Post Authorization Safety Study (PASS) Final Report - 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**.
Report version and date	Version 1.0, 12 JUL 2021
Study type / Study phase	Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS15459
Active substance	Hematological / Octocog alfa / ATC code: B02BD02
Medicinal product	KOVALTRY (Octocog alfa)
Product reference	BAY81-8973
Procedure number	Not applicable
Study Initiator and Funder	Bayer Aktiengesellschaft (AG)
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 is capturing 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.
Country(-ies) of study	Belgium, Canada, Colombia, France, Germany, Greece, Italy, Luxembourg, Netherlands, Slovenia, Spain, region Taiwan and the United States
Author	PPD Bayer

Marketing authorization holder

Marketing authorization holder(s) (MAH)	Bayer AG
MAH contact person	PPD

Confidentiality statement:

Table of contents

Table of tables

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.

2. List of abbreviations

ABR	Annualized Bleeding Rate
AE	Adverse Event
AG	Aktiengesellschaft
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
(e)CRF	(electronic) Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
ED	Exposure Days
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FVIII	Blood clotting/coagulation factor VIII
rFVIII	recombinant blood clotting/coagulation factor VIII
Hemo-SAT	Hemophilia treatment satisfaction questionnaire
HIV	Human Immunodeficiency Virus
ITI	Immune Tolerance Induction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Medical Review Plan
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PK	Pharmacokinetics
PT	Preferred Term
PUP	Previously Untreated Patient
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
TFLs	Tables, Figures and Listings
Veritas-PRO	Validated Hemophilia Regimen Treatment Adherence Scale

US(A)	United States (of America)
WHO DD	World Health Organization Drug Dictionary

3. Investigators

A list of all investigators is provided in a stand-alone document (see Annex 1) which is available upon request.

4. Other responsible parties

4.1 Sponsor contact names

Function:	Study safety lead
Name:	PPD
Function:	Study medical expert
Name:	PPD [1]
Function:	Study conduct responsible
Name:	PPD
Function:	Study statistician
Name:	PPD
Function:	Study data manager
Name:	PPD [1]
Function:	Study epidemiologist
Name:	PPD [1]
Function:	Study health economics and outcomes research (HEOR) responsible
Name:	PPD [1]

Contact details of the responsible parties at Bayer Aktiengesellschaft (AG) are available upon request.

[1] Name within the bracket denotes the predecessor involved in this study according to protocol version 4.1 dated 19 JUN 2019.

4.2 Contract research organization

Contract Research Organization (CRO) contact details:

Kantar Health

Landsberger Straße 284, 80687 Munich, Germany

5. Milestones

Table 1 presents milestones that are planned for the project.

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection (First Patient First Visit)	Q3 2016	14 OCT 2016 IMPACT field ID: 3200	
End of data collection (Last Patient Last Visit)	JUN 2021	01 DEC 2020[2]	Premature end of data collection due to COVID-19 pandemic.[3]
Registration in the EU PAS register	26 SEP 2016	26 SEP 2016	
IEC or IRB approval - Study protocol version 1.0*	20 JUN 2016	First approval: 20 JUN 2016 Last approval: 19 MAY 2017	
IEC or IRB approval - Study protocol version 1.1*	26 JAN 2017	First approval: 26 JAN 2017 Last approval: 26 APR 2018	
IEC or IRB approval -Study protocol version 2.0*	19 FEB 2017	First approval: 19 FEB 2017 Last approval: 26 APR 2018	

[2] Database lock for all countries except Italy was conducted on 02 NOV 2020. For Italy, the database lock occurred on 11 JAN 2021. The database hard lock for the study was done on 01 MAR 2021.

[3] As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy (refer to Bayer Note To File (NTF) dated 15 JUN 2020, Annex 1). Considering the importance of Italy for TAURUS due to the high number of study patients and the improvements in sanitary conditions and operational capacity at the investigational centers, it was justified to continue data documentation in this country. Italy continued data documentation as described in the protocol version 4.1 until Last Patient Last Visit 01 DEC 2020.

Milestone	Planned date	Actual date	Comments
IEC or IRB approval -Study protocol version 3.0*	22 MAR 2018	First approval: 22 MAR 2018 Last approval: 15 NOV 2018	
IEC or IRB approval -Study protocol version 4.0*	10 DEC 2018	First approval: 10 DEC 2018 Last approval: 23 SEP 2019	
First interim analysis	Not applicable	2018	It was planned to have an interim analysis after 30% of the planned study population is enrolled and has completed 6 months of treatment.
Second interim analysis	Not applicable	2019	Additional interim analyses were planned to be performed at least once per year to have interim efficacy and safety information, and also to allow some countries to provide ad-hoc reports to IRBs, clinical sites, administration or ethics committees and publications, if needed. All recruited patients were analyzed in this interim analysis regardless of their time in the study.
Final analysis	Q2 2021	Q2 2021	Premature end of data collection due to COVID-19 pandemic.[4]

[4] As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy (refer to Bayer NTF dated 15 JUN 2020, Annex 1). Thus, the date for final analysis and report was shifted to Q2/Q3 2021.

Milestone	Planned date	Actual date	Comments
Database Clean	JUN 2021[5]	01 MAR 2021	
Interim report 1	2019	Q2 2019	
Interim report 2	2019	Q1 2020	
Final report of study results	Q4 2021	Q3 2021	Planned date is according to protocol version 4.1.[6]

*A complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1) which is available upon request.
COVID-19: Coronavirus Disease 2019, EU: European Union, IEC: Independent Ethics Committee, IRB: Institutional Review Board, PAS: Post Authorization Study.

6. Rationale and background

Hemophilia A is a X-linked, genetic bleeding disorder characterized by deficiency of Blood clotting/coagulation 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 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 blood clotting/coagulation factor VIII (rFVIII) product, formulated with sucrose (3). It has the same amino acid sequence as Kogenate® FS/Kogenate® Bayer but 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 (4, 5). 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) (6, 7, 8). 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.

In LEOPOLD I study, ~ 30% of the study population (adolescents and adults) received KOVALTRY on 2x weekly dosing regimen at physician's discretion, however, the reason for choice of dosing frequency was not captured in the study (6). 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

[5] The database clean was originally planned for JUN 2021, before the study sponsor decided to close the study prematurely in all countries.

[6] As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy (refer to Bayer NTF dated 15 JUN 2020, Annex 1). Thus, the date for final analysis and report was shifted to Q2/Q3 2021.

period (8). The median (Q1; Q3) annualized bleeding rate (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) (6). 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 65 IU/kg compared with a mean weekly dose of 96 IU/kg with the 3-times-weekly regimen (6). 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 (8). Most bleeds occurring during prophylaxis were trauma related and successfully treated with 1 or 2 injections of KOVALTRY (8). 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) (9). Theoretically, the increased half-life seen with KOVALTRY may allow for reduced prophylaxis dosing frequency in some patients.

Analysis of specialty pharmacy data on FVIII usage in 2014 (United States [US] market research) suggest that ~ 20% and ~ 50% of hemophilia patients are prescribed 2x and 3x weekly prophylaxis, respectively, with Kogenate® FS (Data on file, Bayer HealthCare) (10). 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.

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.

7. Research question and objectives

7.1 Primary objective

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

7.2 Secondary objectives

The secondary objectives in this study were 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 (Hemophilia Treatment Satisfaction Questionnaire [Hemo-SAT]) after one year and two years of treatment (in countries where validated and applicable)
- Changes in treatment adherence (Validated Hemophilia Regimen Treatment Adherence Scale [VERITAS-PRO]) after six months, one year and two years of treatment (in countries where validated and applicable)
- Evaluation of safety in patients treated with KOVALTRY for up to two years
- Describe approach to PK dosing and collection of KOVALTRY PK data if performed

8. Amendments and updates

Amendments and changes to the study protocol are summarized in Table 2. For a complete list of changes, see Annex 7 of the study protocol version 4.1 (Annex 1).

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
AM01	13 JAN 2017	Several	Abstract: Country(ies) of study added, population treated updated. Section 9.2.6: Representativeness updated. Section 9.2.8:Information patient reported outcomes updated. Section 9.7.1: Information added for the statistical analyses to address differences in inclusion criteria of different countries and differences in the previously used FVIII products, if applicable. Section 9.7.2: Addition of the most recent FVIII product used in the baseline disease characteristics. Section 9.8.2: Definition of subset of patients for quality review updated. Section 9.9: Limitations of the research methods updated	According to protocol review committee – observational study (PRC-OS) feedback, to specify study population, the limitation and statistical consideration which were caused by local amendment for Spain.

No.	Date	Section of study protocol	Amendment / Update	Reason
AM02	13 JAN 2017	Several	Abstract and Section 9.2.1: Population treated updated. Section 9.2.2: update of inclusion criterion to include KOGENATE Bayer treated patients.	In order to be in accordance with national regulations for observational studies in Spain the patients to be recruited are those with moderate to severe hemophilia A currently treated with KOGENATE Bayer. Local amendment.
AM03	19 JUL 2017	Several	Abstract: Population treated updated to include history of inhibitors. Section 9.1: north America changed to America in the study design. Sections 9.2.1, 9.2.2, 9.2.3: Information updated to include patients with or without history of inhibitors and Immune Tolerance Induction (ITI) treatment in the eligibility and inclusion criteria. ITI treatment at the time of enrollment was excluded. Section 9.2.7: Information on patient history of inhibitors updated for the visit/ initial visit. Section 9.2.8: Electronic Data Capture (EDC) based questionnaires changed to paper in the patient reported outcomes. Section 9.3: Adaption of variable for inhibitor during initial visit. Sections 9.7.1, 9.7.4, 9.7.5, 9.7.6: Addition of history of inhibitors to the analyses.	Global protocol amendment to adapt the eligibility to allow the inclusion for patients with inhibitor history. Subgroup analyses is added in 9.7 Data analysis. Administrative changes including also EU Post-Authorization Study (PAS) register number.

No.	Date	Section of study protocol	Amendment / Update	Reason
AM04	05 FEB 2018	Several	Abstract, Section 9.7: Information on data analysis of patient group on KOVALTRY prior to study start updated. Addition of interim analyses. Section 9.2.2: Inclusion criterion updated for patients currently on or plan to start prophylaxis therapy with KOVALTRY. Section 9.2.7, tabulated overview of variables collected during the study, sections 9.3.6, 9.3.7: Updates for enrollment / initial visits regarding variables (previous treatment, previous KOVALTRY treatment), clarification on last visit, prior and concomitant medication / treatments. Section 9.2.8: Addition of parent/caregiver to fill out Veritas-PRO questionnaire and patients to document all injections in the patient diary. Section 9.3.6: Inclusion of historical KOVALTRY treatment regimen and its changes in prior and concomitant medication/ treatments. Section 9.7.1: Updated statistical considerations to include tables stratified by subgroups of patients with less versus more than 3 months on KOVALTRY prior to the study as well as performance of sensitivity analysis to investigate whether there are difference in outcomes within these subgroups. Also inclusion of additional interim analyses to be performed once per year.	Global protocol amendment to adapt the inclusion criterion "Currently on (started within 3 months of study enrollment) or plan to start prophylaxis therapy with KOVALTRY" to "Currently on or plan to start prophylaxis therapy with KOVALTRY" to allow centers to recruit also patients who have been treated with KOVALTRY more than three months. Addition of subgroup and sensitivity analysis for patients with KOVALTRY less than 3 months versus more than 3 months on KOVALTRY prior to the study; Addition annual interim analysis; Adaption on description on patient questionnaires analysis. Addition/updates of collected variables. Update of Limitations of the research methods regarding "new user" group (<3 months use at enrollment) and "prevalent user" group (>3 months use at enrollment). Administrative changes/clarifications in patient reported outcomes, study timelines, participating countries and study core team members, data sources, list of stand-alone documents.

