Observational Study Information

Acronym / Title	**TAURUS**: A Mul***T***inational Ph***A***se IV Study Eval***U***ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY (Octocog alfa)
Product reference	KOVALTRY
Procedure number	Not applicable
Marketing authorization holder(s)	Bayer AG
Reference therapy	Not applicable
Research question and objectives	The primary objective of this study is to investigate weekly prophylaxis dosing regimens used in standard clinical practice. In addition the study will capture reported bleed rate, pattern of change in KOVALTRY prophylaxis dose & dosing frequency, reason for choice of treatment regimen, FVIII product switch pattern, patient treatment satisfaction and adherence, KOVALTRY pharmacokinetic data (if performed), KOVALTRY consumption, as well as safety data.
Country(-ies) of study	France, Germany, Italy, Netherlands, Switzerland, and the United States (and potentially other countries)
Author	Sarah Rybowski, MD

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of Contents

2. List of abbreviations

ABR	Annualized bleed rate
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
FVIII	Factor VIII
FVIII:C	Factor VIII Coagulant activity
FPFV	First patient first visit
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
Hemo-SAT	Hemophilia treatment satisfaction questionnaire
HEOR	Health Economics and Outcomes Research
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IT	Information Technology
IU	International units
IV	Intravenous
Kg	Kilogram
LEOPOLD	**L**ong-term **E**fficacy **O**pen label **P**rogram in severe hem**O**phi**L**ia a **D**isease
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
OS	Observational Study
NNH	Number Needed to Harm
PAS	Post-Authorization Study
PBRER	Periodic benefit-risk evaluation report
PASS	Post-Authorization Safety Study
PK	Pharmacokinetics

PSUR	Periodic Safety Update Report
PTPs	Previously treated patients
PUPs	Previously untreated patients
Q1	Quarter 1
Q1;Q3	Quartile 1; Quartile 3
Q2	Quarter 2
QoL	Quality of life
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
Veritas-PRO	Validated Hemophilia Regimen Treatment Adherence Scale
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

3.1 Study initiator and funder / MAH

Function: Study safety lead

Name: Elke Detering, MD

Function: Study medical expert

Name: Sarah Rybowski, MD

Function: Study conduct responsible

Name: Monika Brunn, MD

Function: Study statistician

Name: Claudia Tueckmantel

Function: Study data manager

Name: Dalila Lakbir

Function: Study epidemiologist

Name: Paul Petraro, ScD., MPH

Function: Study health economics and outcomes research (HEOR) responsible

Name: Jennifer Pocoski, PharmD

3.2 Collaborators / Committees

Contact details on the coordinating and / or principal physicians, co-physicians and other site personnel for each country and site participating in the study are listed in a stand-alone document (see Table 3: List of stand-alone documents, Annex 1) which is available upon request.

Administrative changes of responsible persons and / or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym / Title	**TAURUS**: A Mul***T***inational Ph***A***se IV Study Eval***U***ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
Author	Sarah Rybowski, MD Global Medical Affairs Hematology
Rationale and background	KOVALTRY is intended for the treatment of bleeds and for prophylaxis in children and adults with hemophilia A. The safety and efficacy of KOVALTRY for treatment of bleeds, perioperative management and routine prophylaxis with both a lower dose 2 times-weekly, as well as standard dose 3 times-weekly, has been demonstrated in 3 clinical trials in adult and pediatric previously treated severe hemophilia A patients. At time of launch, KOVALTRY will be the only unmodified FVIII product indicated for 2x weekly dosing. Supplementing KOVALTRY's pivotal trial evidence with real world data to further substantiate the proportion of patients who may be managed effectively at less frequent dosing, and potentially lower annual factor consumption is important from a pharmacoeconomic perspective.
Research question and objectives	Primary Objective: The primary objective of this study is to investigate weekly prophylaxis dosing regimens used in standard clinical practice. Secondary Objectives: • Effectiveness in prophylaxis • Prophylaxis dosing regimen in different age groups and countries • Consumption of KOVALTRY • Determinants for decisions on different prescribed

	regimens • Changes in treatment satisfaction (Hemo-SAT) after one year of treatment (in countries where validated) • Changes in treatment adherence (VERITAS-PRO) after 6 months and one year of treatment (in countries where validated) • Evaluation of safety in patients treated with KOVALTRY for one year • Describe approach to PK dosing and collection of KOVALTRY PK data if performed
Study design	Open label, prospective, non-interventional, single arm study in patients receiving KOVALTRY as prophylaxis therapy.
Population	Previously treated children and adults with moderate to severe hemophilia A (≤ 5% FVIII.C), ≥ 50 exposure days to any FVIII products and no history of inhibitors.
Variables	The outcome variables for the primary objective are: • Proportion of patients on 2x and 3x weekly prophylaxis at end of observation period The outcome variables for the secondary objectives are: • Annualized number of reported bleeds (total, spontaneous, joint and trauma) • Prophylaxis dosing by age group and country • Change in prophylaxis dosing frequency (study start to end of observation period) • The total annualized factor consumption • Physician decision determinants of prophylaxis regimen • Change in treatment satisfaction (Hemo-SAT) from start to end of observation period • Change from baseline to 6 months and end of observation period in Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-PRO) • Occurrence of adverse events (AEs) and serious adverse events (SAEs) • Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life, in-vivo recovery)

Data sources	The physician is requested to collect historic data (demographic and clinical characteristics) from medical records, and to collect treatment related data during visits that take place in routine clinical practice. Patient reported outcomes are collected via a separate portal in the Electronic Data Capture system or via paper data capture form where applicable.
Study size	A sample size of 350 patients is planned.
Data analysis	Statistical analyses will be explorative. All variables will be analyzed descriptively by frequency tables and/or summary statistics. Changes from baseline will be provided for continuous variables, if appropriate. In case of low subject number for single variables, listings will be provided instead of summary tables. All analyses will be performed for the total study population, by prophylaxis dosing regimen and by hemophilia severity. Separate analyses for each participating country will be provided if patient numbers are sufficient and if required for local reasons. Patients with documented initial dose of prophylaxis treatment with KOVALTRY will be included in the analysis. It is planned to have an interim analysis after 30 % of the planned study population is enrolled and has completed 6 months of treatment. For the primary analysis the proportion of patients on 2x and 3x weekly prophylaxis at end of study and 95% confidence intervals for the proportions will be presented.
Milestones	Start of data collection will be at enrollment of first patient (first patient first visit; FPFV) in Q3 2016. With an anticipated recruitment period of 2 years and an observation period of 1 year, last patient last visit (LPLV) is planned for Q3 2019.

