treated animals and patients. Additional expected findings in test animals are development of neutralizing and non-neutralizing antibodies directed against the human FVIII protein (i.e., immunogenicity), with the potential to cross-react and neutralize endogenous FVIII in wild-type animals.

Nonclinical Findings

Pharmacology

Nonclinical pharmacology studies with KOVALTRY were conducted in a rodent model of hemophilia A (i.e., mice with a naturally occurring mutation/deletion of FVIII function), and in normal, FVIII-replete (i.e., wild-type) rats, and rabbits

Hemophilic mice were dosed intravenously with KOVALTRY, or another approved recombinant human FVIII product in a cross-over study design. Dosing of hemophilic mice with KOVALTRY at doses approximately equivalent to the human starting dose restored the *ex vivo* whole blood clotting time (WBCT) activity and activated partial thromboplastin times (aPTT) to within normal limits, and the results were comparable to those obtained following dosing with the predecessor FVIII product previously licensed and marketed by the Applicant. There were no effects of KOVALTRY or the other FVIII preparation on the hematology profiles in the mice as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported. In summary, animal studies with KOVALTRY showed the expected pro-coagulant pharmacologic activity in a rodent model of hemophilia A, and the results were similar to those obtained with another approved recombinant human FVIII product.

Secondary pharmacology studies with KOVALTRY in wild-type rats showed no elevations of *ex vivo* biomarkers of thrombosis (i.e., thrombin, thrombin-anti-thrombin complex, D-dimer and prothrombin fragments 1+2 formation) at doses up to 5-fold greater than the maximum KOVALTRY clinical dose. Results for these biomarkers after KOVALTRY dosing were similar to those achieved in rats dosed with the comparator groups of either an approved recombinant human FVIII product, or a marketed human plasma-derived FVIII concentrate. No abnormal tissue pathology, and only sporadic evidence of *in situ* thrombosis with no apparent relationship in the incidence or severity to the FVIII dose level were observed on microscopic examination of lung and other tissues from rats dosed with KOVALTRY at up to 5-fold greater doses than the maximum clinical dose of 40 to 50 IU/kg. There was no evidence of undesirable *in vivo* secondary pharmacologic activity, i.e., thrombogenesis, in FVIII-replete rats and FVIII-replete rabbits dosed with KOVALTRY at dose levels up to 8-fold greater than the equivalent human KOVALTRY starting dose. There were no effects of KOVALTRY or the other approved FVIII

preparation on the hematology profiles in the rats or rabbits as compared to prior to dosing (i.e., baseline), and no serious adverse effects or evidence of thrombogenicity were reported.

These data were used as proof-of-concept to support the rationale for entering KOVALTRY into clinical trials, and to support the pharmacology section of the KOVALTRY BLA Package Insert (PI).

Pharmacokinetics

Pharmacokinetic (PK) studies with KOVALTRY were conducted concurrently with the pharmacology studies in Hemophilia A mice described above, and FVIII activity was measured by both the OC and CS assays. With both assays, the PK profiles from hemophilic mice dosed with KOVALTRY showed dose-dependent effects in all parameters measured, and were comparable to those obtained when the mice were dosed with the approved, human recombinant FVIII comparator. Similar PK profiles were obtained in FVIII-replete, wild-type rats dosed with KOVALTRY or an approved, human FVIII comparator product. A series of PK studies in FVIII-replete, wild-type rats and rabbits showed that the KOVALTRY product tested in the nonclinical safety program was comparable to those lots used in clinical trials, and that there were no meaningful changes in the critical PK parameters.

Toxicology

Overall, no unexpected findings or significant concerns were identified in toxicity studies conducted in wild-type, FVIII-replete rabbits and rats. Rabbits dosed with a single, intravenous injection of KOVALTRY at doses up to 8-fold greater than the clinical starting dose demonstrated no systemic or tissue pathologies. A repeat-dose toxicity study with KOVALTRY was conducted in rabbits; animals were dosed daily for 5 days by bolus intravenous injection with KOVALTRY doses equal to, and up to 8-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis), the findings were not consistent or dose-related between the KOVALTRY dose groups, and no corresponding histopathological findings were detected. The findings in the KOVALTRY dosed rabbits were comparable to those in rabbits receiving an equivalent dose of either an approved, recombinant human FVIII product or a human plasma-derived FVIII concentrate as comparators, suggesting that the safety profile of KOVALTRY is similar to that of other, approved FVIII products. In a repeat dose toxicity study with KOVALTRY in rats, the animals were dosed daily for 5 days by bolus intravenous injection with KOVALTRY doses equal to, and up to 20-fold greater than the clinical starting dose. Although statistically significant differences in some measured parameters of toxicity were reported (e.g., hematology, prothrombin time and aPTT, serum chemistry and urinalysis) and were consistent and dose-related between the KOVALTRY dose groups, no corresponding histopathological findings were detected and the findings were not considered toxicologically meaningful. The hematology findings in the toxicity studies in FVIII replete animals were expected and consistent with exaggerated pharmacologic effects of exogenous FVIII, which have previously been demonstrated in animal studies with other recombinant and plasma-derived FVIII products.