No.	Date	Section of study protocol	Amendment / Update	Reason
			Section 9.4: Updated sentence in data sources to combine wording into one paragraph for patient diary. Sections 9.7.2, 9.7.4, 9.7.5: Analyses for baseline characteristics, primary and secondary outcomes updated to include duration of KOVALTRY treatment before study. Section 9.9: Limitations of the research methods updated.	
AM05	12 NOV 2018	Several	Abstract: Countries of study updated, inclusion of data collection on two years after treatment for Hemo-SAT and Veritas-PRO questionnaires, addition of one stage or chromogenic assay, updated milestones. Section 6: Last Patient First Visit (LPFV) in DEC 2019, end of data collection in JUN 2022 and final report on study results in Q4 2022. Section 8.2: updated secondary objectives to include data on Hemo-SAT, Veritas-PRO and safety two years after treatment. Section 9.1: updated study design to extend recruitment period to 3.5 years and follow-up observation period to 2 years. Sections 9.1.2, 9.3, 9.3.2: updated secondary endpoints to change from baseline to one year and two years for Hemo-SAT and Veritas-PRO analyses, addition of one stage and chromogenic assay.	Global protocol amendment to prolong patient's enrollment for one year and observational period from one year to two years with the aim to reach planned patient target. Collect Veritas and Collect Hem-SAT patient questionnaire additionally at two years. Additional data relating to KOVALTRY PK added.

No.	Date	Section of study protocol	Amendment / Update	Reason
			Section 9.2.8: updated patient reported outcomes to include data on Hemo-SAT and Veritas-PRO one and two years after treatment (end of study). Section 9.7.1: updated statistical considerations to summarize data from patients who completed one year of observation before AM05 and did not join the study for the second year. Section 9.9: Limitations of the research methods updated to consider the fact that not all patients who have completed one year follow up could be extended to two years, also affecting the patient diary data.	
Update 1	27 SEP 2019	Several	Abstract, section 8.2, section 9.1, section 9.2.7, section 9.2.8, section 9.7.1, : Adaptions due to timeline changes. Section 6: End of data collection in JUN 2021, final report of study results in Q4 2021. Section 9.2.7: Deletion of target joints from follow-up visits in accordance with AM03. Sections 9.7.3 and 9.7.4: updated analysis of treatment data for inclusion of patients who reached 1 year and 2 years of treatment duration. Section 9.9: Limitations due to the timeline changes were added.	Administrative changes and adaption in several sections due to operational timeline adaption.

9. Research methods

9.1 Study design

This was 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.

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 allowed for the accurate measurement of exposure variables and multiple outcomes as defined by the primary and secondary endpoint measures. All patients prescribed KOVALTRY for a medically appropriate use, fulfilling the selection criteria and consenting to participate, were eligible for enrollment into the study. Patients were to be followed up for an observation period of minimum 1 up to about 2 years or until the end of the treatment with KOVALTRY.[7] Patient's clinical information was documented at time of the initial visit and thereafter during routine clinic visits according to local clinical practice. Additionally, patients entered data on injections and bleeds in a patient diary.

As a consequence of the Coronavirus disease 2019 (COVID-19) pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy. This decision had no impact on the safety, physical or mental well-being of the study participants. The impact on the primary objective was considered to be minor since all patients were to be included in the analysis. The actual observation period of the prematurely discontinued patients was considered to be long enough to allow a meaningful interpretation of the statistical results (refer to Bayer note to file [NTF] dated 15 JUN 2020, Annex 1).

9.1.1 Primary endpoint

The primary endpoint was:

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

9.1.2 Secondary endpoints

The secondary endpoints were:

- 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

[7] As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy (refer to Bayer NTF dated 15 JUN 2020, Annex 1).

- Change from baseline to one year and two years[8] in treatment satisfaction (Hemo-SAT)
- Change from baseline to six months, one year and two years[9] in treatment adherence VERITAS-PRO
- Occurrence of adverse events (AEs) and serious AEs (SAEs)
- Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life, in-vivo recovery and assay [one stage or chromogenic assay][10])

9.2 Setting

The study was conducted in America, Europe, and Asia. The study started after KOVALTRY was authorized and made commercially available in the countries involved in the study with a recruitment period of 3.5 years[11].

A sample size of 350 patients was planned.

The physician documented an initial visit, follow-up visit(s) and a final visit for each patient in the Electronic Data Capture (EDC) system. Follow-up visit(s) were documented as they occurred per routine practice. The study protocol did not define exact referral dates for those visits (see study protocol version 4.1, section 9.2.7, Annex 1). The final data collection (last visit) was after a minimum of 1 year or after up to about 2 years[12] of observational period in the study[13] or at discontinuation of therapy (whatever is earlier). Paper questionnaires (Veritas PRO, Hemo-Sat A [adult] and Hemo-Sat P [parent]) and diary were to be completed by the patient where applicable (see study protocol version 4.1, section 9.2.8, Annex 1).

Table 3 presents an overview of different variables documented during the study.

[8] Global protocol amendment (AM05, 12 NOV 2018) to collect Hemo-SAT patient questionnaire additionally at two years.

[9] Global protocol amendment (AM05, 12 NOV 2018) to collect VERITAS patient questionnaire additionally at two years.

[10] Global protocol amendment (AM05, 12 NOV 2018) to add data of one stage or chromogenic assay relating to KOVALTRY PK.

[11] Global protocol amendment (AM05, 12 NOV 2018) to update study design to extend recruitment period to 3.5 years.

[12] Global protocol amendment (AM05, 12 NOV 2018) to update follow-up observation period to 2 years.

[13] As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy (refer to Bayer NTF dated 15 JUN 2020, 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 and treatment 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	X
Veritas PRO questionnaire[b]	X	X	X
Hemo-SAT questionnaire[c]	X	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 physician's discretion
b. Completed at initial visit, after 6 months, 1 year and at end of study by the patient
c. Completed at start, 1 year 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 Subjects

9.3.1 Eligibility

Previously treated male patients with moderate to severe (≤5% FVIII:C) hemophilia A, with ≥50 exposure days (EDs) to any FVIII product and with or without history of inhibitors who have been prescribed KOVALTRY for a medically appropriate use were eligible to be included into this study. Indications and contraindications according to the local market authorization were to be carefully considered.

Patients were enrolled after the decision for treatment with KOVALTRY had been made by the physician and patient or legal representative.

9.3.2 Inclusion criterion/criteria

- Male patients diagnosed with moderate to severe hemophilia A (≤5% FVIII:C)
- Any age
- ≥50 EDs to any FVIII product
- Patients with or without history of inhibitors
    - Patient with previous history of inhibitors (after AUG 2017)[14], with at least 2 consecutive negative inhibitor tests and on standard prophylaxis therapy for at least 1 year prior to study entry
    - No current evidence[15] of FVIII inhibitor or clinical suspicion[16] of FVIII inhibitor
- Currently on or plan to start prophylaxis therapy with KOVALTRY
- Written informed consent

9.3.3 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
- Patients on ITI treatment at the time of enrollment

9.4 Variables

9.4.1 Variables to determine the primary endpoint

The variable for primary objective was:

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

9.4.2 Variables to determine the secondary endpoints

The outcome 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 (Hemo-SAT) (11, 12)
- Score for treatment adherence (VERITAS-PRO) (13)

[14] Global protocol amendment (AM03, 19 JUL 2017) to adapt the eligibility to allow the inclusion for patients with inhibitor history.
[15] Evidence of FVIII inhibitor as measured by the Nijmegen-modified Bethesda assay (<0.6 Bethesda units [BU/mL]) or Bethesda assay (<1.0 BU/mL) in 2 consecutives samples.
[16] Documented or clinical suspicion of shortened FVIII half-life (<6 hours).

- Incidence of AEs and 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])

9.4.3 Demography

For demographic/socio-demographic assessment, the following data were to 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)

9.4.4 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 were to be documented:

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

9.4.5 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 were still present. They had to be documented in the Medical History/Concomitant Diseases section.

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

9.4.6 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 and had to be documented:

- Hemophilia treatment regimen at inclusion (prophylaxis or episodic)
    - FVIII concentrate
    - Dose

- Dosing frequency

- Historical KOVALTRY treatment regimen and its changes
  - Concomitant medications for comorbid conditions

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

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

9.4.7 Exposure / treatment

Data collected by the physician included:

- Date of first dose
- Planned/prescribed dose
- Planned/prescribed dosing frequency/week
- Reason for selection of dose/dosing frequency at baseline (physician to choose and rank in order of importance the top three reasons from predefined list)
- PK assessment
- 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 were used:

- Patient event diary
- Patient prophylaxis injection diary

Patient diary

Any bleeding event was documented in the patient diary including:

- Number of prophylaxis injections and dose per injection per day
- Date of and type of bleed (spontaneous, joint and trauma)
- Severity of bleed (mild, moderate, severe)
- Date of treatment
- Number of injections and dose per injection per bleeding event
- Response to treatment (excellent, good, moderate, no response)

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

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

9.4.8 Inhibitor measurement

Data documented by physician, if collected, included:

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

9.5 Data sources and measurement

The physician collected historic data (demographic and clinical characteristics) from medical records if available. Likewise, the physician collected treatment related data during visits that took place in routine practice. The patient documented injections for prophylaxis and 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.

9.6 Bias

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 manual 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 was only altered by bleeding episodes, there is dosing information that was obtained during these additional time points which in combination with the injection diary allowed for a strong estimate of treatment patterns and adherence. The vast majority of the study participants (around 90%) were expected to have been previously being treated with Kogenate or Helixate (same molecules).

With the study protocol amendment version 3, the original “new user” group (<3 months use at enrollment) was complemented with a “prevalent user” group (>3 months use at enrollment). Due to well-known possible selection biases with prevalent users (“attrition of susceptible”, “healthy user effect”) both groups were analyzed also separately and a sensitivity analysis was performed to examine possible duration of use effects on the outcomes.

With the study protocol amendment version 4, patients were to be followed up to two years, if possible. However, about 30% of patients had already completed the study after the initially planned 1-year observation period. Due to the fixed study end date, further patients would be observed for less than 2 years. Thus, the information available after 2 years of treatment would be limited.

9.7 Study size

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. The sample size assessment was based on the precision of estimates for the primary objective which is given by the length of the 95% confidence intervals (CI) for the observed proportion of patients treated with either prophylaxis regimen (twice or three times per week). The actual length of the CI would depend on the observed proportion. However, with a sample size of 315 patients the maximal half-width of the 95% CI for any proportion is 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.)

9.8 Data transformation

Calculated data and transformations are provided in Statistical Analysis Plan (SAP) version 3.0 section 4.6, see Annex 1.