5. Amendments

None.

Table 1: Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
Not applicable	Not applicable	Not applicable	Not applicable

6. Milestones

Definitions:

Start of data collection: date of first data entry in database.

End of data collection: date of last data entry in database

Final report: final report of study results 12 months after clean database

Table 2 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are kept as stand-alone document (Table 3: List of stand-alone documents, Annex 1) that is available upon request.

Table 2: Milestones

Milestone	Planned date
Start of data collection (First Patient First Visit)	Q3 2016
Last Patient First Visit	Q3 2018
End of data collection (Last Patient Last Visit)	Q3 2019
Final report of study results	Q1 2020

7. Rationale and Background

Hemophilia A is a X-linked, genetic bleeding disorder characterized by deficiency of clotting factor VIII (FVIII). [1] [2] Hemophilia A comprises approximately 80% of all hemophilia cases, with an annual incidence of approximately 1 in 5,000 live male births. [1] [2] All races and economic groups are affected equally. [1] [2]

The two main approaches to treatment of hemophilia A are on-demand therapy, in which the patient is treated in response to a bleed, or prophylactic treatment, in which the patient is treated regularly to prevent bleeding episodes. [1] Prophylaxis is now considered standard of care in many developed countries, especially in the pediatric and adolescent population, as it

has been shown to reduce complications from repeated bleeds, particularly joint outcomes. [1] [2]

KOVALTRY is an unmodified full-length recombinant human coagulation factor VIII (rFVIII) product, formulated with sucrose. [3] It has the same amino acid sequence as Kogenate® FS/Kogenate® Bayer but is manufactured using improved technologies. [3] [4] In the LEOPOLD trials, KOVALTRY demonstrated efficacy for treatment of bleeds, perioperative management and prophylaxis given as twice- or 3-times-weekly dosing regimen, whether dosing frequency was determined by the treating physician based on the patient's clinical profile (LEOPOLD I, LEOPOLD Kids) or was a randomly determined high- or low-dose regimen (LEOPOLD II). [4] [5] [6] In all completed LEOPOLD trials, there were no safety concerns with KOVALTRY. The safety profile of the drug is comparable to the predecessor drug Kogenate® FS/Kogenate® Bayer. No previously treated patients (PTPs) developed inhibitory antibodies to FVIII in completed studies. [4] [5] [6] As the clinical trial in previously untreated patients (PUPs) is ongoing, data on efficacy and safety, including inhibitor incidence, in PUPs are not yet available.

In LEOPOLD I study, ~ 30% of study population (adolescents & adults) received KOVALTRY on 2x dosing regimen at physician's discretion, however the reason for choice of dosing frequency was not captured in the study. [4] In the 6 month LEOPOLD kids, 95% of the 22 patients assigned to 2x weekly prophylaxis regimen remained on 2x weekly prophylaxis at end of study period. [6] The median (Q1; Q3) ABR was 1.0 (0; 8.0) in patients with twice-weekly dosing in LEOPOLD I, which was similar to the efficacy observed with patients on 3x weekly dosing - median (Q1; Q3) ABR; 2.0 (0.5; 5.0). [4] The dose/kg/injection was similar between the subgroups, resulting in a lower weekly dose with the twice-weekly regimen, with a mean nominal weekly dose of approximately 64 IU/kg compared with a mean weekly dose of 96 IU/kg with the 3-times-weekly regimen. [4] In LEOPOLD kids, median (Q1; Q3) ABR was 1.86 (0.0; 14.1) in patients with twice-weekly dosing and 1.97 (0.0; 18.1) in patients on > 2x weekly prophylaxis treatment regimen. [6] Most bleeds occurring during prophylaxis were trauma related and successfully treated with 1 or 2 injections of KOVALTRY. [6] Pharmacokinetic assessments in the LEOPOLD I trial showed non-inferiority of KOVALTRY versus Kogenate® FS/Kogenate® Bayer. KOVALTRY had a favorable pharmacokinetic profile compared with Kogenate® FS/Kogenate® Bayer, with a higher area under the curve (AUC), slightly longer half-life and mean residence time, and lower clearance (all differences were statistically significant). [7] Theortically, the increased half-life seen with KOVALTRY may allow for reduced prophylaxis dosing frequency.

Analysis of specialty pharmacy data on FVIII usage in 2014 (US market research) suggest that ~ 20% & ~ 50% of hemophilia patients are prescribed 2x and 3x weekly prophylaxis respectively with Kogenate® FS (Data on file, Bayer HealthCare). [8] Since clinical trials are conducted under strict supervision and have clearly defined inclusion/exclusion criteria for treatment, the observed treatment pattern distribution, efficacy and outcomes in LEOPOLD I and LEOPOLD Kids studies may not be adequately representative of patient outcomes for treatment occurring outside of clinical trials. Additionally, there is wide variation in real world treatment patterns with respect to dosing and frequency of administration, and neither the extent of variation in prescribing, nor the discrepancy between prescribing and patient adherence, and patient's satisfaction with prescribed prophylaxis regimen are well characterized.

At time of launch, KOVALTRY will be the only unmodified FVIII product indicated for 2x weekly dosing. Supplementing KOVALTRY's pivotal trial evidence with real world data to further substantiate the proportion of patients who may be managed effectively at less frequent dosing, and potentially lower annual factor consumption is important from a pharmacoeconomic perspective.