Special Toxicology Studies

A repeat-dose exploratory study in hemophilia A mice was conducted to compare the immunogenicity of KOVALTRY DP with KOGENATE FS, the predecessor recombinant FVIII product previously licensed and marketed by the Applicant. No remarkable toxicities were reported in mice after once weekly intravenous dosing for 5 doses with either the KOGENATE or KOVALTRY, and there were no statistically significant differences in the incidence of immunogenicity in mice dosed with KOGENATE compared to animals injected with KOVALTRY. Comparable exposures to human rFVIII, as measured by the *Area Under the Concentration versus Time Curve*, were demonstrated in PK studies in rats and rabbits after a single intravenous injection of either the KOGENATE or KOVALTRY products. These nonclinical data suggest that the same doses of either recombinant FVIII product result in similar pharmacologic activity, toxicity, exposure and potential for immunogenicity in hemophilia A

mice, and support the Applicant's conclusion that the safety profile of KOVALTRY is comparable to that of their previously approved, recombinant FVIII product KOGENATE.

Toxicologic Risk Assessment Analysis

A toxicological risk assessment analysis, providing identification and safety qualification of the extractable and potential leachable substances from the components used in the KOVALTRY manufacturing process, was also provided in this submission. The results of this risk analysis indicated that the levels of potential leachable or extractable impurities appear acceptable, as they were significantly lower than the maximally allowed daily exposure levels identified from extensive clinical and nonclinical experience. Additionally, the safety of these extractable and leachable compounds can be considered adequately qualified because several lots of KOVALTRY were used in the nonclinical toxicology testing, at daily doses of rFVIII exceeding the recommended clinical dose by up to 8-fold. The risk of the presence of these compounds, at the levels identified, to patients with hemophilia A receiving intravenous doses of KOVALTRY is considered minimal, and acceptable considering the benefit of FVIII replacement therapy in this population.

There were no animal studies with KOVALTRY to assess carcinogenicity, *in vitro* or *in vivo* mutagenicity, fertility, reproductive toxicity or teratogenicity. KOVALTRY is a recombinant, human protein and animals receiving repeated doses of the product developed antibodies against FVIII that both accelerated clearance of the protein and, in some cases, neutralized its pro-coagulant activity. Therefore, long-term, repeat-dose toxicity studies, as well as the standard carcinogenicity bioassay (i.e., 2 years of daily KOVALTRY dosing in both rats and mice), were not feasible to conduct.

Because KOVALTRY is a protein, the standard battery of genotoxicity testing as recommended in the International Conference on Harmonization (ICH) S2 guidance documents would not provide information to address potential mutagenicity of the rFVIII, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics, these studies were not required. The lack of carcinogenicity, mutagenicity and chronic toxicity data are addressed in the appropriate section of the package insert.

No nonclinical reproductive or developmental toxicity studies were conducted in support of this submission. Hemophilia A is an X-linked disorder and affects mostly male subjects; therefore, it is highly unlikely that a pregnant or lactating woman would receive KOVALTRY. KOVALTRY received a Pregnancy and Lactation designation in the labeling that includes statements that nonclinical reproductive and developmental toxicity studies with KOVALTRY have not been conducted, that the risks to the developing fetus are unknown, and that the product should be used in a pregnant woman only if clearly needed. This labeling is consistent with that included in prescribing information for other approved recombinant human coagulation factors for the treatment of hemophilia A or B.

c) Recommendation

The results from the nonclinical program, including the safety profile and hemostatic activity of KOVALTRY and the toxicological risk assessment support KOVALTRY's use for the proposed indications.

III. Nonclinical Labeling for the Package Insert (PI) for STN 125574/0

The label was revised to reflect current labeling guidelines and the relevant information for prescribing data based on nonclinical and clinical experience using KOVALTRY™.

Clean Revised Version of Label for Nonclinical

Section 8 Use in Specific Populations

8.1 Pregnancy

Risk summary

There are no data with KOVALTRY use in pregnant women to inform on drug-associated risk. Animal Reproduction studies have not been conducted using KOVALTRY. It is not known whether KOVALTRY can because fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOVALTRY should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KOVALTRY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KOVALTRY and any potential adverse effects on the breastfed infant from KOVALTRY or from the underlying maternal condition.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of KOVALTRY or other studies to determine the effects of KOVALTRY on fertility have not been performed. KOVALTRY was negative in the modified *in-vitro* [Mammalian Mutation and Chromosome Aberration Assay with Mouse Lymphoma Cells] genotoxicity test. KOVALTRY is expected to have no mutagenic potential.

Section 13 and 13.2 Animal Toxicology and/or Pharmacology was removed.

FDA Revisions to Applicant's Label

Applicant's Language (Section edited):

Pregnancy Category C

8.1 Pregnancy

Animal reproduction studies have not been conducted with Kovaltry. It is also not known whether Kovaltry can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. Kovaltry should be given to a pregnant woman only if clearly needed.

FDA Revision: Section 8.1 was modified to reflect labeling guidelines as per 21 CFR 201.57 Pregnancy and Lactation Label Rule (PLLR) revision.

8.1 Pregnancy

Risk summary

There are no data with KOVALTRY use in pregnant women to inform on drug-associated risk. Animal Reproduction studies have not been conducted using KOVALTRY. It is not known whether KOVALTRY can because fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOVALTRY should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Justification: Revised the language to be consistent with that provided in the CFR to describe the Pregnancy Category C designation for ADYNOVATE to reflect PLLR revises the PLR content and format requirements for subsections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential of the USE IN SPECIFIC POPULATIONS section of the full prescribing information (FPI) described in 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), which removes pregnancy categories and provides descriptive data.

Applicant's Language (Section edited):

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Kovaltry is administered to a nursing woman.