9.9 Statistical methods

9.9.1 Main summary measures

This report describes the final analysis for the study. The statistical analysis is described in detail in the SAP (version 3.0, dated 25 JUN 2020) and can be found in Annex 1 as a stand-alone document.

All variables were 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 [SD], minimum [Min], median, quartiles and maximum [Max]). For categorical variables changes to baseline were presented by means of shift tables, if applicable. Continuous variables were described by absolute value and as change from baseline per analysis time point, if applicable. Selected continuous variables were categorized in a clinically meaningful way (for details see the Appendix of SAP, version 3.0, dated 25 JUN 2020 found in Annex 1 as a stand-alone document). The statistical evaluation was performed by using the software package SAS release 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were performed using MOSTO (version 5 or higher) standard programs, where applicable. The creation of tables followed the standard as described in the document *Global Standards Tables for GNIS.*

All analyses were performed for the total study population based on the respective analysis sets as defined in section 9.9.2.2. Whenever reasonable, data were stratified by subgroups with possible predictive validity.

9.9.2 Main statistical methods

9.9.2.1 General Statistical Considerations

Statistical analyses were purely exploratory and descriptive. The study was not aimed to confirm or reject pre-defined hypotheses. Instead, measures for precision of estimates for observed proportion of patients treated with either prophylaxis regimen (≤2.5 or >2.5 times per week)[17] were provided (i.e. 95% CI).

Stratifications by further subgroups were conducted, if they were medically justified or necessary, to understand propensities in the non-interventional setting. A sensitivity analysis was conducted to investigate if the time on KOVALTRY (>3 or ≤3 months) prior to the study had an influence on outcomes.

All analyses were performed for the total study population and stratified by age group (0 to <6 years, 6 to <12 years, 12 to <18 years, 18 years and above), baseline prophylaxis dosing regimen (≤2.5x per week, > 2.5x per week) and hemophilia severity at initial diagnosis (0 to <1%, 1 to 5%) as well as the

[17] These cut-off values were chosen to distinguish between the label-based regimens 2x/week and 3x/week, while at the same time covering other frequencies in between that might be reported (14).

combination between the two latter parameters as specified in SAP version 3.0, Table 4.2 (see Annex 1). Analysis per country/ region was only to be performed if patient numbers were sufficient and local legal or regulatory requests made it necessary. As a sensitivity analysis, all Tables, Figures and Listings (TFLs) were stratified by pretreatment with KOVALTRY (patients who had been on KOVALTRY prior to baseline up to 3 months versus patients who had been more than 3 months on KOVALTRY prior to baseline). Selected tables were to be additionally stratified by the parameters specified in SAP version 3.0, Table 4.2 (see Annex 1) if patient numbers in the different categories were sufficient (categories could be combined to reach a sufficient number of patients per category).

9.9.2.2 Analysis sets

Full Analysis Set (FAS)

The population used for primary and secondary outcomes is the FAS, which is defined as all patients who fulfill all inclusion and exclusion criteria with documented initial dose of prophylaxis treatment with KOVALTRY and documented end of observation. In detail the FAS comprises all patients who meet the following criteria:

- Male patient diagnosed with moderate to severe hemophilia A (≤5% FVIII:C)
- ≥50 EDs to any FVIII product
- Patient with no history of inhibitors OR patient with previous history of inhibitors, with at least 2 consecutive negative inhibitor tests and on standard prophylaxis therapy for at least 1 year prior to study entry and NO current evidence of FVIII inhibitor or clinical suspicion of FVIII inhibitor
- Until FEB 2018: Currently on (started within 3 months of study enrollment) or plan to start prophylaxis therapy with KOVALTRY
- Since FEB 2018: Currently on or plan to start prophylaxis therapy with KOVALTRY
- Written informed consent
- Only for Spain: Patient previously treated with Kogenate Bayer
- Patient NOT participating in an investigational program with interventions outside of routine clinical practice
- Patient with NO additional diagnosis of any bleeding/ coagulation disorder other than hemophilia A
- Patients NOT on ITI treatment at the time of enrollment
- Initial total weekly dose or dosing frequency of prophylaxis treatment with KOVALTRY documented
- Only for final analysis: End of observation documented

Safety Analysis Set (SAF)

The SAF is applied to safety evaluations. A patient was included in the SAF if he/she:

- Received at least one dose of KOVALTRY (documented by physician or entered in patient diary within study observational period), and
- Has the informed consent signed

9.9.2.3 Population Characteristics

9.9.2.3.1 Patient disposition

All patients screened were tabulated by eligibility inclusion and exclusion criteria. The numbers of patients enrolled and included in the analysis populations were displayed as well as the reasons for exclusion of patients from the analysis populations. The observation period and the main reasons for end of observation were tabulated.

9.9.2.3.2 Demographic and baseline characteristics

Demographics and baseline disease characteristics were described by presenting frequency distributions and/or basic summary statistics for the FAS and SAF. These tables comprise demographics and vital signs, hemophilia medical and treatment history including the most recent FVIII treatment prior to KOVALTRY, number of bleeds prior to study entry and patient inhibitor history and co-morbidities. For details see the list of TFLs in Annex 1.

Any relevant medical findings were summarized using frequency tables on patient basis by classified data. The classification was done according to the Medical Dictionary for Regulatory Activities (MedDRA) coding system using System Organ Class (SOC) and Preferred Term (PT) . Medical findings that were present before baseline (date of initial visit) were classified as prior disease (also findings with missing start date). Diseases which did not stop before baseline (stop date later than date of initial visit, stop date missing or disease 'ongoing') were classified as concomitant disease.

9.9.2.3.3 Concomitant medications

Concomitant medications were categorized by World Health Organization Drug Dictionary (WHO-DD) Anatomical Therapeutic Chemical (ATC) code and summarized by frequency tables for FAS and SAF. Any active treatment not explicitly withdrawn before baseline (date of initial visit) was classified as concomitant therapy. Concomitant medications were displayed on ATC levels 1 and 3.

9.9.2.4 Analysis of Primary Outcome Variable(s)

The primary objective of this study was to investigate weekly prophylaxis dosing regimens (2x or 3x weekly prophylaxis, other) used in standard clinical practice. The proportion of patients per prophylaxis regimen as prescribed by the investigator at study entry and at end of observation were presented with 95% CI for the FAS. In addition, a shift table from study entry to end of observation was also displayed.

The analyses of the primary objective were stratified by the parameters as detailed in section 9.9.2.1.

9.9.2.5 Analysis of Secondary Outcome Variable(s)

These following secondary endpoints were analyzed for the FAS in total and also stratified by the parameters specified in section 9.9.2.1:

- Reported and annualized number of reported bleeds from the patient diary were displayed by summary statistics separately for total, spontaneous, trauma, undefined spontaneous/trauma and total joint, spontaneous joint, trauma joint bleeds. Frequency tables were presented for categorized number of bleeds including patients without any bleeds for total, spontaneous, trauma and joint bleeds as well. Summary statistics were provided for the difference of annualized number of reported bleeds during observation period and annualized number of bleeds prior to study entry in total and for joint bleeds. Same was done for the difference of

annualized number of reported bleeds during observation period and annualized number of bleeds prior to initiation of KOVALTRY, also in total and for joint bleeds.

- The prescribed prophylaxis dose per week over the observational period was calculated and presented in summary tables. This was done for the mean dose per patient as well as for the prescribed dose at baseline and end of observation. Also, summary statistics for the change in prescribed prophylaxis dose per week (IU/kg) from prior to KOVALTRY to baseline and from prior to KOVALTRY to end of observation as well as from baseline to end of observation were presented. In addition, a shift table for prescribed prophylaxis dose per week (IU/kg) prior to KOVALTRY vs. baseline, prior to KOVALTRY vs. end of observation and baseline vs. end of observation was provided, respectively. The following categories were used for the shift table: <20; 20 to <40; ≥40 to <60 and ≥60.
- In addition to the shift table of prophylaxis dosing regimens from study entry to end of observation specified in section 9.9.2.4, frequency tables for the number of changes in prophylaxis dosing frequency per patient as well as the reasons for change were presented. This information was also presented in a listing.
- The total annualized factor consumption was calculated from the patient diary and displayed in summary tables.
- The physician determinants for choice of the initial prophylaxis regimen were provided in frequency tables, separately for each rank and as an overall multiple response table.
- Changes in treatment satisfaction as measured by the Hemo-SAT questionnaire were analyzed by summary tables for the difference of the total score and subscores from baseline to one year after baseline, two years after baseline and last post-baseline questionnaire for the subgroup of patients with Hemo-SAT questionnaire assessments at baseline (up to 30 days after initial visit) and about one year after baseline (between 300 and 420 days after initial visit), two years after baseline (between 660 and 780 days after initial visit) or post-baseline questionnaire (at least 300 days after initial visit), respectively.
- Changes in treatment adherence as measured by the VERITAS-PRO questionnaire were analyzed by summary tables for the difference of the total score and subscores from baseline to six months, one year after baseline, two years after baseline and last post-baseline questionnaire for the subgroup of patients with VERITAS-PRO questionnaire assessments at baseline (up to 30 days after initial visit) and about six months (between 120 and 240 days after initial visit), one year after baseline (between 300 and 420 days after initial visit), two years after baseline (between 660 and 780 days after initial visit) or post-baseline questionnaire (at least 300 days after initial visit), respectively.
- Number of PK assessments during observation period were analyzed descriptively by frequency tables in total and by assay used. In addition, number of assessments for FVIII: C activity, Factor VIII half-life, AUC, clearance, FVIII trough, FVIII peak level and FVIII recovery per patient was displayed. PK findings were listed, for details see SAP version 3.0 Appendix, Annex 1.

Evaluation of safety in patients treated with KOVALTRY was analyzed for the SAF and is covered in section 9.9.2.7.

9.9.2.6 Analysis of treatment data

Treatment data was analyzed by summary tables of the patient diary entries on bleeds and injections for the FAS. In detail, summary tables for quantitative outcomes were presented for total number of injections, annualized number of injections, total dose, annualized total dose, dose per kg, annualized dose per kg, mean total dose per injection and mean dose per kg per injection overall and separately for injections to treat bleeds as well as for prophylactic injections. Injections for treated bleeds were additionally separated into the categories all treated bleeds, spontaneous bleeds, trauma bleeds, undefined spontaneous/trauma bleeds and all treated joint bleeds, spontaneous joint bleeds, trauma joint bleeds.

For the treatment of bleeds mean total dose per bleed and mean dose per kg per bleed were also calculated considering the initial as well as all follow-up treatments of a bleed. Number of injections per bleed were also displayed in a frequency table.

For prophylactic injections also mean total dose per week and mean dose per kg per week was calculated and displayed. The proportion of patients who documented a mean of 2 and a mean of 3 prophylaxis injections in the injection diary was presented by month and overall in a frequency table whereas the category of 2 injections per week incorporates calculated mean values between ≥1.5 and <2.5 and the category of 3 injections per week incorporates calculated mean values between ≥2.5 and <3.5. Other calculated mean values of prophylactic injections per week were displayed in the categories <1.5 prophylaxis injections per week and ≥3.5 prophylaxis injections per week.

For injections because of surgeries total dose and annualized total dose were calculated and presented in summary tables, if applicable.