8. Research questions and objectives

8.1 Primary objective

The primary objective of this study is to investigate weekly prophylaxis dosing regimens used in standard clinical practice.

8.2 Secondary objective(s)

The secondary objectives in this study are to evaluate:

- Effectiveness in prophylaxis
- Prophylaxis dosing regimen in different age groups and countries
- Consumption of KOVALTRY
- Determinants for decisions on different prescribed regimens
- Changes in treatment satisfaction (Hemo-SAT) after one year of treatment (in countries where validated)
- Changes in treatment adherence (VERITAS-PRO) after 6 and 12 months of treatment (in countries where validated)
- Evaluation of safety in patients treated with KOVALTRY for one year
- Describe approach to PK dosing and collection of KOVALTRY PK data if performed

9. Research methods

9.1 Study design

This is a multinational, open label, prospective, non- interventional, single arm Phase 4 study in previously treated male patients with moderate to severe Hemophilia A (≤ 5% FVIII:C) receiving KOVALTRY. The study will be conducted in North America, Europe, and Asia.

The study will start after KOVALTRY has been authorized and made commercially available in the countries involved in the study with a recruitment period of 2 years.

All patients prescribed KOVALTRY for a medically appropriate use, fulfilling the selection criteria and consenting to participate, are eligible for enrollment into the study. Patients will be followed up for an observation period of 1 year or until the end of the treatment with KOVALTRY. Patient's clinical information will be documented at time of the initial visit and thereafter during routine clinic visits according to local clinical practice. Additionally, patients will enter data on injections and bleeds directly into the electronic data capture (EDC) system on a monthly base via a secure web portal or via paper data capture form where applicable.

9.1.1 Primary endpoint(s)

The primary endpoint is:

- Proportion of patients on 2x and 3x weekly prophylaxis at end of observation period

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

- Annualized number of reported bleeds (total, spontaneous, joint and trauma)
- Prophylaxis dosing by age group and country
- Change in prophylaxis dosing frequency and reason for change (study start to end of observation period)
- The total annualized factor consumption
- Physician decision determinants of prophylaxis regimen
- Change from baseline to end of observation period in treatment satisfaction (Hemo-SAT)
- Change from baseline to 6 months and end of observation period in Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (VERITAS-PRO)
- Occurrence of adverse events (AEs) and serious adverse events (SAEs)
- Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life and in-vivo recovery)

9.1.3 Strength of Study design

A prospective cohort design was chosen in order to reflect real world characterization of prophylaxis dosing regimen used in children and adults with moderate to severe Hemophilia A (≤ 5% FVIII:C). The prospective nature of the study will allow for the accurate measurement of exposure variables with the potential measurement of multiple outcomes as defined by the primary and secondary endpoint measures.

9.2 Setting

9.2.1 Eligibility

Previously treated male patients with moderate to severe (≤ 5% FVIII:C) hemophilia A, with ≥ 50 exposure days (EDs) to any FVIII product and no history of inhibitors who have been prescribed KOVALTRY for a medically appropriate use will be eligible to be included into this study. Indications and contraindications according to the local market authorization should carefully be considered.

Patients will be enrolled after the decision for treatment with KOVALTRY has been made by the physician and patient or legal representative.

9.2.2 Inclusion criterion/criteria

- Male patients diagnosed with moderate to severe hemophilia A (≤ 5% FVIII:C)

- Any age
- ≥ 50 exposure days (EDs) to any FVIII product
- Patients with no history of inhibitors
- Currently on (started within 3 months of study enrollment) or plan to start prophylaxis therapy with KOVALTRY
- Written informed consent

9.2.3 Exclusion criterion/criteria

- Patients participating in an investigational program with interventions outside of routine clinical practice
- Patients with an additional diagnosis of any bleeding/coagulation disorder other than hemophilia A

9.2.4 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient can refuse to further participate or may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether he agrees that the data collected so far can be used. In case the patient does not agree, these data will not be used for any patient level analysis of study data. This includes safety data with the exception that data already captured in the company's safety database will be kept. However, data which are relevant for primary outcomes might be displayed on an aggregated level to assess a potential bias. In case a patient would like to withdraw the consent given earlier, he should inform his doctor and the site should document the withdrawal in the Case Report Form as well as in the patient medical records.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

The eligibility criteria have been selected to allow for a broad representation of patients within the study. The study will enroll previously treated moderate to severe hemophilia A patients. When combined, patients with moderate to severe disease represent approximately 75% of the patient population with hemophilia. Prophylaxis therapy is recommended standard of care for patients with severe disease and those with moderate disease with severe bleeding phenotype. By enrolling eligible patients with moderate to severe disease with or without other comorbidities, the study will be representative of real world. Previously untreated hemophilia A patients are not eligible for this study as safety of KOVALTRY in this patient population has not been established. Given the incidence rate of hemophilia A, 1 in 5000 live male births, PUPs represent ~ 2% of hemophilia patient population. Thus the study population is representative of moderate to severe hemophilia A population even when PUPs are excluded.

9.2.7 Visits

The physician documents an initial visit, follow-up visit(s) and a final visit for each patient in the EDC system. Follow-up visit(s) are documented as they occur per routine practice. The study protocol does not define exact referral dates for those visits.

Enrollment / Initial visit

Once a patient is found eligible for inclusion, the physician will inform the patient about the study. This will include discussing the consent form and asking the patient/legal representative to read and – when agreeing to participate – sign the informed consent.

The following information will be collected by reviewing the patient chart, or during the clinical examination:

- Date of first visit
- Demographics (age, ethnic background)
- General medical/surgical history
- Hemophilia medical and treatment history (date of diagnosis, age at initiation of prophylaxis therapy, family history of hemophilia, family history of inhibitors)
- Bleed history prior to study entry (total number of bleeds & joint bleeds in past 6 months)
- Date at initiation of prophylaxis treatment with KOVALTRY
- Length of time on continuous prophylaxis
- Most recent FVIII product used (prior to prophylaxis with KOVALTRY)
    - Start date, stop date, dose and dosing frequency
- KOVALTRY prophylaxis regimen prescribed (dose, dosing frequency, length of period covered by prescription, reason for selection of dose/dosing frequency)
- Concomitant medication
- Physical examination
    - Weight
    - Height
    - Vital signs
- Number of target joints at study entry (Target joint is defined as a joint in which 3 or more spontaneous bleeds have occurred within a consecutive 6-month period) [2]
- Any KOVALTRY PK analysis performed as per routine clinical practice

Follow-up visit(s) during treatment

The clinician follow-up assessments will be completed in the EDC system. These assessments do not require the scheduling of any additional office visit(s) outside of the standard of care.