FDA Revision: Section 8.3 was modified to reflect labeling guidelines as per 21 CFR 201.57 PLLR revision and relabeled section 8.2 Lactation in alignment with new PLLR.

8.2 Lactation

Risk Summary

There is no information regarding the presence of KOVALTRY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KOVALTRY and any potential adverse effects on the breastfed infant from KOVALTRY or from the underlying maternal condition.

Justification: This section was revised to reflect PLLR revises the PLR content and format requirements for subsections 8.1 through 8.3 of section 8 USE IN SPECIFIC POPULATIONS of the FPI [21 CFR 201.56(d)(1) and 21 CFR 201.57(c)(9)(i) through (c)(9)(iii)], which provides descriptive data for this section.

Applicant's Language (Section edited):

13 NONCLINICAL TOXICOLOGY

Nonclinical studies evaluating Kovaltry in hemophilia A mouse efficacy models demonstrated restoration of hemostasis. The nonclinical safety program did not identify any concerns for humans based on safety, pharmacology, acute toxicity, repeated-dose toxicity and genotoxicity studies.

FDA Revision: Language immediately under and including the header for Section 13 was removed.

Justification: Removed entire header under Section 13 due to redundancy. The product testing and findings in animals are not essential for clinical prescribing information; the KOVALTRY product was evaluated in clinical trials and the results and safety profile are appropriately described in the clinical sections of the label.

Applicant's Language (Section edited):

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Embryo-fetal development studies have not been assessed in animals since factor VIII is an endogenous replacement protein; also the patient population is mainly male.

No effect on male reproductive organs was seen in repeated administration toxicity studies. Factor VIII is an endogenous protein, and no effect on fertility has been seen in humans with this protein.

Kovaltry has been shown to be non-genotoxic in the mouse lymphoma assay. Carcinogenic studies in animals have not been performed since factor VIII is an endogenous replacement protein and rFVIII has not shown any genotoxic or carcinogenic potential.

FDA Revision: Section 13.1

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of KOVALTRY or other studies to determine the effects of KOVALTRY on fertility have not been performed. KOVALTRY was negative in the modified *in-vitro* [Mammalian Mutation and Chromosome Aberration Assay with Mouse Lymphoma Cells] genotoxicity test. KOVALTRY is expected to have no mutagenic potential.

Justification: Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility section was edited to convey important information that was omitted by the Applicant (i.e., an assessment of carcinogenic risk was performed, although *in vivo* animal carcinogenicity testing was not conducted), and needed to be added to the label. Since there were no animal studies complete all other information has been removed from this section.

Applicant's Language (Section edited):

13.2 Animal Toxicology and/or Pharmacology

Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any toxicity in single and multiple dose studies in rats, rabbits and dogs.

Kovaltry has been shown to be comparable to the predecessor product, Kogenate FS, with respect to its biochemical and physiochemical properties, as well as its non-clinical *in vivo* pharmacology and toxicology.

FDA Revision: Language immediately under and including the header for Section 13.2 was removed.

Justification: Removed entire Section 13.2 due to redundancy. The product testing and findings in animals are not essential for clinical prescribing information; the KOVALTRY product was evaluated in clinical trials and the results and safety profile are appropriately described in the clinical sections of the label.

IV. Background

Hemophilia A is a recessive sex-linked hereditary disease characterized by congenital FVIII deficiency, and is usually treated by replacement therapy with clotting factor VIII. Historical data demonstrate that FVIII replacement therapy is the most widely utilized and effective therapy. Although adverse events can occur from repeated rFVIII use including thromboembolic events, anaphylactic (allergic) reactions, antibody formation and increased inhibitor titers, the longstanding use and efficacy of FVIII therapy substantiate its usefulness in the treatment of Hemophilia A.

Bayer's KOVALTRY™, recombinant Factor VIII Formulated with Sucrose (rFVIII-FS) with Modified Bulk Drug Substance Manufacturing Process (for improved production process), is an anti-hemophilic product indicated for the control and prevention of bleeding episodes in adult and adolescent (12 to less than 18 years) Hemophilia A patients. Recombinant FVIII-FS is a third generation anti-hemophilic product, and its predecessors have a long-standing history of use worldwide. Bayer claims the new product, Bay 81-8973, (b) (4) as currently marketed rFVIII (Kogenate FS), but has an improved cell bank and production process derived from the addition of a heat shock protein (hsp70), modification of viral inactivation and filtration steps, and removal of human plasma protein additives and animal (origin) derived raw materials (i.e., uses serum free media) from processing (processing and purification). KOVALTRY is indicated for treatment for on-demand treatment and control of bleeding episodes, peri-operative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes, in adults and children with congenital FVIII deficiency (Hemophilia A).

Because this product has undergone the aforementioned manufacturing changes in comparison to its predecessor Kogenate FS®, the scope of the major process changes substantiates the need for preclinical safety evaluation of the product. The Applicant claims that these changes improve the quality of the product while maintaining the product's efficacy, and intends to phase out production of Kogenate FS® and replace it with KOVALTRY based on aforementioned claims.

V. Proposed Use and Doses

The Applicant proposes that KOVALTRY™ will be administered intravenously (bolus) in patients with Hemophilia A. KOVALTRY™ is a full length recombinant antihemophilic factor indicated for use in adults and children with Hemophilia A for:

1. Routine prophylactic treatment to prevent or reduce the frequency of bleeding episodes
2. Control and prevention of bleeding episodes
3. Peri-operative management (surgical prophylaxis)

The dosage and duration depend on the severity of Factor VIII deficiency, the location and extent of the bleeding, and the patient's clinical condition. Adjust dose to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, incremental recovery) and clinical responses to KOVALTRY™.