A frequency table based on all documented injections was displayed for reason of injection, i.e. prophylactic injection, initial trauma bleed injection, initial spontaneous bleed injection, initial undefined spontaneous/trauma bleed injection, follow-up injection for treatment of bleed, injection for surgery. Documented injections were also listed in a separate listing including all relevant details (see SAP version 3.0 Appendix, Annex 1).

The overall annualized total consumption combining consumptions for prophylaxis, bleeds, and other events was also presented.

9.9.2.7 Safety Analysis

All analyses of AEs and Treatment-Emergent AEs (TEAE) were presented for the SAF in form of patient-based incidence tables and stratified by age group as defined in section 9.9.2.1. Treatment-emergent is defined as any event arising or worsening after the start of KOVALTRY treatment until 7 days after the last KOVALTRY treatment.

An overview table provided overall incidences for patients with any event, any serious event, any drug related event, any serious drug related event, any event with outcome death, any event leading to discontinuation of KOVALTRY and any event related to inhibitor development. Same overview table was generated for TEAEs. Incidence tables by MedDRA SOC and PT were presented for all AEs, TEAEs, SAEs, drug-related AEs, serious drug-related AEs, AEs causing discontinuation of KOVALTRY and AEs with outcome death.

A detailed listing was provided for AEs related to the development of an inhibitor or positive inhibitor measurements, including information on history of inhibitors. In addition SAEs, drug-related AEs, AEs causing discontinuation of KOVALTRY and AEs with outcome death were listed.

9.9.3 Missing values

No imputation of missing information was applied except for partial dates and for weight assessments (see SAP version 3.0, section 4.3, Annex 1).

Number of patients with missing data characterized by outcomes like 'not done', 'not available', 'unknown', 'missing' were presented as separate category. In general, relative frequencies were calculated based on all values of the patient set. In special cases, where the basis differs from total population, this was mentioned.

9.9.4 Sensitivity analyses

Sensitivity analysis was conducted to investigate whether there are differences in outcomes for patients less versus more than 3 months on KOVALTRY prior to the study. Thus, all TFLs were stratified by pretreatment with KOVALTRY (patients who had been on KOVALTRY prior to baseline up to 3 months versus patients who had been more than 3 months on KOVALTRY prior to baseline). Also, TFLs were stratified by patients who completed one year of observational period and patients who completed two years of observational period[18]. Sensitivity analyses regarding the primary objective were performed by applying multiple stratifications including number of patients who discontinued prematurely or did not reach the maximum observation period of 1 or 2 years. Further sensitivity analyses for the primary objective were done based on the previously used FVIIII products (Kogenate / Helixate versus other products) (see SAP version 3.0, 4.6, Annex 1). As completeness of diary documentation could not be guaranteed, sensitivity analyses were performed on all diary table output with regards to prophylaxis by reducing analyses to the patient subgroup with relatively complete prophylaxis injection diaries. For that purpose the subgroup was defined as all patients with no time interval of 21 or more days without any documented injection within the time period between the first documented injection in the diary after initial visit and the last documented injection in the diary before end of observation. In addition a time period of at least 90 days between initial visit and end of observation had to be documented in the patient diary to be valid for the subgroup analysis.

9.9.5 Amendments to the statistical analysis plan

Certain adaptations were made for SAP version 2.0 due to amendments to the study protocol version 3.0 (18559_KV1601_TAURUS_Protocol_Version3.0_5FEB2018) (see SAP version 3.0, section 7, Annex 1).

For SAP version 3.0 adaptations were made due to amendments to the study protocol version 4.1 (18559_KV1601_TAURUS_Protocol_Version 4.1_2019_06_19). These changes include adaptation of multiple sections to include extension of observation period of study to 2 years, modification of stratification parameters, additional sensitivity analyses and assessments for FVIII PK analysis.

9.10 Quality control

Before study start at the sites, all physicians were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. A physician meeting was organized to provide general training on the study protocol, safety reporting procedures, data collection

[18] Global protocol amendment (AM05, 12 NOV 2018) to update statistical considerations summarizing data from patients who completed one year of observation before AM05 and did not join the study for the second year.

requirements and general EDC system overview. Physicians had the chance to discuss and develop a common understanding of the study protocol and the case report form (CRF).

A CRO was 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 were recorded in a standardized CRF. After data entry, missing or implausible data were queried and the data were validated. A check for multiple documented patients was done.

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the Data Management Plan (DMP). The same plan specifies measures for handling of missing data and permissible clarifications. The DMP is available upon request (see Annex 1).

Medical Review of the data was performed according to the Medical Review Plan (MRP). The purpose of the Medical Review was 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 is described in the MRP, which is available upon request (see Annex 1).

In a subset of patients (at least 1000 data items/data item groups and a minimum of 125 patients) source data verification was to 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 were to access medical records on site for data verification. Detailed measures for quality reviews are described in the Quality Review Plan (QRP). However, due to premature termination of the study the quality review was stopped after the telephone interviews, i.e., no on-site data review at sites selected at random took place. The QRP and the Final Quality Review Report are available upon request (see Annex 1).

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (eCRF) were validated according to 21 Code of Federal Regulations Part 11 (Food and Drug Administrations) (15).

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 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 was recommended to also store documents for a retention period of at least 15 years.

10. Results

All analyses for the FAS described in the report refer to the main analyses unless explicitly stated otherwise. Thus, all references to FAS tables refer to data from main results (TFL Main Results, see Annex 1).

In the main analyses for the FAS described below, results are presented for the overall population and for subgroups by prophylaxis dosing regimen at baseline (i.e. ≤2.5x/week and >2.5x/week) and / or by prophylaxis dosing regimen at baseline and switch of prophylaxis dosing regimen from baseline to end of observation (i.e. ≤2.5x/week and no switch of prophylaxis dosing regimen, >2.5x/week and no switch of prophylaxis dosing regimen, and switcher of prophylaxis dosing regimen). Switcher and no

switch patients were defined based on the prophylaxis dosing regimen at end of observation compared to that at baseline (initial visit, see the Appendix of SAP, version 3.0, dated 25 JUN 2020 found in Annex 1 as a stand-alone document):

- "No switch of prophylaxis dosing regimen", if last prescribed dosing frequency during observational period = prescribed dosing frequency at initial visit
- "Increase of prophylaxis dosing frequency", if last prescribed dosing frequency during observational period > prescribed dosing frequency at initial visit
- "Decrease of prophylaxis dosing frequency", if last prescribed dosing frequency during observational period < prescribed dosing frequency at initial visit.

All analyses for the SAF (overall population and subgroups) are contained in one document (TFL [SAF], see Annex 1). Thus, all references to SAF tables relate to this document.

10.1 Participants

A total of 320 patients were screened for this study (Table 4). Of these, 318 patients (99.4%) were enrolled.

Table 4: Screening and enrollment of patients

	Total N=320 n (%)
Number of patients screened	320 (100.0%)
Number of patients enrolled	318 (99.4%)
Number of patients not enrolled and reasons for non-enrollment (multiple response)	2 (0.6%)
Until AUG 2017: Patients with history of inhibitors	1 (0.3%)
Not currently on (until FEB 2018: started within 3 months of study enrollment) or no plan to start prophylaxis therapy with KOVALTRY	1 (0.3%)

FAS: Full Analysis Set, n: number of patients, N: number of patients in analysis set, SAF: Safety Analysis Set.
Source : FAS/SAF-Table 14.1.1/1

The reasons for non-enrollment of the two patients were history of inhibitors (until AUG 2017[19]) and not on (until FEB 2018, started within 3 months of study enrollment[20]) or no plan to start prophylaxis therapy with KOVALTRY for one patient each.

Table 5 summarizes the different analysis sets calculated for this final report.

[19] Eligibility criteria were adapted in protocol amendment AM02 and AM03 to also include patients with a history of inhibitors. Until August 2017 only patients without a history of inhibitors could be enrolled.

[20] The restriction "started within 3 months of study enrollment" was removed in protocol amendment AM04.

Table 5: Analysis sets

	Total N=318 n (%)
Number of patients enrolled	318 (100.0%)
Number of patients in FAS	302 (95.0%)
Number of patients not in FAS and reasons for exclusion from FAS (multiple response)	16 (5.0%)
Later violation of inclusion/exclusion criterion*	10 (3.1%)
No initial total weekly dose or dosing frequency of prophylaxis treatment with KOVALTRY documented	5 (1.6%)
No end of observation documented	9 (2.8%)
Number of patients in SAF	313 (98.4%)
Number of patients not in SAF and reasons for exclusion from SAF (multiple response)	5 (1.6%)
No documented dose of KOVALTRY	5 (1.6%)

*: Reasons for later violation of inclusion/exclusion criteria are described in the Validity Review and Data Decision Report, Version 1.0, 24 FEB 2021, see Annex 1.
FAS: Full Analysis Set, n: number of patients, N: number of patients in analysis set, SAF: Safety Analysis Set.
Source: FAS/SAF-Table 14.1.1/2

Of the 318 patients enrolled in the study, 302 patients (95.0%) were included in the FAS (i.e. patients who fulfilled all inclusion and exclusion criteria with documented initial dose of prophylaxis treatment with KOVALTRY and documented end of observation). The most frequent reason for not including the remaining 16 patients in this analysis set was "later violation of inclusion/exclusion criterion" (10 patients, 3.1% of total patients) followed by "no end of observation documented" (9 patients, 2.8% of total patients).

A total of 313 patients (98.4%) were included in the SAF (i.e. patients who received at least one dose of KOVALTRY [documented by physician or entered in patient diary within study observational period] and have signed the informed consent). Due to "no documented dose of KOVALTRY", 5 patients (1.6% of total patients) were not included in this analysis set.

The duration of the observation period and reason for end of observation are summarized in Table 6.

Table 6: Observation period FAS and SAF

	FAS N=302	SAF N=313
Documentation of follow-up visits n (%)		
No follow-up visit	0 (0.0%)	1 (0.3%)
1 follow-up visit	47 (15.6%)	50 (16.0%)
2 follow-up visits	112 (37.1%)	116 (37.1%)
3 follow-up visits	84 (27.8%)	86 (27.5%)
4 follow-up visits	33 (10.9%)	34 (10.9%)
5 follow-up visits	13 (4.3%)	13 (4.2%)
6 follow-up visits	6 (2.0%)	6 (1.9%)
7 follow-up visits	2 (0.7%)	2 (0.6%)
8 follow-up visits	3 (1.0%)	3 (1.0%)
9 follow-up visits	2 (0.7%)	2 (0.6%)
Observation period (days)		
n	302	313
Nmiss	0	0
Mean	451.4	446.5
SD	176.8	183.3
Median	393.5	389.0
Min, Max	20, 790	1, 1015
Main reason for end of observation n (%)		
Missing	0 (0.0%)	5 (1.6%)
Patient died	2 (0.7%)	2 (0.6%)
Patient withdrew consent	3 (1.0%)	3 (1.0%)
Patient lost to follow-up	10 (3.3%)	11 (3.5%)
Non-compliance with study drug	0 (0.0%)	2 (0.6%)
Regular end of study	216 (71.5%)	217 (69.3%)
On demand therapy	0 (0.0%)	1 (0.3%)
Switch to other therapy	36 (11.9%)	36 (11.5%)
Site Closure	1 (0.3%)	1 (0.3%)
Premature termination by Sponsor due to COVID-19 pandemic	28 (9.3%)	28 (8.9%)
Other	6 (2.0%)	6 (1.9%)

COVID-19: Coronavirus Disease 2019, FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SAF: Safety Analysis Set, SD: standard deviation.
Source : FAS/SAF-Table 14.1.1/3

In the FAS and the SAF, 37.1% of patients had 2 follow-up visits followed by 27.8% and 27.5%, respectively, with 3 follow-up visits. The mean observation period for the final analysis was 451.4 days for the FAS and 446.5 days for the SAF. For the majority of patients, the main reason for end of observation was “regular end of study” (FAS: 71.5% of patients, SAF: 69.3%). The most common main reasons for not completing the study were “switch to other therapy” (11.9% and 11.5%, respectively) and “premature termination by Sponsor due to COVID-19 pandemic” (9.3% and 8.9%, respectively).