- Date of follow-up visit
- Change in dose and/or dosing frequency of KOVALTRY with the reason for change
- Changes in concomitant medication
- Physical examination
    - Weight
    - Height
- Number of target joints (Target joint is defined as a joint in which 3 or more *spontaneous bleeds have occurred within a consecutive 6-month period)* [2]
- Inhibitor measurement
- Adverse events

Final Visit and End of Observation period

The final data collection (last visit) is after completion of 12 months of prophylaxis treatment with KOVALTRY or at discontinuation of therapy (whatever is earlier). At this final observation point, the patient's condition and a treatment assessment will be documented as a follow-up visit with additional information on:

- Regular end of observation, or
- Discontinuation of observational period with the reason for discontinuation (e.g. end of therapy with KOVALTRY)
- Reason if product is changed

9.2.8 Patient reported outcomes

The questionnaires (Veritas PRO, Hemo-SAT) will be completed by patient via a separate portal within the EDC system. The event diary and prophylaxis injection diary will also be completed by patient via a separate portal within the EDC system or via paper data capture form where applicable.

Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis (Veritas-PRO)

This is a prophylactic treatment adherence scale. It is a self-/parent-report questionnaire consisting of 24 questions on six (four-item) subscales (time, dose, plan, remember, skip, communicate) that takes approximately 10 min to complete. Patient completes Veritas-PRO questionnaire at study entry, after 6 months and at end of study.

Hemophilia treatment satisfaction questionnaire (Hemo-SAT)

This is a haemophilia-specific treatment satisfaction questionnaire. Hemo-SAT questionnaire has a version for adults and for children consisting of 34 items pertaining to 6 dimensions (ease & convenience, efficacy, burden, specialist/nurses, center/hospital, general satisfaction). Patient completes Hemo-SAT questionnaire at start and end of study.

Patient event diary

For the duration of the study, patients will document any bleeding event and all events that require an injection additionally to their prophylaxis regimen in a diary. In order to get complete data, monthly reminder to document the events will be sent out to the patient.

Patient prophylaxis injection diary

For the duration of the study, patients will document all injections. Monthly reminder to document the injections will be sent out to the patient, if applicable.

9.3 Variables

The physician collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the physician collects treatment related data during initial visit and follow-up visit(s). The physician documents the study-relevant data for each patient in the EDC system. The CRF is available upon request (see Table 3: List of stand-alone documents, Annex 1).

Table 3: Tabulated overview on variables collected during the study

Variables	Initial visit	Follow-up visit(s)	Final visit
Demography	X		
Co-morbidities (medical history, concomitant diseases)	X		
Disease history	X		
Prior medication	X		
Concomitant medication	X	X	X
Exposure/treatment	X	X	X
Physical examination (weight, height)	X	X	X
Number of target joints	X	X	X
KOVALTRY PK data[a]	X	X	X
Adverse Events	X	X	X
Inhibitors		X	X
Veritas PRO questionnaire[b]	X	X	X
Hemo –SAT questionnaire[c]	X		X
Patient event diary[d]	X	X	X
Patient prophylaxis injection diary[e]	X	X	X
End of study documentation			X

a. KOVALTRY PK analysis is at physicians discretion
b. Completed at initial, after 6 months and at end of study by the patient
c. Completed at start and end of study by the patient
d. Completed during the complete observation period by the patient in case of an event requiring an injection
e. Completed during the study by the patient

9.3.1 Variables to determine the primary endpoint(s)

The variable for primary objective is:

- Prophylaxis regimen (2x or 3x weekly prophylaxis) at end of observation period

9.3.2 Variables to determine the secondary endpoint(s)

The outcome variables for secondary objectives are:

- Number of reported bleeds (total, spontaneous, joint and trauma)
- Prophylaxis regimen per age group and country
- Factor consumption: prophylaxis dose per/kg per injection overall per age group and country

- Physician decision determinants of prophylaxis regimen
- Score for treatment satisfaction (Hemo-SAT)
- Score for treatment adherence (VERITAS-PRO)
- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of events of special interest, such as inhibitors
- Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life, in-vivo recovery)

9.3.3 Demography

For demographic / socio-demographic assessment, the following data will be recorded:

- Year of birth
- Age
- Sex
- Race (e.g. White, Black, Asian, not reported) (only where legally permitted)
- Ethnicity (e.g. not Hispanic or Latino, Hispanic or Latino, not reported) (only where legally permitted)

9.3.4 Disease history

Disease history describes any medical findings that are relevant to the underlying disease and were present before inclusion into the study. Findings and diagnosis meeting the criteria listed below have to be documented:

- Date of diagnosis (at least year)
- Family history of hemophilia
- Family history of inhibitors
- Factor VIII level at initial diagnosis
- Age at start of prophylaxis therapy
- Patient history of inhibitors
- Number and location of target joints

9.3.5 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, as they pertain to the study indication, that were present before start of therapy with KOVALTRY independent of whether or not they are still present. They have to be documented in the Medical History / Concomitant Diseases section.

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

9.3.6 Prior and concomitant medication / treatments

All medication taken /treatments obtained before study start (initiated and stopped before study start) is termed prior medication /treatments. Prior medication /treatments meeting the criteria listed below are considered to be relevant to the study indication have to be documented:

- Hemophilia treatment regimen at inclusion (prophylaxis or episodic)
    - Factor VIII concentrate
    - Dose
    - Dosing frequency
- Concomitant medications for comorbid conditions

All medication taken /treatments obtained in addition to the KOVALTRY for any indication (either initiated before study start or during the study) is termed concomitant medication/treatments.

