Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

1. 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**.
Report version and date **Author**	Version 1.0, 12 JUL 2021 PPD Bayer
Keywords	Hemophilia A, FVIII, Hematology, Octocog alfa, KOVALTRY
Rationale and background	Hemophilia A is a X-linked, genetic bleeding disorder characterized by deficiency of blood clotting factor VIII (FVIII), with an annual incidence of approximately 1 in 5,000 live male births. KOVALTRY is an unmodified full-length recombinant human blood coagulation factor VIII (rFVIII) product, formulated with sucrose without human or animal derived proteins used during the manufacturing process and an increased N-glycan branching and sialylation that could improve its pharmacokinetics (PK) profile. Safety and efficacy of KOVALTRY given as 2 or 3 times-weekly dose, has been demonstrated in three clinical trials in adult and pediatric hemophilia A patients. KOVALTRY is approved for treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency). It can be used for all age groups. 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	The primary objective of this study was to investigate weekly prophylaxis dosing regimens used in standard clinical practice. In addition the study captured reported bleed rate, pattern of change in KOVALTRY prophylaxis dose and 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.
Study design	Open label, prospective, non-interventional, single arm, Phase IV study.

Setting	The study was conducted in America, Europe, and Asia. The recruitment period was 3.5 years and patients were followed up for an observational period of up to about 2 years or until the end of treatment with KOVALTRY.
Subjects and study size, including dropouts	A sample size of 350 patients was planned. Assuming a drop-out rate of 10%, 315 patients were estimated to be available for the analysis.
Variables and data sources	The variable for primary objective was prophylaxis regimen (2x or 3x weekly prophylaxis) at end of observation period. The variables for secondary objectives were: • 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 (Hemophilia treatment satisfaction questionnaire [Hemo-SAT]) • Score for treatment adherence (Validated Hemophilia Regimen Treatment Adherence Scale [VERITAS-PRO]) • Incidence of adverse events (AEs) and serious AEs (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, assay [one stage or chromogenic assay]) Physicians collected historic data (demographic and clinical characteristics) from medical records, and treatment related data during visits that took place in routine clinical practice. Patients documented injections for prophylaxis, bleeding events and all other events that required injections in a patient diary. Validated patient questionnaires (Hemo-SAT, VERITAS-PRO) were used as sources for the patient assessment on satisfaction and treatment adherence.
Results	A total of 318 patients were enrolled in the study with the full analysis set (FAS) and safety analysis set (SAF) comprising 302 (95.0%), and 313 (98.4%) patients, respectively. The mean

	observation period for the final analysis was 451.4 days for the FAS and 446.5 days for the SAF. All of the 302 patients in the FAS had prior FVIII treatment documented with majority (75.5%) treated with KOGENATE FS/Bayer. The dose frequency of most recent prophylaxis FVIII treatment regimen prior to KOVALTRY was ≤2.5x/week in 107 patients (37.0%) and >2.5x/week in 181 patients (62.6%). The most common reason for the initial switch to KOVALTRY in the FAS was "physician's decision". The most frequent reasons for selection of initial dose/dosing frequency of KOVALTRY were "current treatment regimen" (55.3%), "patient/caregiver preference" (37.1%), "bleeding history with current treatment regimen" (30.8%), "adherence/compliance history" (28.1%), "activity level" (22.2%), "pharmacokinetic data" (19.2%),"number of target joints" (16.2%), "institution guidelines" (14.2%), and "age" (12.9%). In the FAS, 124 patients (41.1%) were on a ≤2.5x/week prophylaxis dosing regimen and 178 patients (58.9%) on a >2.5x/week prophylaxis dosing regimen at baseline. At the end of observation 128 patients (42.4%) were on a ≤2.5x/week prophylaxis dosing regimen and 174 patients (57.6%) on a >2.5x/week prophylaxis dosing regimen, the most frequent treatment regimens being 3 times per week (41.4%) and 2 times per week (35.1%). Analyses of weekly prophylaxis dosing regimen for the overall population and by country and age category (<12 years and ≥12 years) showed that the most common dosing regimens were 3 times per week, 2 times per week and every other day at baseline and at end of observation. The majority of patients in the FAS had no dose / regimen changes until the end of observation: 58.6%, 60.5% and 57.3% for the total, ≤2.5x/week and >2.5x/week at baseline prophylaxis dosing regimen groups, respectively. The majority of patients in the FAS overall and in the subgroups by country and age category (<12 years and ≥12 years) remained in the same dosing regimen (≤2.5x/week or >2.5x/week) at end of observation as at baseline. In line with results for the overall population, analyses of weekly prophylaxis dosing regimen by country and age category (<12 years and ≥12 years) also showed that the majority of patients did not alter their dosing frequency from baseline to end of observation (most frequent being 3 times per week, followed by 2 times per week and every other day at baseline and at end of observation).