Observation period by prophylaxis dosing regimen at baseline and switch of regimen is presented in FAS-Table 14.1.1/4.

10.2 Descriptive data

10.2.1 Demographic and baseline disease characteristics

A summary of the demographic characteristics and vital signs overall, by prophylaxis dosing regimen at baseline (i.e. ≤2.5x/week and >2.5x/week), and by prophylaxis dosing regimen at baseline and switch of prophylaxis dosing regimen from baseline to end of observation (i.e. ≤2.5x/week and no switch of prophylaxis dosing regimen, >2.5x/week and no switch of prophylaxis dosing regimen, and switcher of prophylaxis dosing regimen) is presented in Table 7.

Table 7: Demography and vital signs at baseline overall and by prophylaxis dosing regimen at baseline and switch of regimen for FAS

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Sex n (%)						
Male	107 (100.0%)	148 (100.0%)	47 (100.0%)	124 (100.0%)	178 (100.0%)	302 (100.0%)
Female	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Age (years)						
n	107	148	47	124	178	302
Nmiss	0	0	0	0	0	0
Mean	29.1	24.4	31.4	29.3	25.7	27.2
SD	16.3	14.8	19.9	16.7	16.0	16.4
Median	PPD					
Min, Max						

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Country n (%)[a]						
Belgium	0 (0.0%)	PPD	PPD	PPD		13 (4.3%)
France	PPD					25 (8.3%)
Germany		23 (15.5%)				41 (13.6%)
Netherlands		PPD				30 (9.9%)
United States of America	12 (11.2%)			12 (9.7%)	15 (8.4%)	27 (8.9%)
Spain	PPD	20 (13.5%)		13 (10.5%)	22 (12.4%)	35 (11.6%)
Italy	25 (23.4%)	PPD		30 (24.2%)	30 (16.9%)	60 (19.9%)
Colombia	PPD			PPD		17 (5.6%)
Greece						15 (5.0%)
Canada						14 (4.6%)
Slovenia						PPD
Taiwan, province of China						
Race n (%)[b]						
PPD						

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Ethnicity n (%)[b]						
PPD						
Weight at baseline (kg)						
n	104	144	45	120	173	293
Nmiss	3	4	2	4	5	9
Mean	69.38	64.40	68.49	68.33	65.73	66.80
SD	21.18	24.39	28.37	22.21	25.19	24.01
Median	PPD					
Min, Max						
Height at baseline (cm)						
n	99	129	40	114	154	268
Nmiss	8	19	7	10	24	34
Mean	168.28	164.97	163.01	166.71	165.30	165.90
SD	16.65	20.76	24.16	19.10	20.57	19.94
Median	PPD					
Min, Max						

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
BMI at baseline (kg/m²)						
n	99	129	40	114	154	268
Nmiss	8	19	7	10	24	34
Mean	23.781	22.302	24.240	23.661	22.750	23.138
SD	5.201	5.385	6.361	5.254	5.686	5.515
Median	PPD					
Min, Max						

[a]: Of the 14 countries planned, only 12 countries enrolled patients who were valid for analysis. In Luxembourg only one patient was enrolled but was excluded from all analyses because the patient did not receive any dose of KOVALTRY during the study period. Participation of Slovakia in the study was cancelled before any study-related activities were started.
[b]: In France no race and ethnicity information was collected.
BMI: Body Mass Index, FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation.
Source : FAS-Table 14.1.2/1, Table 14.1.2/2, Table 14.1.2/3 and Table 14.1.2/4

All patients of this study were male and the majority of them were PPD with a median age of PPD in the FAS.

In the analyses of the FAS by prophylaxis dosing regimen at baseline, 124 of 302 patients had a dosing regimen of ≤2.5x/week at baseline and 178 patients had a dosing regimen of >2.5x/week at baseline. Patients with a dosing regimen ≤2.5x/week were older than patients with a dosing regimen >2.5/week.

Analyses were also performed by prophylaxis dosing regimen at baseline and switch of regimen. In the FAS, 107 of 302 patients had a dosing regimen of ≤2.5x/week at baseline and no switch of prophylaxis dosing regimen, 148 patients had a dosing regimen of >2.5x/week at baseline and no switch of prophylaxis dosing regimen while 47 patients switched prophylaxis dosing regimen from baseline to end of observation (for details, see Section 10.4.1). Patients with a dosing regimen of >2.5x/week at baseline and no switch of prophylaxis dosing regimen were slightly younger than patients with a dosing regimen of ≤2.5x/week at baseline and no switch of prophylaxis dosing regimen and patients who switched prophylaxis dosing regimens were eldest.

For the other demographic characteristics and vital signs, no major differences were observed in the subgroups by prophylaxis dosing regimen at baseline and by prophylaxis dosing regimen at baseline and switch of regimen (FAS).

Of the 14 countries planned, only 12 countries enrolled patients who were valid for analysis. In Luxembourg only one patient was enrolled but was excluded from all analyses because the patient did not receive any dose of KOVALTRY during the study period. Participation of Slovakia in the study was cancelled before any study-related activities were started. Among the countries, Italy, Germany, Spain, and the Netherlands had high number of patients enrolled.

Results for the SAF (overall and by prophylaxis dosing regimen at baseline) can be found in SAF-Table 14.1.2/1 for demographic characteristics and in SAF-Table 14.1.2/6 for vital signs.

10.2.2 Hemophilia medical and treatment history

For the FAS, the median time from hemophilia A diagnosis to the baseline measurement was 15.5 years (range: 0.19 to 64.82 years). With regard to the subgroups by prophylaxis dosing regimen at baseline, the >2.5x/week group had a shorter median time since diagnosis (15.1 years; range: 0.68 to 64.08 years) as compared to the ≤2.5x/week group (16.0 years; range: 0.19 to 64.82 years). In the total, ≤2.5x/week and >2.5x/week groups, the majority of the patients, 84.4%, 79.0% and 88.2%, respectively, had a 0% to <1% FVIII level at diagnosis (FAS-Table14.1.3/1). These data by prophylaxis dosing regimen at baseline and switch of regimen can be found in FAS-Table14.1.3/2.

Results for the SAF were similar to the FAS (SAF-Table14.1.3/1).

An overview of data on prophylaxis therapy prior to study entry for the FAS is presented in Table 8.

Table 8: Prophylaxis therapy prior to study entry overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Length of continuous regular prophylaxis treatment prior to study entry (years)			
n	104	157	261
Nmiss	20	21	41
Mean	9.605	12.768	11.508
SD	7.738	9.183	8.760
Median	8.000	12.000	10.000
Min, Max	0.00, 38.00	0.01, 49.00	0.00, 49.00
Age at initiation of prophylaxis therapy (years)			
n	98	151	249
Nmiss	26	27	53
Mean	16.3	11.3	13.2
SD	17.0	14.1	15.5
Median	PPD		
Min, Max			
Age at initiation of prophylaxis therapy, categories n (%)			
Missing	26 (21.0%)	27 (15.2%)	53 (17.5%)
<2 years	12 (9.7%)	31 (17.4%)	43 (14.2%)
≥2 to ≤18 years	54 (43.5%)	86 (48.3%)	140 (46.4%)
>18 years	32 (25.8%)	34 (19.1%)	66 (21.9%)
Total exposure days n (%)			
Missing	3 (2.4%)	11 (6.2%)	14 (4.6%)
≤20 ED	0 (0.0%)	0 (0.0%)	0 (0.0%)
21 – 49 ED	0 (0.0%)	0 (0.0%)	0 (0.0%)
50 – 150 ED	10 (8.1%)	2 (1.1%)	12 (4.0%)
>150 ED	111 (89.5%)	165 (92.7%)	276 (91.4%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)

ED: Exposure Day, FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation.
Source: FAS-Table 14.1.3/1

In the FAS, the median length of continuous regular prophylaxis treatment prior to entry into this study was 10.0 years (range: 0.00 to 49.00 years). The mean age to initiate prophylaxis therapy was 13.2 years (median PPD range: PPD with 46.4% of the patients within the age group of ≥2 to ≤18 years. A clear majority of patients (91.4%) had >150 ED, 89.5% and 92.7% in the total, ≤2.5x/week and >2.5/week groups, respectively. Data on ED was missing for 14 patients (4.6%), 3 patients (2.4%), 11 patients (6.2%) in the total, ≤2.5x/week and >2.5/week groups, respectively.

With regard to the subgroups by prophylaxis dosing regimen at baseline, the median length of continuous regular prophylaxis treatment prior to study entry was longer in the >2.5/week group than in the ≤2.5x/week group (12.0 vs. 8.0 years). On comparison of mean age at initiation of prophylaxis therapy in the subgroups by prophylaxis dosing regimen at baseline, patients in the >2.5/week group were younger (11.3 years) than in the ≤2.5x/week group (16.3 years). No other major differences were found.

Medical history regarding the gene mutation in the FVIII gene was not documented for 90 out of 302 patients (29.8%) in FAS. Of the remaining patients, similar proportion of patients had a non-null

(35.4% of total patients) or a null mutation (34.8% of total patients) in this gene. There was a higher proportion of patients with non-null mutation in the ≤2.5x/week baseline prophylaxis dosing regimen group as compared to the >2.5x/week group (42.7% vs. 30.3%). On the other hand, patients with null mutation in the FVIII gene were slightly higher in proportion in the >2.5x/week group as opposed to the ≤2.5x/week group (36.0% vs. 33.1%) (FAS-Table14.1.3/1).

The median time from last assessment of patient history of inhibitor to baseline was 3.187 months (range: 0.00 to 179.35 months, n= 193) in the total group, 4.928 months (range: 0.00 to 130.76 months, n= 95) and 2.333 months (range: 0.00 to 179.35 months, n=98) in the ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. For 102 of 302 patients (33.8%) in the FAS, there was no information available on inhibitor test prior to baseline. A total of 167 patients (55.3%) did not have a history of inhibitors and 33 patients (10.9%) had a history of inhibitors. Among 33 patients positive for inhibitor test, 9 had a baseline prophylaxis dosing regimen of ≤2.5x/week and 24 were in the >2.5x/week group (FAS-Table14.1.3/1). In patients with a positive inhibitor test prior to baseline, the median time from first positive inhibitor test to baseline was 10.835 years (range: 3.75 to 28.22 years, n=24) and the median time from last positive inhibitor test to baseline was 9.535 years (range: 1.47 to 21.51 years). The overall median peak titer of first positive inhibitor test was 4.000 Bethesda units (range: 0.02 to 64.00 Bethesda units). The median time from resolution of last positive inhibitor test to baseline was 9.203 years (range: 1.40 to 21.31 years). Of 33 patients with positive inhibitor tests, 21 patients underwent ITI. The median duration of ITI was 755.500 days (range: 147.00 to 2585.00 days, n=12) (FAS-Table14.1.3/1).