Information to be collected for medication includes: trade name, total daily dose, start date, stop date, and indication.

9.3.7 Exposure / treatment

Data collected by the physician includes:

- Date of first dose
- Planned/prescribed dose
- Planned/prescribed dosing frequency/week
- Reason for selection of dose/dosing frequency at baseline (physician to choose & rank in order of importance the top three reasons from predefined list (see Annex 3)
- PK assessment (see Annex 4)
- Change in dose and/or dosing frequency from prior visit
- Reason for change in dose/dosing frequency
- Change to another FVIII product (if applicable) and reason for change

For data collection by the patient two sources will be used:

- Patient event diary
- Patient prophylaxis injection diary

Patient event diary

Any bleeding event is documented in the patient event diary including:

- Date of and type of bleed (spontaneous, joint and trauma)
- Severity of bleed (mild, moderate, severe) (see Annex 5)

- Date of treatment
- Number of injections and dose per injection per bleeding event
- Response to treatment (excellent, good, moderate, no response) (see Annex 5)

Any other event requiring an injection is also documented in the patient event diary including:

- Reason for the injection (e.g. surgery)
- Date of treatment
- Number of injections and dose per injection per event

Patient prophylaxis injection diary

Data collected by the patient in the patient prophylaxis injection diary includes:

- Number of prophylaxis injections and dose per injection per day

9.3.8 Inhibitor measurement

Data documented by physician, if collected, include:

- Date of measurement
- Inhibitor (no/yes)
- Titer of inhibitor (Bethesda Units)

9.4 Data sources

The physician collects historic data (demographic and clinical characteristics) from medical records if available. Likewise, the physician collects treatment related data during visits that take place in routine practice. The patient documents bleeding events and all other events that require injections in an event diary. The patient additionally documents prophylaxis injections in a prophylaxis injection diary. Validated patient questionnaires (Hemo-SAT, Veritas PRO) are used as sources for the patient assessment on satisfaction and treatment adherence.

9.5 Study Size

A sample size of 350 patients is planned. Assuming a drop-out rate of 10%, 315 patients will be available for the analysis. The sample size assessment is based on the precision of estimates for the primary objective which is given by the length of the 95% confidence intervals for the observed proportion of patients treated with either prophylaxis regimen (twice or three times per week). The actual length of the confidence interval will depend on the observed proportion. However, with a sample size of 315 patients the maximal half-width of the 95% confidence interval for any proportion will be 0.06 (6%) with a probability of >99%.

(The procedure ‘proc power’ in SAS 9.2 was used to calculate the probability of reaching an exact Clopper-Pearson confidence interval with the specified precision.)

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request (Table 3: List of stand-alone documents, Annex 1). Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request (see Table 3: List of stand-alone documents, Annex 1).

For information on quality control, refer to section 9.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses will be of explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline, if applicable. In case of low subject number for single variables, listings will be provided instead of summary tables.

All statistical details including calculated variables, and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock.

All analyses will be performed for the total study population (overall analysis) and by prophylaxis dosing regimen and hemophilia severity (if patient numbers are sufficient). The prophylaxis dosing regimen as prescribed by the investigator will be used for stratification. In case of changes of the regimen during study, patients will be analyzed in a separate category. Separate analyses for each participating country will be provided if patient numbers are sufficient and if required for local reasons. Further subgroups (e.g. age, baseline characteristics) will be specified in the SAP. Patients with documented initial dose of prophylaxis treatment with KOVALTRY will be included in the analysis. This will include patients who were not followed up for one complete year of prophylaxis.

Sample size and disposition information including reasons for discontinuation will be displayed in a frequency table.

Depending on the number of patients who discontinued prematurely sensitivity analyses including the number of patients who completed 1 year of prophylaxis treatment will be done.

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

It is planned to have an interim analysis after 30 % of the planned study population is enrolled and has completed 6 months of treatment. The interim analysis will be based on a treatment

period of 6 months for all patients. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

9.7.2 Analysis of demography, disease details, prior and concomitant medication and other baseline data

Demographics and baseline disease characteristics will be described by frequency tables or summary statistics. Some continuous variables will be categorized and presented in frequency tables in addition to summary statistics. Categories will be defined in the SAP.

Number of bleeds prior to study will be analyzed in total and by kind of pretreatment (on-demand vs. prophylaxis).

Prior and concomitant medications and medical history will be presented in incidence tables.

9.7.3 Analysis of treatment data

Summary statistics for the treatment duration will be provided.

For the analysis of treatment administration for bleeds the following variables will be calculated based on event diary information and analyzed by summary statistics: number of injections for bleeds, annualized number of injections for bleeds, total dose for bleeds (IU), annualized total dose for bleeds (IU/year), dose per kg for bleeds (IU/kg), annualized dose per kg for bleeds (IU/kg/year), total dose per injection for bleeds (IU/injection), dose per kg per injection for bleeds (IU/kg/injection), total dose per bleed (IU/bleed), dose per kg per bleed (IU/kg/bleed). The number of bleeds treated with 1, 2, … injections will be provided in a frequency table. All variables will be calculated separately for all bleeds, spontaneous bleeds, joint bleeds, and trauma bleeds.

For the analysis of other events requiring injection (e.g. surgery), total dose (IU) and annualized total dose (IU/year) will be calculated and summary statistics will be presented. In addition, a listing presenting data on event level will be provided.

The following variables will be calculated and summary statistics will be presented for the analysis of prophylactic treatment administration: number of prophylaxis injections, annualized number of prophylaxis injections, total dose for prophylaxis (IU), annualized total dose for prophylaxis (IU/year), dose per kg for prophylaxis (IU/kg), annualized dose per kg for prophylaxis (IU/kg/year), total dose per injection for prophylaxis (IU/injection), dose per kg per injection for prophylaxis (IU/kg/injection), total dose per week (IU/week), dose per kg per week (IU/kg/week).