	The median number of annualized reported total treated bleeds documented in patient diary was 1.112 (range: 0.00, 57.93), 1.114 (range: 0.00, 57.93) and 1.112 (range: 0.00, 21.49) for the total FAS, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. The median number of annualized reported total joint bleeds was 0.658 (range: 0.00 to 57.93) and 0.506 (range: 0.00 to 19.18), respectively and the median number of annualized reported spontaneous bleeds was 0.682 (range: 0.00 to 57.93) and 0.00 (range: 0.00 to 19.18) in these groups, respectively. There were no differences in the median number of annualized reported trauma and undefined spontaneous / trauma bleeds among the subgroups by prophylaxis dosing regimen at baseline. The median total annualized factor consumption for prophylaxis, bleeds and other events was 3923.002 IU/kg/year, 3383.774 IU/kg/year and 4307.538 IU/kg/year for the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. PK assessments since start of KOVALTRY were not performed for the majority of patients in the FAS: one stage assay (64.6%), chromogenic assay (91.1%), FVIII C activity assessments (56.3%), FVIII half-life assessments (87.7%), area under the curve (AUC) assessments (98.7%), clearance assessments (97.4%), FVIII trough assessments (82.1%), FVIII peak level assessments (81.1%) and FVIII recovery assessments (93.4%). In general, among patients with documented performance of PK assessments, a higher proportion of patients in the >2.5x/week baseline prophylaxis dosing regimen group had 1 or 2 assessments performed than in the ≤2.5x/week group. The satisfaction level (Hemo-SAT A and Hemo-SAT P) among patients in the FAS at one and two years after initial visit did not change drastically. The adherence level among patients in the FAS at half year, one year and two years after initial visit remained relatively stable and no major differences were observed between the subgroups by baseline prophylaxis dosing regimen. However, results should be interpreted with caution due to few documented Hemo-SAT A, Hemo-SAT P and VERITAS questionnaires at the later time points in both the prophylaxis dosing regimen groups. Of the 313 patients in SAF, 96 patients (30.7%) experienced an AE. All reported AEs were treatment-emergent AEs (TEAEs). Three patients (≥ 18 years) were documented with any drug-related AE. At Preferred Term (PT) level, nausea, arthralgia, and pruritus were observed in one patient each (0.4%), but none of these events were serious. The events of nausea and pruritus

	in these two patients led to discontinuation of KOVALTRY treatment. Two fatal AEs were observed in this study (PTs: osmotic demyelination syndrome and pancreatic carcinoma metastatic). The causality of both AEs was not related to the treatment of this study. No AEs related to the development of an inhibitor or positive inhibitor measurement were observed.
Discussion	Data analyzed in this final analysis indicate that prophylaxis treatment regimens before and after initiation of KOVALTRY remained stable for most of the patients during the treatment period. While patients did switch their prophylaxis dosing frequency between baseline and end of observation, many of these switches were temporary. Similarly subgroup analyses for weekly prophylaxis dosing regimen by age and country showed that majority of patients in all countries remained in the same prophylaxis dosing regimen at end of observation as at baseline. This confirms and extends clinical trial results, demonstrating effective prophylaxis with KOVALTRY in a real-world setting. No AEs related to the development of an inhibitor or positive inhibitor measurement were observed. There were two fatal AEs but none were related to the treatment. There were no other safety concerns with KOVALTRY. Based on currently available data, the benefit-risk analysis for KOVALTRY for its indications in hemophilia A is considered favorable.
Marketing Authorization Holder(s)	Bayer AG
Names and affiliations of principal investigators	A list of all investigators is provided in a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request.