About half of the patients in the FAS had a family history of hemophilia (48.7%, 50.0%, and 47.8% in total, the ≤2.5x/week and the >2.5x/week baseline prophylaxis dosing regimen groups, respectively). The majority of patients did not have family history of inhibitors (70.5%, 71.0%, and 70.2%, respectively) (FAS-Table14.1.3/1). Information on blood groups can be found in FAS-Table14.1.3/1.

The mean (± SD) number of target joints at baseline observed in the FAS were 1.0 ± 1.8 (median: 0.0, n=302) in the total group, 1.0 ± 1.5 (median: 0.0, n=124) in the ≤2.5x/week baseline prophylaxis dosing regimen group and 1.0 ± 1.9 (median: 0.0, n=178) in the >2.5x/week group. The majority of patients had no target joints at baseline (57.9%, 54.8%, 60.1% in total, the ≤2.5x/week and the >2.5x/week baseline prophylaxis dosing regimen groups, respectively) (FAS-Table14.1.3/1).

Results for the SAF were in line with the FAS (SAF- Table 14.1.3/1).

An overview of data on number of (joint) bleeds prior to study for the FAS is presented in Table 9.

Table 9: Number of (joint) bleeds prior to study overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Number of bleeds in the last 6 months prior to baseline			
n	124	175	299
Nmiss	0	3	3
Mean	1.9	1.6	1.7
SD	4.5	2.6	3.5
Median	0.0	0.0	0.0
Min, Max	0, 28	0, 13	0, 28
Number of bleeds in the last 12 months prior to baseline*			
n	124	175	299
Nmiss	0	3	3
Mean	3.8	3.2	3.4
SD	8.9	5.2	7.0
Median	0.0	0.0	0.0
Min, Max	0, 56	0, 26	0, 56
Number of joint bleeds in the last 6 months prior to baseline			
n	124	178	302
Nmiss	0	0	0
Mean	1.6	1.1	1.3
SD	3.9	2.6	3.2
Median	0.0	0.0	0.0
Min, Max	0, 26	0, 24	0, 26
Number of joint bleeds in the last 12 months prior to baseline*			
n	124	178	302
Nmiss	0	0	0
Mean	3.1	2.3	2.6
SD	7.9	5.2	6.4
Median	0.0	0.0	0.0
Min, Max	0, 52	0, 48	0, 52

*: Number of (joint) bleeds in the last 12 months is calculated by number of (joint) bleeds in the last 6 months * 2.
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation.
Source: FAS-Table 14.1.3/1

Patients in the FAS had a mean (± SD) number of 1.7 ± 3.5 bleeds (median: 0.0 bleeds, n=302 patients) in the last 6 months prior to baseline and 3.4 ± 7.0 bleeds (median: 0.0 bleeds) in the last 12 months[21] prior to baseline. The number of joint bleeds for these time points was slightly lower (FAS-Table14.1.3/1).

In the SAF, the number of bleeds and joint bleeds were similar to the FAS (SAF-Table14.1.3/1).

[21] Number of (joint) bleeds in the last 12 months (annualized) is calculated by number of (joint) bleeds in the last 6 months * 2 (SAP version 3.0 section 4.6, see Annex 1).

Further details on the number of (joint) bleeds prior to baseline analyzed according to the pretreatment by demand or regular prophylaxis, the number of (joint) bleeds prior to start with KOVALTRY treatment overall and analyzed according to the pretreatment by demand or regular prophylaxis, and the number of target joints at baseline and at the start of KOVALTRY treatment overall and analyzed according to the pretreatment by demand or regular prophylaxis is provided in FAS/SAF-Table14.1.3/1. Also, the location of target joints at baseline and at start of KOVALTRY treatment for subgroup of patients with target joints overall and by prophylaxis dosing regimen at baseline can be found in FAS/SAF-Table14.1.3/1.

Only 13 patients in the FAS had on demand treatment as most recent FVIII treatment prior to KOVALTRY. These patients had a mean number of 2.9 ± 5.6 bleeds (median: 1.0) and 2.8 ± 5.6 joint bleeds (median: 2.0) in the last 6 months prior to baseline. The mean number of bleeds for 286 patients in the FAS with regular prophylaxis treatment as most recent FVIII treatment prior to KOVALTRY was 1.7 ± 3.4 bleeds (median: 0 0). This information was not available for three patients. The mean number of joint bleeds for 289 patients in the FAS with regular prophylaxis treatment as most recent FVIII treatment prior to KOVALTRY was 1.2 ± 3.1 joint bleeds (median: 0 0) (FAS-Table14.1.3/1).

An overview of the most recent FVIII treatment prior to KOVALTRY is presented in Table 10.

Table 10: Most recent FVIII treatment prior to KOVALTRY overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	**>2.5x/week N=178**	**Total N=302**
Most recent FVIII treatment prior to KOVALTRY			
Patients with documented prior FVIII treatment n (%)	124 (100.0%)	178 (100.0%)	302 (100.0%)
AAFACT	0 (0.0%)	1 (0.6%)	1 (0.3%)
ADVATE	5 (4.0%)	5 (2.8%)	10 (3.3%)
ADYNOVATE	1 (0.8%)	0 (0.0%)	1 (0.3%)
AFSTYLA	1 (0.8%)	0 (0.0%)	1 (0.3%)
BERIATE	3 (2.4%)	3 (1.7%)	6 (2.0%)
ELOCTATE	0 (0.0%)	8 (4.5%)	8 (2.6%)
FACTANE	3 (2.4%)	4 (2.2%)	7 (2.3%)
FANHDI	0 (0.0%)	1 (0.6%)	1 (0.3%)
HELIXATE FS/NexGen	10 (8.1%)	18 (10.1%)	28 (9.3%)
HEMOFIL M	1 (0.8%)	0 (0.0%)	1 (0.3%)
KOGENATE FS/Bayer	95 (76.6%)	133 (74.7%)	228 (75.5%)
NOVOEIGHT	1 (0.8%)	0 (0.0%)	1 (0.3%)
NUWIQ	1 (0.8%)	0 (0.0%)	1 (0.3%)
OCTANATE	1 (0.8%)	0 (0.0%)	1 (0.3%)
OCTOCOG ALFA	1 (0.8%)	1 (0.6%)	2 (0.7%)
RECOMBINATE	0 (0.0%)	1 (0.6%)	1 (0.3%)
REFACTO	1 (0.8%)	2 (1.1%)	3 (1.0%)
REFACTO AF	0 (0.0%)	1 (0.6%)	1 (0.3%)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Time from recent FVIII treatment to initiation of KOVALTRY			
Time from start of most recent FVIII treatment prior to KOVALTRY to initiation of KOVALTRY treatment (years)			
n	69	112	181
Nmiss	55	66	121
Mean	7.029	7.931	7.587
SD	6.020	5.847	5.913
Median	5.046	6.991	6.407
Min, Max	0.23, 29.75	0.07, 25.26	0.07, 29.75
Time from end of most recent FVIII treatment prior to KOVALTRY to initiation of KOVALTRY treatment (days)			
n	91	135	226
Nmiss	33	43	76
Mean	9.9	20.3	16.1
SD	40.8	71.9	61.4
Median	2.0	2.0	2.0
Min, Max	0, 368	-2, 646	-2, 646
Duration of most recent FVIII treatment prior to KOVALTRY initiation (years)			
n	58	92	150
Nmiss	66	86	152
Mean	7.303	8.125	7.807
SD	6.132	6.109	6.110
Median	5.290	6.988	6.546
Min, Max	0.46, 29.74	0.07, 25.26	0.07, 29.74
Dose and schedule			
Total weekly dose of most recent FVIII treatment prior to KOVALTRY (IU/kg)			
n	111	169	280
Nmiss	13	9	22
Mean	57.789	80.355	71.409
SD	26.506	47.190	41.716
Median	53.191	75.000	66.667
Min, Max	7.87, 166.67	11.90, 333.33	7.87, 333.33
Schedule of most recent FVIII treatment prior to KOVALTRY n (%)			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
On demand	9 (7.3%)	4 (2.2%)	13 (4.3%)
Regular prophylaxis	115 (92.7%)	174 (97.8%)	289 (95.7%)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Frequency - Subgroup of patients with regular prophylaxis schedule for most recent FVIII treatment prior to KOVALTRY			
n	115	174	289
Dose frequency for most recent prophylaxis FVIII treatment prior to KOVALTRY (n %)			
Every 24 hours	0 (0.0%)	2 (1.1%)	2 (0.7%)
4 times per week	0 (0.0%)	4 (2.3%)	4 (1.4%)
Every other day	5 (4.3%)	44 (25.3%)	49 (17.0%)
3 times per week	21 (18.3%)	103 (59.2%)	124 (42.9%)
2.5 times per week	1 (0.9%)	0 (0.0%)	1 (0.3%)
Every 3 days	2 (1.7%)	1 (0.6%)	3 (1.0%)
2 times per week	73 (63.5%)	14 (8.0%)	87 (30.1%)
Every 4 days	0 (0.0%)	1 (0.6%)	1 (0.3%)
1.5 times per week	2 (1.7%)	0 (0.0%)	2 (0.7%)
Every week	11 (9.6%)	2 (1.1%)	13 (4.5%)
As needed	0 (0.0%)	1 (0.6%)	1 (0.3%)
3 to 4 times per week	0 (0.0%)	2 (1.1%)	2 (0.7%)
Dose frequency for most recent prophylaxis FVIII treatment prior to KOVALTRY (categories) n (%)			
Missing	0 (0.0%)	1 (0.6%)	1 (0.3%)
≤2.5x/week	89 (77.4%)	18 (10.3%)	107 (37.0%)
>2.5x/week	26 (22.6%)	155 (89.1%)	181 (62.6%)
KOVALTRY treatment start before baseline			
n	124	178	302
Pretreatment with KOVALTRY more than 3 months before initial visit n (%)			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients started KOVALTRY more than three months before initial visit	65 (52.4%)	76 (42.7%)	141 (46.7%)
Patients started KOVALTRY up to three months before initial visit	44 (35.5%)	64 (36.0%)	108 (35.8%)
Patients started KOVALTRY at or after initial visit	15 (12.1%)	38 (21.3%)	53 (17.5%)
Start of KOVALTRY treatment in relation to baseline n (%)			
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)
More than 5 months prior to baseline	55 (44.4%)	67 (37.6%)	122 (40.4%)
Within 5 months prior to baseline	4 (3.2%)	5 (2.8%)	9 (3.0%)
Within 4 months prior to baseline	6 (4.8%)	4 (2.2%)	10 (3.3%)
Within 3 months prior to baseline	11 (8.9%)	26 (14.6%)	37 (12.3%)
Within 2 months prior to baseline	15 (12.1%)	18 (10.1%)	33 (10.9%)
Within 1 month prior to baseline	18 (14.5%)	20 (11.2%)	38 (12.6%)
At or after baseline	15 (12.1%)	38 (21.3%)	53 (17.5%)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Time from initiation of KOVALTRY treatment to baseline (days)			
n	124	178	302
Nmiss	0	0	0
Mean	238.3	220.7	227.9
SD	316.6	379.8	354.8
Median	102.0	83.0	86.5
Min, Max	-134, 2155	-83, 2886	-134, 2886

FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation.
Source: FAS-Table 14.1.3/3

All of the 302 patients in the FAS had prior FVIII treatment documented with the majority (75.5%) treated with KOGENATE FS/Bayer. A median time of 6.407 years (range: 0.07 to 29.75 years) from the start and 2.0 days (range: -2 to 646 days) from the end of the most recent FVIII treatment prior to initiation of KOVALTRY was seen. The median duration of the most recent FVIII treatment prior to KOVALTRY initiation was 6.546 years. The mean total weekly dose of this most recent FVIII treatment prior to KOVALTRY was 71.409 IU/kg. Most patients received regular prophylaxis (95.7%). 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%). Among the patients with regular prophylaxis, the most common dosing frequencies were 3 times per week (42.9%), 2 times per week (30.1%) and every other day (17.0%). Of the total patients in FAS, 46.7% of patients had pretreatment with KOVALTRY more than three months before initial visit, 35.8% of patients had pretreatment with KOVALTRY up to three months before initial visit, and in 17.5% of patients KOVALTRY treatment start was at or after baseline. The median time from KOVALTRY treatment initiation to baseline was 86.5 days (range: -134 to 2886 days).

With regard to the subgroups by prophylaxis dosing regimen at baseline, patients in the ≤2.5x/week group had a shorter time from start of the most recent FVIII treatment to initiation of KOVALTRY treatment and a shorter treatment duration than patients in the >2.5x/week group. Mean weekly doses of the most recent FVIII treatment were also lower in the ≤2.5x/week group than in the >2.5x/week group. Understandably, for patients with regular prophylaxis in the ≤2.5x/week group, the most common dosing frequency was 2 times per week and it was 3 times per week for the >2.5x/week group. The median time from KOVALTRY treatment initiation to baseline was longer in the ≤2.5x/week group than in the >2.5x/week group. These data for the FAS by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table14.1.3/4.

Table 27 in Annex 2 presents data on FVIII treatment (on-demand versus regular prophylaxis) prior to KOVALTRY treatment and at end of observation by age categories (<6 years, ≥6 - <12 years, ≥12 - <18 years and ≥18 years).

Data on weekly dose of most recent FVIII treatment prior to KOVALTRY and for KOVALTRY at end of observation by different age categories (<6 years, ≥6 - <12 years, ≥12 - <18 years and ≥18 years) are presented in Table 28 in Annex 2.

Results for the SAF are provided in SAF-Table14.1.3/1 and Table 14.1.3/6.

10.2.3 Medical history and concomitant medications

10.2.3.1 Prior diseases

In the SAF a total of 147 of 313 patients (47.0%) had prior diseases. The most common prior diseases in this set at SOC level were musculoskeletal and connective tissue disorders (56 patients, 17.9%), infections and infestations (48 patients, 15.3%), vascular disorders (25 patients, 8.0%), surgical and medical procedures (24 patients, 7.7%), and metabolism and nutrition disorders (17 patients, 5.4%). The most common prior diseases at PT level were hepatitis C (29 patients, 9.3%), haemophilic arthropathy (25 patients, 8.0%), hypertension (23 patients, 7.3%), human immunodeficiency virus (HIV) infection (14 patients, 4.5%), knee arthroplasty (10 patients, 3.2%) and haemarthrosis (9 patients, 2.9%). Data on the prophylaxis regimen dosing in the SAF was missing for two patients and one of them had prior diseases documented with PTs diabetes mellitus and hypertension (SAF-Table 14.1.4/1).

In the ≤2.5x/week baseline prophylaxis dosing regimen group, 62 patients (47.0%) experienced prior diseases. The most common prior diseases at SOC level were infections and infestations (25 patients, 18.9%), followed by musculoskeletal and connective tissue disorders (20 patients, 15.2%), vascular disorders, surgical and medical procedures and metabolism and nutrition disorders (9 patients, 6.8% each). At PT level, hepatitis C (15 patients, 11.4%), haemophilic arthropathy (10 patients, 7.6%), hypertension (9 patients, 6.8%), and HIV infection (7 patients, 5.3%) occurred most frequently.

In the >2.5x/week baseline prophylaxis dosing regimen group, prior diseases were reported for 84 patients (46.9%). Musculoskeletal and connective tissue disorders (36 patients, 20.1%), infections and infestations (23 patients, 12.8%), surgical and medical procedures (15 patients, 8.4%), vascular disorders (15 patients, 8.4%) and gastrointestinal disorders and nervous system disorders (9 patients, 5.0% each) were documented most frequently at SOC level. At PT level the most common prior diseases were haemophilic arthropathy (15 patients, 8.4%), hepatitis C (14 patients, 7.8%), hypertension (13 patients, 7.3%), HIV infection (7 patients, 3.9%), knee arthroplasty (7 patients, 3.9%) and haemarthrosis (6 patients, 3.4%) (SAF-Table 14.1.4/1).

In the FAS a total of 143 out of 302 patients (47.4%) had prior diseases. No major differences were found between the FAS and the SAF regarding prior diseases (FAS-Table 14.1.4/1). Data for the FAS by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.4/2.

10.2.3.2 Concomitant diseases

A total of 132 of 313 patients (42.2%) in the SAF had concomitant diseases. Among them, musculoskeletal and connective tissue disorders (53 patients, 16.9%), infections and infestations (38 patients, 12.1%), vascular disorders (24 patients, 7.7%) and metabolism and nutrition disorders (18 patients, 5.8%) were the most frequent concomitant diseases at the SOC level. At the PT level, haemophilic arthropathy (25 patients, 8.0%), hypertension (23 patients, 7.3%), hepatitis C (17 patients, 5.4%) and HIV infection (14 patients, 4.5%) were reported most frequently. For two patients in the SAF, no prophylaxis regimen dosing was documented and one of them had concomitant diseases with PTs diabetes mellitus and hypertension (SAF-Table 14.1.4/6).

In the ≤2.5x/week baseline prophylaxis dosing regimen group, concomitant diseases were reported for 56 patients (42.4%). The most common concomitant diseases at SOC level were infections and infestations (21 patients, 15.9%), musculoskeletal and connective tissue disorders (19 patients, 14.4%), metabolism and nutrition disorders (10 patients, 7.6%), vascular disorders (9 patients, 6.8%),

investigations (7 patients, 5.3%) and surgical and medical procedures and congenital, familial and genetic disorders (6 patients, 4.5% each). At PT level, haemophilic arthropathy, hepatitis C (10 patients, 7.6% each), hypertension (9 patients, 6.8%), and HIV infection (7 patients, 5.3%) were most common.

In the >2.5x/week baseline prophylaxis dosing regimen group, 75 patients (41.9%) experienced concomitant diseases. The most frequent SOCs were musculoskeletal and connective tissue disorders (34 patients, 19.0%), infections and infestations (17 patients, 9.5%), vascular disorders (14 patients, 7.8%), surgical and medical procedures (10 patients, 5.6%) and gastrointestinal disorders (8 patients, 4.5%). At PT level, haemophilic arthropathy (15 patients, 8.4%) was documented most frequently, followed by hypertension (13 patients, 7.3%), HIV infection, hepatitis C (7 patients, 3.9% each), and knee arthroplasty (6 patients, 3.4%) (SAF-Table 14.1.4/6).

A total of 129 of 302 patients (42.7%) had concomitant diseases in FAS. No major differences were found between the FAS and the SAF regarding concomitant diseases. (FAS-Table 14.1.4/3). Data for the FAS by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.4/4.

10.2.3.3 Concomitant medications

In the SAF, 147 of 313 patients (47.0%) had any concomitant medication. The most frequently reported concomitant medication at ATC level 1 was alimentary tract and metabolism (69 patients, 22.0%) followed by nervous system (64 patients, 20.4%), musculo-skeletal system (48 patients, 15.3%), cardiovascular system (46 patients, 14.7%), dermatologicals (41 patients, 13.1%), blood and blood forming organs (38 patients, 12.1%), respiratory system (36 patients, 11.5%) and antiinfectives for systemic use (35 patients, 11.2%). The prophylaxis dosing regimen at baseline was not documented for two patients in the SAF and for one of them concomitant medication was documented (SAF-Table 14.1.4/11).

In the ≤2.5x/week baseline prophylaxis dosing regimen group, 59 patients (44.7%) reported concomitant medications. The most common concomitant medications at ATC level 1 were alimentary tract and metabolism (30 patients, 22.7%), nervous system (22 patients, 16.7%), cardiovascular system (21 patients, 15.9%), dermatologicals (20 patients, 15.2%), antiinfectives for systemic use (19 patients, 14.4%), musculo-skeletal system (18 patients, 13.6%), and blood and blood forming organs (15 patients, 11.4%).

In the >2.5x/week baseline prophylaxis dosing regimen group, 87 patients (48.6%) received concomitant medications. The most common at ATC level 1 were nervous system (42 patients, 23.5%), alimentary tract and metabolism (38 patients, 21.2%), musculo-skeletal system (29 patients, 16.2%), cardiovascular system (24 patients, 13.4%), blood and blood forming organs (23 patients, 12.8%), respiratory system (21 patients, 11.7%) and dermatologicals (20 patients, 11.2%) (SAF-Table 14.1.4/11).

Of 302 patients in the FAS, 145 patients (48.0%) had any concomitant medication. No major differences were found between the FAS and SAF regarding concomitant medications (FAS-Table 14.1.4/5). Data for the FAS by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.4/6.

10.3 Outcome data

The number of documented patients across the categories of the main outcomes are provided in section 10.2 for demographic and disease characteristics. The results for the primary endpoint are presented in section 10.4.1. The following list provides sections presenting results for different secondary endpoints:

- Annualized number of reported bleeds (total, spontaneous, joint and trauma) – section 10.4.2
- Prophylaxis dosing by age group and country – section 10.4.1
- Change in prophylaxis dosing frequency and reason for change (study start to end of observation period) - section 10.4.1
- The total annualized factor consumption - section 10.4.2
- Physician decision determinants of prophylaxis regimen - section 10.4.1
- Change from baseline to one year and two years in treatment satisfaction (Hemo-SAT) – section 10.4.6
- Change from baseline to six months, one year and two years in treatment adherence (VERITAS-PRO) – section 10.4.7
- Occurrence of AEs and SAEs – section 10.6
- Frequency and type of data relating to KOVALTRY PK (e.g. FVIII trough, peak levels, half-life, in-vivo recovery, and assay [one stage or chromogenic assay]) – section 10.4.3

10.4 Main results

10.4.1 Study medication and bleeds as documented by investigator

Among 302 patients in the FAS, 221 patients (73.2%) self-infused KOVALTRY, 80 patients (26.5%) did not self-infuse. For one patient (from >2.5x/week group), information on self-infusion was missing. A higher proportion of patients (75.8%) in the >2.5x/week baseline prophylaxis dosing regimen group self-infused KOVALTRY than in the ≤2.5x/week group (69.4%).