The proportion of patients who documented a mean of 2 and a mean of 3 prophylaxis injections in the injection diary will be presented by month and overall in a frequency table.

The overall annualized total consumption (IU/year) combining consumptions for prophylaxis, bleeds, and other events will be presented.

Sensitivity analyses will be done in case of incomplete prophylaxis injection diaries (exclusion of patients with incomplete documentation and/or exclusion of undocumented periods from annualizations).

9.7.4 Analysis of primary outcome

The proportions of patients per prophylaxis regimen (including 2x /week and 3x/week) at end of the observation period and 95% confidence intervals for the proportions will be presented. The regimen as prescribed by the investigator will be used. Results will be stratified by age group and country.

9.7.5 Analysis of secondary outcome(s)

Summary statistics for the reported as well as the annualized number of total, spontaneous, joint and trauma bleeds will be presented. The proportion of patients without any bleed and without any joint bleed will be provided. Frequency information for the categorized number of joint bleeds will be shown.

Summary statistics for the prescribed prophylaxis dose will be provided. The prescribed dose per week for prophylaxis will be calculated and presented in summary statistics. Stratifications by age group and country will be shown.

A transition table will be provided to compare baseline regimens with end of study regimens as prescribed by the investigator.

The physician determinants for choice of a prophylaxis regimen will be provided in frequency tables, separately for each rank and overall.

Changes in prescribed frequency and/or dose and reasons for change will be listed, as well as reasons for change of FVIII product. If the number of changes is high, frequency tables will be provided.

Appropriate scores for questionnaire results and changes from baseline will be analyzed by summary statistics. Further details of the analysis will be described in the SAP.

Secondary outcomes related to treatment data are described in section 9.7.3.

A frequency table will be provided for approaches to PK dosing. Summary statistics will be displayed for PK measurement results on patient level, if numbers are sufficient (FVIII trough levels, FVIII peak levels, in-vivo recovery). Otherwise, listings will be provided.

9.7.6 Analysis of safety data

An overview table displaying all adverse events will be created. This overview table will provide overall incidences for: any event, any serious event, any drug related event, maximum intensity of events, events with outcome death, events leading to discontinuation of study drug, events related to inhibitor development.

All subsequent tables will show incidences based on MedDRA preferred terms within the corresponding system organ class. This will be done for all adverse events, serious adverse events, drug-related adverse events, serious drug-related adverse events, adverse events causing discontinuation of study drug, adverse events with outcome death, and maximum intensity of adverse events. Sensitivity analyses will be conducted as needed.

A detailed listing will be provided for adverse events related to the development of an inhibitor.

9.8 Quality control

9.8.1 Data quality

Before study start at the sites, all physicians will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Physicians will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Table 3: List of stand-alone documents, Annex 1).

Medical Review of the data will be performed according to the Medical Review Plan (MRP). The purpose of the Medical Review is to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study. Detailed information on the Medical review will be described in the MRP, which is available upon request see Table 3: List of stand-alone documents Annex 1).

National and international data protection laws as well as regulations on observational studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [9]. The documentation is available upon request (Table 3: List of stand-alone documents, Annex 1).

9.8.2 Quality review

In a subset of patients (at least 5% of key data at approximately 10% of study sites or 10% of patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request (see Table 3: List of stand-alone documents, Annex 1).

9.8.3 Storage of records and archiving

The marketing authorization holder (MAH) will make sure that all relevant documents of this non-interventional study including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Other instructions for storage of medical records will remain unaffected.

The physicians participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the MAH and/or local

authorities. It is recommended to also store documents for a retention period of at least 15 years.

9.8.4 Certification/qualification of external parties

A physician meeting will be organized to provide general training on the study protocol, safety reporting procedures, data collection requirements and general EDC system overview.

9.9 Limitations of the research methods

In general data collected in this study may suffer from biases (either by systematic differences in data recording or different interpretation of information on exposure or outcome for different patients, reporting as well as selection bias). Information bias with respect to injection data occurs due to manually injection. Additionally, adherence to treatment is prone to be biased by adherence to documentation. Further, prospective studies are prone to bias from loss to follow-up or change in methods over time. Since treatment is only altered by bleeding episodes, there is dosing information that will be obtained during these additional time points which in combination with the injection diary allows for a strong estimate of treatment patterns and adherence.

10. Protection of human subjects

10.1 Ethical conduct of the study

This study is an observational study where KOVALTRY is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [10]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [11], ENCePP [12]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on good pharmacovigilance practices (GVP [13], [14]) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A [14].

10.3 Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC / IRB is required, documented approval from appropriate IECs / IRBs will be obtained for all participating centers prior to study start.

When necessary, an extension, amendment or renewal of the IEC / IRB approval must be obtained and also forwarded to the MAH. The IEC / IRB must supply to the MAH, upon request, a list of the IEC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to applicable laws and regulations.

10.4 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient/legal representative in writing. In countries where required by law or regulation, the physician must have the IECs / IRB written approval / favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.5 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the physicians and, respectively, the institutions involved provide sufficient protection for both patient and physician.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

Bayer as well as all physicians ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The physicians are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the MAH. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the MAH. Study findings stored on a computer will be stored in accordance with local data protection laws.

The physician will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the physician.

11. Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [13].

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator product
- Off label use, occupational exposure, lack of drug effect, medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)
- Product exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a product is implied by the use of the term “adverse event”.

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An AR is any AE judged as having a reasonable suspected causal relationship to <product>.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)

Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the product caused disorientation that may have caused the event; cancer developing a few days after the first product administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

The temporal sequence from product administration: The event should occur after the product is given. The length of time from product exposure to event should be evaluated in the clinical context of the event.

Recovery on product discontinuation (de-challenge), recurrence on product re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.

Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication or treatment: The other products the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is ‘sudden death’ where no cause has been established. In this instance, ‘sudden death’ should be regarded as the AE and ‘fatal’ as its reason for being ‘serious’.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as serious, unless the admission is:

- planned before subject's inclusion in the study (i.e. elective or scheduled surgery) or
- ambulant (shorter than 12 hours) or
- part of the normal treatment or monitoring of the studied disease (i.e. not due to a worsening of the disease)

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a SAE dependent on

clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

Events of Special Interest:

The following events of special interest are monitored and reported:

- Inhibitor development: inhibitors needs to be assessed as mandatory serious and reported to MAH within 24 hours of awareness.
- Hypersensitivity reactions including skin related and systemic reactions, such as anaphylactic reactions, (seriousness should be a case by case decision)
- Thrombosis and thromboembolic events, such as cardiovascular events

Any bleeding event occurring during the study will not be documented as AE, as long as it is not considered to have a 'causal relationship' to the product. The events are captured in the assessment of effectiveness. However, if the bleed requires hospitalization, it must be reported as a SAE.

11.2 Collection

Starting with the first application of KOVALTRY after enrollment into the study, all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / EDC system and forwarded to the MAH within 7 calendar days *(for EU countries or if required by local regulations of participating country)* / 60 days *(for countries outside the EU)* of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness). For each AE, the physician must assess and document the seriousness, duration, relationship to product, action taken and outcome of the event.

If a pregnancy occurs during the study, although it is not a serious adverse event itself, it should be documented and forwarded to the MAH within the same time limits as a serious adverse event. The result of a pregnancy will be followed-up according to applicable Bayer SOPs. Any data on abnormal findings concerning either the mother or the baby will be collected as adverse events.

The documentation of any AE / SAE ends with the completion of the observation period of the patient.

As long as the patient has not received any KOVALTRY within the frame of the study AEs /SAEs do not need to be documented as such in this observational study. However, they are part of the patient's medical history.

For any serious product-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs will be followed up and documented. Where required, physicians might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with KOVALTRY that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI [14]) and according to national regulations by the MAH; however, all physicians must obey local legal requirements.

For non-serious ARs occurring under non-Bayer products the physician has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, physicians might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the MAH for SAEs related KOVALTRY treatment; however, all physicians must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer products the physician has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an physician, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to section 11.2 and 11.3). If a potential safety signal is

suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov" <and in in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”>. Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [15], STROBE [16]). No individual physician may publish on the results of this study, or their own patients, without prior approval from the MAH.

13. References

[1] National Hemophilia Foundation, https://www.hemophilia.org/About-Us/Fast-Facts. Accessed June 2015.

[2] Srivastava A et al. Haemophilia, 2013. 19: e1–e47.

[3] Vogel JH et al. Hemophilia 2010 World Congress, Buenos Aires, Argentina, July 10–14, 2010.

[4] Saxena K et al. International Society on Thrombosis and Hemostasis (ISTH), Amsterdam , Netherlands, June 29–July 4, 2013.

[5] Kavakli K et al. Journal of Thrombosis & Hemostasis. Accepted Article', doi, 10.1111/jth.12828.

[6] Ljung R et al. Haemophilia. 2015 Dec 9. doi: 10.1111/hae.12866. [Epub ahead of print].

[7] Shah A et al. Haemophilia, 2015 Nov;21(6):766-71. doi: 10.1111/hae.12691. Epub 2015 May 8.

[8] Data on File. Bayer HealthCare Pharmaceuticals.

[9] FDA, "Code of Federal Regulations.," *Title 21, Volume 1. 21CFR11: Electronic records; electronic signatures.,* 01 Apr 2012.

[10] EU, "Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council," *Official Journal of the European Union,* 20 Jun 2012.

[11] EFPIA, "Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals," Oct 2007.

[12] EMA, "ENCePP guide on methodological standards in pharmacoepidemiology.," 05 Nov 2010.

[13] ICH, "ICH Harmonized Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2D)," Nov 2003.

[14] EMA, "GPV Module VI - Management and reporting of adverse reactions to medicinal products," *Guideline on good pharmacovigilance practices,* 22 Jun 2012.

[15] C. Graf, W. P. Battisti, D. Bridges, V. Bruce-Winkler, J. M. Conaty, J. M. Ellison, E. A. Field, J. A. Gurr, M. E. Marx, M. Patel, C. Sanes-Miller and Y. E. Yarker, "International Society for Medical Publication Professionals. Research Methods & Reporting. Good publication practice for communicating company sponsored medical research: the GPP2 guidelines," *BMJ,* 2009.

[16] E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, "STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin

Epidemiol. 2," *J Clin Epidemiol.*, 2008.

[17] EU, "Eudralex - Volume 9A of the Rules Governing Medicinal Products in the European Union: the Guidelines on Pharmacovigilance for Medicinal Products for Human Use," 2008.

[18] EMA, "GPV Module VIII - Post-authorisation safety studies," *Guideline on good pharmacovigilance practices,* 09 Jul 2012.

[19] EMA, Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products; EMA/873138/2011; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf, 22 Jun 2012.

Annex 1: List of stand-alone documents

Table 3: List of stand-alone documents

Number	Document Name / Reference number	Date	Title
1	tbd	tbd	<Physician list>
2	18559_CRF	tbd	<CRF>
3	tbd	tbd	<EDC System>
4	18559_DMP	tbd	<DMP>
5	18559_SAP	tbd	<SAP>
6	tbd	tbd	<EDC System Validation>
7	18559_QRP	tbd	<QRP>
8	18559_MRP	tbd	<MRP>

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols (Version 2)

Study title:
A **TAURUS**: A Mul***T***inational Ph***A***se IV Study Eval***U***ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Study reference number:
18559

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	9, 10
1.1.2 End of data collection[2]	X	☐	☐	9, 10
1.1.3 Study progress report(s)	☐	X	☐	
1.1.4 Interim progress report(s)	☐	X	☐	
1.1.5 Registration in the EU PAS register	☐	X	☐	
1.1.6 Final report of study results.	X	☐	☐	32

Comments:

This study will be registered in in the EU PAS register prior to submitting for Ethics Committee review.
Results will be disclosed in a publicly available database within the standard timelines

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	7, 10
2.1.2 The objective(s) of the study?	X	☐	☐	7, 8, 12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	X	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	X	☐	☐	22

Comments:

There is no formal hypothesis being tested since this is a real-life evidence non-interventional study

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	X	☐	☐	8, 12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X	☐	☐	13
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	X	☐	

Comments:

Statistical analyses will be of explorative and descriptive nature.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	X	☐	☐	14
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	X	☐	14
4.2.2 Age and sex?	X	☐	☐	
4.2.3 Country of origin?	☐	X	☐	14
4.2.4 Disease/indication?	X	☐	☐	
4.2.5 Co-morbidity?	☐	X	☐	
4.2.6 Seasonality?	☐	X	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	X	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	X	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	X	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	X	☐	
5.5 Does the protocol specify whether a dose-	☐	X	☐	

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
dependent or duration-dependent response is measured?				