Routine Prophylaxis

For prophylaxis of bleeding episodes, a pharmacokinetic-tailored dose between 20 to 50 U/kg twice weekly, three times weekly, or every other day may be utilized.

- Individualize the patient's dose based on clinical response.
- Adults and adolescents: 20 to 40 IU of KOVALTRY per kg of body weight two or three times per week.

- Children ≤ 12 years old: 20 to 50 IU of KOVALTRY per kg body weight twice weekly, three times weekly, or every other day according to individual requirement

On-demand Treatment and Control of Bleeding Episodes

For treatment of on-demand and control of bleeding episodes, an on-demand dose between 20-100 IU/kg will be utilized.

Perioperative Bleeding (surgical prophylaxis)

For treatment of bleeding episodes, an on-demand dose between 30-100 IU/kg will be utilized.

VI. General Comments

- KOVALTRY™ is the second generation, improved version of Kogenate® FS (Approved STN 103332; cross reference for additional safety data)
- There appear to be alterations in the KOVALTRY™ product composition versus the predecessor and comparators that resulted in spontaneous deaths in animals following repeat administration of drug at least 20 days after the start of treatment, and were likely due to immunogenicity. These results were corroborated in clinical trials with confirmation of antibody formation in patients, but there were no deaths or inhibitor antibodies in patients.
- KOVALTRY™ (BAY 81-8973) appears to be as potent and effective in patients with Hemophilia A as its Kogenate® (rFVIII-FS [KGN]) predecessor.

VII. List of Pre-clinical Studies in STN 125574/0

1. **Study Report PCD2008-001**- BAY 81-8973 (Developmental Lot) Comparison of Efficacy with rFVIII-FS in Hemophilia A Mice
2. **Study Report PCD2008-013** – BAY 81-8973 (Clinical Lot) Comparison of Efficacy with FVII-FS in Hemophilia A Mice
3. **Study Report TOXT4078423** – Influence of Cardiovascular Hemodynamics and ECG in Anesthetized Dogs after Short Intravenous Infusion
4. **Study Report TOXT4078829** – Effects of BAY 81-8973 on Pulmonary Function of Conscious Unrestrained Rats after Single Intravenous Administration
5. **Study Report MB5013** – Determination of BAY 14-2222 and BAY 81-8973 in Rat (b) (4) and Rabbit (b) (4) and Dog (b) (4)
6. **Study Report TOXT5079568** – BAY 81-8973 and BAY 14-2222: Determination of Similarity of the Pharmacokinetic Behavior of Both Test Articles in Male (b) (4) Rats After Single Intravenous Administration

7. **Study Report TOXT6079569** – BAY 81-8973 and BAY 14-2222: Determination of Similarity of the Pharmacokinetic Behavior of Both Test Articles in (b) (4) Rabbits After Single Intravenous Administration
8. **Study Report T5079261** – A Single Intravenous Toxicity Study in (b) (4) Rabbits
9. **Study Report T6079262** – A Single Intravenous Toxicity Study in Male (b) (4) Rats
10. **Study Report T8079264** – 5-Day Repeat Dose Intravenous Toxicity Study in Male (b) (4) Rats
11. **Study Report T7079263** – BAY 81-8973 5-Day Repeat Dose Intravenous Toxicity Study in Male (b) (4) Rabbits
12. **Study Report PCD2008-014** – Exploratory Assessment of the Antigenicity of BAY 81-8973 and rFVIII-FS in Hemophilia A Mice

VIII. Summary of Pre-clinical Studies in STN 125574/0

Reviewer comment: The KOVALTRY product has numerous codenames including KGN rFVIII-FS, BAY 81-8973, and Kogenate® FS codenames include BAY 14-2222, rFVIII-FS, KGN and rFVIII.

The nonclinical program evaluated the safety and efficacy of KOVALTRY in several studies and animal models (*in vitro* and *in vivo*). Based on these data, KOVALTRY appears to be as safe and as pharmacologically active as the Applicant's currently marketed FVIII product Kogenate® FS, and the clinical data corroborate these findings.

In summary:

PEL (pharmacologically effective level) = 1- 12 IU/kg

tSF (tentative safety factor) = 15.56 for the clinical acute and repeat dosing (prophylactic) regimens proposed, using the 35 IU/kg clinical dose

NOAEL = 120 IU/kg, although immunogenicity concerns persist relating to formation of neutralizing and binding antibodies following repeat/prolonged use of the product in animals

Common Abbreviations

TAT=thrombin-antithrombin

DDM=D-dimer s.c=subcutaneous

PT=prothrombin time

HR=heart rate

aPTT=activated partial thrombin time

KO=knock-out

rFVIII variants= Bayer's rFVIII-FS (BAY 81-8973) and Kovaltry

KGN rFVIII-FS (or BAY 14-2222) Kogenate

FIB=fibrinogen

volm.= volume

CVS=cardiovascular system (cardiotoxic signs, BP, ECG,)

NOAEL= no observed adverse effect level

i.v. = intravenous

TK= toxicokinetics

wt.=weight

macro. = macroscopic sign

TEG=thromboelastography

NOEL=No observed effect level

s.s. = statistically significant

WBCT=whole blood clotting time (coagulation) i.e. FIB, aPTT, PT

*Buffer (vehicle) contains sucrose, histidine, glycine, NaCl, CaCl₂, Tween 80 (referred to as lot no. 270930K)

Necropsy (histopathology) consists of the following organs:

Adrenals - cortex and medulla

Brain - cerebellum, cerebrum, midbrain and medulla

Eyes-includes eyelids

Femur – with joint

Harderian glands

Head-with skull cap and nasal cavity

Heart - included aorta, auricular and ventricular regions

Intestines-Payers patch, Sacculus rotundus, duodenum, jujenum, ileum, cecum/appendix, colon, rectum

Kidneys - included cortex, medulla and papilla regions

Liver - section from two main lobes

Lymph nodes- mandibular, mesenteric, popliteal

Lungs - section from two major lobes, including bronchi

Optic nerve

Pancreas

Pharynx

Pituitary gland

Salivary glands-parotid, submandibular, sublingual

Sciatic nerve

Seminal vesicle/Glandula vesicularis

Skeletal muscle (thigh)

Skin with mammary

Spinal cord – cervical, thoracic, lumbar

Sternum - included bone marrow

Stomach - included body and antrum

Testes

Thymus

Thyroid glands-with parathyroids

Tongue

Trachea

Urethra

Uterus

Urinary bladder

Study Report CB-2006-28 A Pharmacologic Evaluation of BAY 81-8973 using an Acute FVIII Dependent Bleed Model in the Hemophilic A (FVIII -/-) Mouse

The purpose of this study was to assess the biologic activity (affect blood loss) of BAY 81-8973 vs. KGN rFVIII-FS in the tail-clip bleeding model in Hemophilia A mice (FVIII-KO mice), at two dose levels of KGN FS FVIII; 1, 2.5 or 5 U/kg). In addition, the pharmacokinetic/pharmacodynamic (PK/PD) parameters were measured to provide relevant correlation to safety assessment in hemophilia conditions. A positive control group of (b) (4) mice (n~30/gr. for efficacy and ~ 10/dose/gr. for PK/PD timepoints) were dosed prophylactically via tail vein (0, 1, 2.5 or 5 U /kg rFVIII; variants or albumin) 24 hrs. prior to tail cut and then blood loss was measured for 15 mins. Blood from the satellite animals was collected at 4 and 24 hrs. for PK/PD testing. Control (b) (4) mice administered 5% albumin exhibited minimal bleeding following the procedure. There were no s.s changes in blood loss between groups of FVIII-KO mice dosed with the different FVIII variants. Based on the results of this study, BAY 81-8973 was just as effective as KGN rFVIII-FS in the FVIII-KO mice tail clip model. This study was preliminary, to determine the design of subsequent efficacy studies, was completed in August 2007 at Bayer HealthCare, (b) (4), and was non-GLP compliant.

Study Report PCD2008-001 (Report Number CB-2008-20) - BAY 81-8973 (Developmental Lot) Comparison of Efficacy with rFVIII-FS in Hemophilia A Mice

The purpose of this study was to assess the biologics (affect blood loss) of BAY 81-8973 vs. KGN rFVIII-FS in the tail-clip bleeding model in Hemophilia A mice (FVIII-KO mice). Mice (n=20/gr.) were dosed acutely via jugular vein (12 or 40 IU/kg BAY 81-8973, Lot no. 27-2007-268-20) or rFVIII-FS KGN [Lot 27N1190]) 5 mins. prior to tail cut injury, or prophylactically via tail vein (40 or 120 IU/kg BAY 81-8973 or rFVIII-FS KGN) 24 hrs. prior to tail cut injury. Blood loss was measured for 15 min. after injury. There were no s.s changes in blood loss for mice after acute dosing 5 min. prior to tail cut injury. However, after prophylactic dosing there was a trend for a reduction in blood loss for mice dosed with BAY 81-8973 vs. rFVIII-FS at 120 IU/kg, but no s.s. difference at 40 IU/kg between the two FVIII variants. Based on the results of this study, BAY 81-8973 was just as effective as KGN rFVIII-FS in FVIII-KO mice tail clip model, taking into account the high degree of variability in blood loss at equal doses. This study was completed in June 2008 at Bayer HealthCare, (b) (4), and was non-GLP compliant.

Study Report PCD2008-013 (Study Report CB-2009-05) – BAY 81-8973 (Clinical Lot) Comparison of Efficacy with FVII-FS in Hemophilia A Mice

The purpose of this study was to assess the biologic activity (affect blood loss) of clinical-grade BAY 81-8973 (Lot 27N1R50) vs. KGN rFVIII-FS (Lot 27N1190) in the tail-clip bleeding model in Hemophilia A mice (FVIII-KO mice). In addition, the pharmacokinetic/pharmacodynamic (PK/PD) parameters were measured to provide relevant correlation to safety assessment in hemophilia conditions. Mice (n=20/gr. for effectiveness measures, and 5/dose/gr. for PK/PD timepoints) were dosed acutely via jugular vein with 12 or 40 IU/kg of the rFVIII variants 5 mins. prior to tail cut, or prophylactically via the tail vein (40 or 120 IU/kg of the FVIII variants) 24 hrs. prior to tail cut, and then blood loss was measured for 15 mins. post-injury. Blood was collected from the satellite animals at 5 min, 1, 2, 4, 8, 26 and 24 hrs. for PK/PD testing. Results indicated that rFVIII variants displayed equivalent effects in improving coagulation at all doses and routes of administration, based on rFVIII plasma levels (measured by the chromogenic substrate assay) and the degree of hemostatic protection (i.e., reduction of blood loss). The two rFVIII variants displayed equivalent FVIII exposure in mice, with comparable AUC Values; however, the biological half-life and mean residence times (MRT) were slightly higher for BAY 81-8973 than for rFVIII-FS. The Applicant claims that rFVIII variants are comparable in all parameters tested, and it appears BAY 81-8973 is comparatively as safe as rFVIII-FS and will not pose greater risk in use in patients with Hemophilia A. This study was completed in January 2009 at Bayer HealthCare, (b) (4), and was non-GLP compliant.