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	X	☐	☐	8, 18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	X	☐	

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	X	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	X	☐	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	X	☐	☐	21
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	X	☐	☐	21
8.1.3 Covariates?	☐	X	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	20
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	X	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	X	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	X ☐	☐ X	☐ ☐	21
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	X	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	X	☐	☐	9, 21

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	X	☐	
10.2 Is the choice of statistical techniques described?	X	☐	☐	21-24
10.3 Are descriptive analyses included?	X	☐	☐	21-23
10.4 Are stratified analyses included?	☐	X	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	X	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	X	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	X	☐	☐	23
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	25
11.3 Are methods of quality assurance described?	X	☐	☐	25
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	X	☐	
11.5 Is there a system in place for independent review of study results?	☐	X	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	X	☐	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	X	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	21
12.3 Does the protocol address other limitations?	X	☐	☐	26

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	26
13.2 Has any outcome of an ethical review procedure been addressed?	☐	X	☐	
13.3 Have data protection requirements been described?	X	☐	☐	27

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	X	☐	☐	10

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	32
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	32

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3: Reasons for prophylaxis dosing decision

Select top 3 reasons

- Age
- i.v. access
- Current treatment regimen
- Bleeding history with current treatment regimen
- Prior history of life threatening bleed
- Number of target joints
- Pharmacokinetic data
- Adherence/Compliance history
- Activity level
- Patient/caregiver preference
- Caregiver support
- Insurance coverage (US)
- Institution guidelines
- Country guidelines
- Other: _____

Rank in order of importance with one being the most important and three being the least important

Annex 4: Pharmacokinectic parameters

- Area under the curve (AUC)
- Clearance (Cl)
- Half-life
- FVIII trough
- FVIII peak levels
- In-vivo recovery

Annex 5: Definitions of bleeding severity and response to treatment

Bleeding severity

Mild: superficial skin bleed, oral bleed, very early joint or muscle bleed, no or minimal swelling, only little pain, no or minimal restriction of motion, solved with one injection.

Moderate: more intense pain, additional symptoms like important restriction of motion and swelling, increase of joint temperature may be present

Severe: intense pain with strong restriction of motion, almost no motion possible and important swelling, in general more than 1 injection needed, needs several days for complete resolution or life threatening intracranial or intra-abdominal bleeds

Response to treatment

Excellent: abrupt pain relief and /or improvement in signs of bleeding within approx. 8 h after a single infusion

Good: definite pain relief and/or improvement in signs of bleeding within approx. 8 h after an infusion, but possibly requiring more than one infusion for complete resolution

Moderate: slight beneficial effect within approx. 8 h after the first infusion, usually requiring more than one infusion

No response: no improvement or condition worsens within approximately 8 hours

Annex 6: Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "*R*eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *RoUtine* Prophylaxi*S*.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Michael Kayser

Date, Signature: March 9th, 2016 M. Kayser

Bayer HealthCare

Signature Page - Study Safety Lead

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "*R*eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *RoUtine* Prophylaxi*S*.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Elke Detering

Date, Signature: 04 Mar 16,

Bayer HealthCare

Signature Page - Study Medical Expert

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "*R*eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *RoUtine* Prophylaxi*S*.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Sarah Rybowski

Date, Signature: 8/3/2016 , _____

Signature Page - Study Conduct Responsible

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Monika Brunn

Date, Signature: 8. 3. 2016, Brunn

Signature Page - Study Statistician

Acronym / Title	**TAURUS**: A Mul***T***inational Ph***A***se IV Study Eval***U***ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Claudia Tueckmantel

Date, Signature: 10-Mar-2016, C. Tückmantel

Bayer HealthCare

Signature Page - Study Data Manager

Acronym / Title	**TAURUS**: A Mul***T***inational Ph***A***se IV Study Eval***U***ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Dalila Lakbir

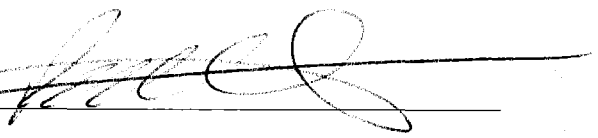
Date, Signature: 8.3.16 , D. Lakbir

Signature Page - Study Epidemiologist

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "***R***eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *Ro**U**tine* Prophylaxi***S***.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Paul Petraro

Date, Signature: 9 March 2016 

Signature Page - Study Health Economics and Outcomes Research (HEOR) Responsible

Acronym / Title	**TAURUS**: A Mul*T*inational Ph*A*se IV Study Eval*U*ating "*R*eal World" Treatment Pattern in Previously Treated Hemophilia A Patients Receiving KOVALTRY (Octocog alfa) for *RoUtine* Prophylaxi*S*.
Protocol version identifier	Version 1
Date of last version of protocol	04 Mar 2016
IMPACT study number	18559
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO Phase IV
EU PAS register number	Study is not registered
Active substance	Hematological/ Octocog alfa /ATC code: B02BD02
Medicinal product	KOVALTRY(Octocog alfa)
Product reference	KOVALTRY

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: Jennifer Pocoski

Date, Signature: 3/15/2016, Jennifer Pocoski