Study Report TOXT4078423 (Study Report AT05107) – Influence of Cardiovascular Hemodynamics and ECG in Anesthetized Dogs after Short Intravenous Infusion

The purpose of this study was to evaluate the cardiotoxic effects of BAY 81-8973 (Batch no. 27N1R50) following administration to Factor VIII (b) (4) dogs. Dogs (n=4/gr.) were dosed via i.v. administration with 0 (vehicle [buffer]), 120 or 400 IU/kg BW) BAY 81-8973, and evaluated for effects on cardio-hemodynamics and telemetric parameters (HR, BP, CO, lead II ECG, etc) while monitoring clinical signs (BW, behavior, etc.), PK (at 5, 60, and 300 mins. post-dose), and clinical chemistry panel (biochemistry, electrolytes, etc.). Dogs were euthanized and subjected to necropsy at study termination. For PK, AUC increased dose-dependently (slightly less than dose-proportional), and Cmax increased slightly more than dose-proportionally. There were no overt toxicities observed in clinical signs, nor any adverse effects that were clearly correlated to treatment with product. There were no changes to blood chemistry or necropsy findings, and it appears that BAY 81-8973 was well tolerated in dogs in relation to the cardiovascular assessments. The NOAEL for cardiotoxic effects was 400 IU/kg, and the doses tested were 3 to 10-fold greater than the recommended clinical dose. This study completed in February 2009 in (b) (4) and was GLP compliant.

Study Report TOXT4078829 (Study Report A45049) – Effects of BAY 81-8973 on Pulmonary Function of Conscious Unrestrained Rats after Single Intravenous Administration

The objective of this study was to investigate the effects of i.v. administered BAY 81-8973 at doses of 0 (vehicle [buffer control], 120 or 400 IU/kg in 0.3 and 1.0 mL/kg, respectively) on respiratory parameters in rats at 0.5-240 mins. following dosing. The results indicate that injection of BAY 81-8973 did not have statistically significant effects on respiratory rate (frequency), tidal volume or minute volume after dosing. However, there was a statistically significant, approximately 40% increase in respiration rate and minute volume for rats in the 400 IU/kg dose group versus control rats (buffer) at 0.5 hrs., that leveled off during the first hour post-dosing. It was concluded that there is a slight, transient stimulation of respiration rate and minute volume after a dose of 400 IU/kg BW (10X proposed clinical dose). This product is considered tolerable based on current respiratory standards. This study was completed in February 2009 in (b) (4), and was GLP compliant.

Study Report MB5013 – Determination of BAY 14-2222 and BAY 81-8973 in Rat (b) (4) and Rabbit (b) (4)) and Dog (b) (4)

The aim of this study was to evaluate the pharmacokinetics in rats, rabbits and dogs following intravenous administration for 5 consecutive days (repeat dosing) of BAY 81-8973 (Batch no. 27N1R50). All PK studies were GLP compliant. There was an additional study (*in vitro*) embedded within the PK study to examine the stability of BAY 81-8973 vs. rFVIII-FS (Lot No. 27N1190) at room temperature for up to three hrs. to bridge the range of concentrations (10, 20, and 400 IU/kg) utilized to treat mice, rats, rabbits and dogs. The product was stable up to 3 hrs at room temp. based on analysis (chromogenic potency assay). This study was completed in February 2009 in (b) (4) and was GLP compliant.

Rats

Male rats (n=10m/gr. or 9 M/gr. satellite animals for blood sampling) were dosed i.v. with vehicle (buffer), 40, 120, or 400 IU/kg BW BAY 81-8973 daily for 5 days. Additional rats were dosed in the same manner (n=5/gr. of buffer and 400 IU/kg BW), with a recovery (treatment-free) period of 4 weeks. During the study, animals were monitored for clinical signs of toxicity (BW, food consumption, ophthalmoscopy, etc.), clinical serum chemistry panel (hematology, electrolytes, biochemistry, WBCT, etc.), TK (15 min, 1, 4, 8, & 24 hrs. after dosing), antigenicity (Days 6, 12, 19, 33), and at termination, by necropsy (including histopathology).

There were no overt toxicities or remarkable changes in any of the parameters tested such as clinical signs, morbidity, wt. changes, etc. in most of the animals. There was s.s. reduction in thymus wt. in the 400 IU/kg recovery gr. when compared to the control gr., but these results were not shown in the main study 400 IU/kg dose gr., and so were “not considered adverse” findings by the Applicant. This change was also not considered treatment-related according to Applicant. Some hematology changes were reported for the 400 IU/kg dose group as compared to the vehicle controls, and included slight decreases in Leu counts, a 28%, s.s. decrease in Lym counts (due to 2 outliers in the treatment gr., as per the Applicant), Ret (the Applicant claims was caused by one outlier animal). Slight increases in PT were observed in rats in the 400 IU/kg dosed recovery gr. (n=5) compared to the control (n=3) recovery groups; but Applicant claims that there were too few animals in groups to statistically compare the results. There were slight changes in clinical chemistry for rats in the 400 IU/kg recovery gr. i.e., decreased LDH, creatine kinase, Na conc.), but these findings were not ss. compared to the control gr., and were within the range of findings for the 400 U/kg main study dose group. The Applicant claims that these changes were due to one outlier control animal. To note, reduced creatinine also occurred in the 120 IU/kg main study gr., but was not s.s. when compared to the control gr. animals. One mortality occurred in a 400 IU/kg satellite gr. rat on Day 22 following blood sampling from the retro-orbital venous plexus for antigenicity testing; the Applicant claims the death was related to the sampling procedure and was not treatment

related. Toxicokinetic analysis revealed that AUC increased dose-dependently, but slightly to moderately less than dose-proportional. Cmax increased less than dose proportionally from the low to the mid-dose, and dose-proportionally from the mid- to the high dose. Toxicokinetic parameters did not differ significantly between the first and last day of dosing. Local irritations were noted at the injection site in animals, and are expected with this type of product injected at high doses. The NOAEL was 120 IU/kg BW (i.e., 3-fold greater than the clinical dose).

Reviewer Comment: Antigenicity testing was not completed for rats in this study, although blood samples were taken for this reason. The omission is likely related Guidance from the addendum to ICH S6 that states if the TK in a repeat dose study does not show increased clearance (e.g., decreased AUC, half-life), then anti-drug antibody development is unlikely and the antigenicity testing does not need to be completed.

Rabbits

Rabbits were dosed i.v. to measure the potency and to re-verify the identity of BAY 81-8973. The potency of BAY 81-8973 remained comparable to rFVIII-FS, and to other vials of BAY 81-8973 product on stability testing.

The aim of this study was to assess the potential toxicity and toxicokinetics of BAY 81-8973 following intravenous repeat dosing in rabbits. Male rabbits (n=6/gr.) were dosed i.v. with vehicle (buffer), or 40, 120, or 400 IU/kg BW BAY 81-8973 for 5 consecutive days, followed by a 4-week, treatment-free recovery period (n=3/gr. for vehicle and 400 IU/kg BW BAY 81-8973 dose groups). Animals were monitored for clinical signs of toxicity (BW, food consumption, ophthalmoscopy, etc.), clinical serum chemistry and hematology panels (including WBCT, hematology counts and differentials, serum electrolytes, biochemistry), TK (samples obtained 15 min, 1, 4, 8, & 24 hrs. after dosing), antigenicity (samples obtained Days 6, 12, 19, 33), and subjected to necropsy and histopathology evaluation at study termination. One animal mortality occurred in the high dose 400 IU/kg BW gr. prior to termination of this study, on Day 25 of the recovery period. The diagnosis at necropsy was spontaneous enteritis in the large Intestine, accompanied by severe hemorrhagic inflammation, and the Applicant claims this disease was spontaneous, and not treatment-related. The enteritis diagnosis is plausible based on historical data and incidences of similar findings in rabbits reported in the literature. In the remaining animals, findings included were changes in organ wt. including s.s. increase in adrenals, kidneys, and testes for 400 IU/kg main gr. and 400 IU/kg recovery gr. rabbits; additionally, spleen wt. were increased in this group, but were not s.s. different from control. These changes were not correlated to any histopathology findings. There were also alterations in aPTT with slight decreases in aPTT on Day 6 (17.3 vs. 15.5-14.0), Day 33 (15.2 vs. 16.6-17.6) and decreases in FIB on Day 33 (4.34 vs. 2.78-2.35) in those animals dosed with BAY 81-8973; but none were s.s., according to the Applicant. Toxicokinetics evaluation indicated that Cmax and AUC increased proportionally with dosing. Local tolerance findings included mild to moderate sensitization at the injection site in all animals including controls. The NOAEL for this study was 400 IU/kg BW (8-fold greater than the recommended clinical dose).

Dogs

No data were submitted to describe the findings for the dogs' safety pharmacology or toxicity assessments following BAY 81-8973 administration.

Study Report TOXT5079568 (Study Report A43910) – BAY 81-8973 and BAY 14-2222: Determination of similarity of the pharmacokinetic behavior of both test articles in Male (b) (4)

Rats after single intravenous administration

The purpose of this study is to assess the pharmacokinetics of BAY 81-8973 vs. rFVIII-FS in rats. Rats (n=20/gr.) were dosed with a single, bolus i.v. injection of 250 IU/kg BW of BAY 81-8973 or rFVIII-FS in a volume of 1mL/kg. Rats were monitored for gross clinical signs of toxicity and blood samples were collected at various time points for up to 24hrs after dosing and analyzed to monitor the following PK parameters: C_{max}, Clearance (CL), Volume of Distribution at Steady State (V_{ss}), AUC and biological half-life (t_{1/2}). The results showed linear, dose-dependent changes in PK parameters, and the findings with the two rFVIII variants were comparable. This study was completed in April 2009 at (b) (4) and was GLP compliant.

Product	Dose (IU/kg)	T _{1/2} hr.	CL L/kg/hr	Vss L/kg (total)	C _{max} (IU/L)	AUC (IU*hr/L)	AUC _{mean} (kg*hr/L)
BAY 81-8973	250	4.28	0.00874	0.0540	2720	28514	114
rFVIII-FS (KGN)	250	4.62	0.0121	0.0806	2028	20555	82.2

Based on the PK parameters tested, the following conclusions were drawn for BAY 81-8973:

- The mean systemic exposure was 1.39-fold higher than BAY 14-2222
- The mean plasma clearance was 0.670-fold lower than BAY 14-2222
- The mean distribution (V_{ss}) was 0.722-fold lower than BAY 14-2222
- The biologic half-lives were similar between the two rFVIII variants

Study Report TOXT6079569 (Study Report A43911) – BAY 81-8973 and BAY 14-2222: Determination of similarity of the pharmacokinetic behavior of both test articles in (b) (4)

Rabbits after single intravenous administration

The purpose of this study is to assess the pharmacokinetics of BAY 81-8973 vs. rFVIII-FS in rabbits. Rabbits (n=20/gr.) were dosed acutely with 100 IU/kg BW of either FVIII variant in 1mL/kg by i.v. bolus injection, and monitored for gross clinical signs and PK parameters up to 48 hrs after dosing. The results showed linear, dose-dependent changes in PK parameters, and the results with the two rFVIII variants were comparable. This study was completed in April 2009 at (b) (4) and was GLP compliant.

Product	Dose (IU/kg)	T _{1/2} hr.	CL L/kg/hr	Vss L/kg (Act.)	MRT (hrs)	C _{max} (IU/L)	AUC mean(kg*hr/L)
BAY 81-8973	100	9.52	0.00341	0.0451	13.2	2720	293
rFVIII-FS (KGN)	100	9.60	0.00557	0.0702	12.6	2028	180

Based on the PK parameters tested, the following conclusions were drawn for BAY 81-8973:

- The mean systemic exposure was 1.63-fold higher than BAY 14-2222
- The mean plasma clearance was 0.609-fold lower than BAY 14-2222
- The mean distribution was 0.612-fold lower than BAY 14-2222
- The biologic half-life were similar between rFVIII variants

Reviewer comment: The following four studies were addressed above, in the summary review of Study Report MB5013 (i.e., the toxicokinetics sub-study report for each of the following toxicity studies). The BAY 81-8973 product appeared to be tolerable following both acute (single) and repeat daily dosing at the proposed clinical levels, with a NOAEL of 400 IU/kg/day (8-fold greater than the clinical dose) in both rats and rabbits following repeat, daily intravenous dosing for 5 days.

Study Report T5079261 – A Single Intravenous Toxicity Study in (b) (4) Rabbits

Study Report T6079262 – A Single Intravenous Toxicity Study in Male (b) (4) Rats

Study Report T8079264 – 5-Day Repeat Dose Intravenous Toxicity Study in Male (b) (4) Rats

Study Report T7079263 – BAY 81-8973 5-Day Repeat Dose Intravenous Toxicity Study in Male (b) (4) Rabbits

Study Report PCD2008-014 – Exploratory Assessment of the Antigenicity of BAY 81-8973 and rFVIII-FS in Hemophilia A Mice

The purpose of this study is to assess the antigenicity (immunogenicity) of BAY 81-8973 (Batch no. 27N1R50) and rFVIII-FS in hemophilia A mice. Male mice (n=10/gr.) were dosed by i.v. injection with 40 or 200 IU/kg of either FVIII variant, and blood samples were obtained on Day 0 pre-dose, Day 22, and Day 36 at necropsy to assess anti-FVIII and neutralizing antibody titers. Mice were monitored for clinical signs of toxicity (i.e., morbidity/mortality, BW). Two mortalities occurred in the 40 IU/kg BAY 81-8973 treated animals, one each on Study Day 27 and Day 35. The Applicant reports that the mortalities may be resultant of fighting, and claims that the “deaths were not treatment related”.

All animals treated developed neutralizing antibodies by end of study, and there were no apparent differences in immunogenicity between hemophilic mice dosed with BAY 81-8973 or the currently marketed KGN rFVIII. There was no necropsy completed for any of these animals. This study was completed in January 2009 in (b) (4) and was a GLP-compliant study.

Leachables and extractables

A risk assessment analysis was completed on the leachables and extractables associated with the manufacturing and storage of KOVALTRY™. The leachables and extractables have been previously qualified using human data and experience for the Kogenate® FS manufacturing process, and by previous use in both pre-clinical and clinical studies. The following excipients were evaluated and reviewed to provide specifications in final product: (b) (4) Trace Metals including but not limited to (b) (4) (also called (b) (4)). These were added during the (b) (4) process and removed from the final product when possible during (b) (4). Specification limits were set for all metals to provide adequate safety margins above the maximal recommended daily average intake values.

The value for insulin exposure from KOVALTRY™ dosing with the recommended clinical dose was corrected from the Applicant’s estimated 50 kg. BW to use a 70 kg/BW, which is more realistic for American subjects. Insulin exposure is expected to be approximately (b) (4) mg/kIU based on (b) (4) times weekly exposure in patients. The estimated permissible limit for exposure is (b) (4). The limit for insulin present in KOVALTRY is at least (b) (4) lower (i.e. (b) (4) safety factor) for average patient use.

A toxicological risk assessment analysis was also completed on the leachables and extractables associated with KOVALTRY use, i.e. the container closure system. The results of analysis indicated that the levels of the leachables/extractables materials observed were within the range of specifications and are at acceptable levels, based on extensive clinical experience.