The most common reason for the initial switch to KOVALTRY in FAS was “physician’s decision” (65.6%, 71.8%, 61.2% in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively). The other common reasons were “prior FVIII product discontinued or about to be discontinued” (16.6%, 10.5% and 20.8%, respectively) and “patient decision” (12.3%, 14.5% and 10.7%, respectively) (FAS-Table 14.1.6/1).

The same three reasons were also documented as most common reasons for all subgroups in the subgroup analysis by prophylaxis dosing regimen at baseline and switch of regimen (FAS-Table 14.1.6/2) and for subgroups by initiation of KOVALTRY by age categories <12 years old and ≥12 years old (FAS-Table 14.1.1/6 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Table 11 summarizes the reasons for selection of initial dose / dosing frequency of KOVALTRY.

Table 11: Reasons for selection of initial dose / dosing frequency overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Reasons for selection of initial dose / dosing frequency (multiple response) n (%)			
Activity level	31 (25.0%)	36 (20.2%)	67 (22.2%)
Adherence / compliance history	35 (28.2%)	50 (28.1%)	85 (28.1%)
Age	20 (16.1%)	19 (10.7%)	39 (12.9%)
Availability of product	2 (1.6%)	0 (0.0%)	2 (0.7%)
Bleeding history with current treatment regimen	38 (30.6%)	55 (30.9%)	93 (30.8%)
Caregiver support	9 (7.3%)	6 (3.4%)	15 (5.0%)
Country guidelines	10 (8.1%)	10 (5.6%)	20 (6.6%)
Current treatment regimen	61 (49.2%)	106 (59.6%)	167 (55.3%)
Institution guidelines	10 (8.1%)	33 (18.5%)	43 (14.2%)
Insurance coverage (US)	3 (2.4%)	0 (0.0%)	3 (1.0%)
i.v. access	10 (8.1%)	8 (4.5%)	18 (6.0%)
Number of target joints	24 (19.4%)	25 (14.0%)	49 (16.2%)
Patient / caregiver preference	53 (42.7%)	59 (33.1%)	112 (37.1%)
Patient's condition	2 (1.6%)	6 (3.4%)	8 (2.6%)
Pharmacokinetic data	28 (22.6%)	30 (16.9%)	58 (19.2%)
Physical activity	2 (1.6%)	0 (0.0%)	2 (0.7%)
Physician preference	2 (1.6%)	2 (1.1%)	4 (1.3%)
Prior history of life-threatening bleed	7 (5.6%)	15 (8.4%)	22 (7.3%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	3 (2.4%)	8 (4.5%)	11 (3.6%)

i.v.: intravenous, FAS: Full Analysis Set, n: number of patients, N: number of patients in analysis set, US: United States.
Source: FAS-Table 14.1.6/1

The most frequent reasons for selection of initial dose / dosing frequency of KOVALTRY in the FAS 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 subgroup analysis by prophylaxis dosing regimen at baseline, the same reasons as for the overall population were most frequently reported in both subgroups. In addition, in patients with a prophylaxis dosing regimen ≤2.5x/week, “country guidelines” and “i.v. access” were equally frequent as “institution guidelines”.

In the subgroup analysis by prophylaxis dosing regimen at baseline and switch of regimen, the same reasons as for the overall population were most frequently reported in patients with >2.5x/week and no switch of prophylaxis dosing regimen (n=148), and in switchers of prophylaxis dosing regimen (n=47). In patients with ≤2.5x/week and no switch of prophylaxis dosing regimen (n=107), “country guidelines” and “caregiver support” were reported more frequently than “institution guidelines” (FAS-Table 14.1.6/2).

The same reasons for selection of initial dose / dosing frequency as for the overall population were most frequently reported for patients ≥12 years old (n=245). In patients <12 years old, “i.v. access” and "prior history of life threatening bleeds” were among the most frequently mentioned reasons, while “number of target joints” and “pharmacokinetic data” were reported less frequently

(FAS-Table 14.1.1/6 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

"Current treatment regimen" was also documented as the most frequent primary reason for selection of initial dose frequency of KOVALTRY in the FAS (40.7%) and in all of the above-mentioned subgroups (FAS-Table 14.1.6/1, FAS-Table 14.1.6/2 and FAS-Table 14.1.1/6 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Table 12 provides an overview of dosing frequency in the FAS.

Table 12: KOVALTRY dosing frequency overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Weekly prophylaxis dosing regimen at baseline n (%)			
Each day	0 (0.0%)	4 (2.2%)	4 (1.3%)
4 times per week	0 (0.0%)	3 (1.7%)	3 (1.0%)
Every other day	0 (0.0%)	39 (21.9%)	39 (12.9%)
3 times per week	0 (0.0%)	131 (73.6%)	131 (43.4%)
2.5 times per week	1 (0.8%)	0 (0.0%)	1 (0.3%)
Every 3 days	1 (0.8%)	0 (0.0%)	1 (0.3%)
2 times per week	105 (84.7%)	0 (0.0%)	105 (34.8%)
Every 4 days	1 (0.8%)	0 (0.0%)	1 (0.3%)
1.5 times per week	2 (1.6%)	0 (0.0%)	2 (0.7%)
Every week	13 (10.5%)	0 (0.0%)	13 (4.3%)
3 to 4 times per week	0 (0.0%)	1 (0.6%)	1 (0.3%)
Every 5 days	1 (0.8%)	0 (0.0%)	1 (0.3%)
Weekly prophylaxis dosing regimen at end of observation n (%) *			
Twice a day	0 (0.0%)	1 (0.6%)	1 (0.3%)
Each day	1 (0.8%)	6 (3.4%)	7 (2.3%)
Every other day	1 (0.8%)	37 (20.8%)	38 (12.6%)
3 times per week	9 (7.3%)	116 (65.2%)	125 (41.4%)
2.5 times per week	2 (1.6%)	2 (1.1%)	4 (1.3%)
Every 3 days	3 (2.4%)	0 (0.0%)	3 (1.0%)
2 times per week	94 (75.8%)	12 (6.7%)	106 (35.1%)
Every 4 days	1 (0.8%)	0 (0.0%)	1 (0.3%)
1.5 times per week	1 (0.8%)	0 (0.0%)	1 (0.3%)
Every week	11 (8.9%)	1 (0.6%)	12 (4.0%)
3 to 4 times per week	0 (0.0%)	2 (1.1%)	2 (0.7%)
Every 5 days	1 (0.8%)	0 (0.0%)	1 (0.3%)
Every 12 hours	0 (0.0%)	1 (0.6%)	1 (0.3%)
Weekly prophylaxis dosing regimen at baseline (categories) n (%)			
≤2.5x/week	124 (100.0%)	0 (0.0%)	124 (41.1%)
>2.5x/week	0 (0.0%)	178 (100.0%)	178 (58.9%)
Weekly prophylaxis dosing regimen at end of observation* (categories) n (%)			
≤2.5x/week	113 (91.1%)	15 (8.4%)	128 (42.4%)
>2.5x/week	11 (8.9%)	163 (91.6%)	174 (57.6%)

* is defined as the last documented regimen change or if no change is documented then regimen at baseline.
FAS: Full Analysis Set, N: number of patients in analysis set, n: number of patients.
Source: FAS-Table 14.1.6/3

Overall in the FAS at baseline, patients were most frequently treated 3 times per week (43.4%), followed by 2 times per week (34.8%) and every other day (12.9%). At this time point, 124 patients (41.1%, 95% [CI]: 35.5% - 46.8%) were on a ≤2.5x/week prophylaxis dosing regimen and 178 patients (58.9%, 95% CI: 53.2% - 64.5%) on a >2.5x/week prophylaxis dosing regimen (see Table 12 and FAS-Table 14.1.6/4). The most common dosing regimens were 2 times per week (84.7%) and every week (10.5%) in the ≤2.5x/week and 3 times per week (73.6%) and every other day (21.9%) in the >2.5x/week baseline prophylaxis dosing regimen subgroups.

At the end of observation overall in the FAS, patients were most frequently treated 3 times per week (41.4%), followed by 2 times per week (35.1%) and every other day (12.6%). At this time point, 128 patients (42.4%, 95% CI: 36.7% - 48.2%)[22] were on a ≤2.5x/week prophylaxis dosing regimen and 174 patients (57.6%, 95% CI: 51.8% - 63.3%)[22] on a >2.5x/week prophylaxis dosing regimen (see Table 12 and FAS-Table 14.1.6/4). The most common dosing regimens were 2 times per week (75.8%) and every week (8.9%) in the ≤2.5x/week and 3 times per week (65.2%) and every other day (20.8%) in the >2.5x/week baseline prophylaxis dosing regimen subgroups.

Of 124 patients (100%) who were on a ≤2.5x/week prophylaxis dosing regimen at baseline, 113 patients (91.1%) remained in the same regimen category at end of observation, while 11 patients (8.9%) switched to >2.5x/week. Of 178 patients (100%) who were on a >2.5x/week prophylaxis dosing regimen at baseline, 163 patients (91.6%) remained in the same regimen category at end of observation, while 15 patients (8.4%) switched to ≤2.5x/week (FAS-shift Table 14.1.6/5).

Most patients (84.4% of 302 patients) had no switch of prophylaxis dosing regimen (i.e., last prescribed dosing frequency during observation period = prescribed dosing frequency at initial visit), 26 patients (8.6%) had an increase of prophylaxis dosing frequency and 21 patients (7.0%) had a decrease of prophylaxis dosing frequency (FAS-switcher Table 14.1.6/5).

Of the 26 switcher patients with an increase of prophylaxis dosing frequency from baseline to end of observation, 16 patients were in the ≤2.5x/week group at baseline. Of these, 5 patients remained in the ≤2.5x/week group at end of observation, in spite of the increased prophylaxis dosing frequency, while 11 patients changed to the >2.5x/week group at end of observation. The other 10 patients with an increase of prophylaxis dosing frequency remained in >2.5x/week group at end of observation. Of the 21 switcher patients with a decrease of prophylaxis dosing frequency from baseline to end of observation, 20 patients were in the >2.5x/week group at baseline. Of these, 5 patients remained in the >2.5x/week group at end of observation, in spite of the decreased dosing frequency, while 15 patients changed to ≤2.5x/week group at end of observation. The other patient with a decrease of prophylaxis dosing frequency remained in the ≤2.5x/week group at end of observation (FAS-Table 14.1.1/48 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Data on regimen shifts between most recent FVIII regimen prior to KOVALTRY versus baseline KOVALTRY regimen and versus KOVALTRY end of observation are also presented in FAS-shift Table 14.1.6/5. Data on KOVALTRY dosing frequency and shift tables by prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.6/6 and FAS-Table 14.1.6/7, respectively.

[22] At end of observation for the weekly prophylaxis dosing regimen is defined as the last documented regimen change or if no change is documented then regimen at baseline.

Overall, many changes in the prophylaxis dosing regimen were temporary, primarily as a consequence of bleeds, surgery, or AEs. A listing of the subgroup of patients with at least one documented dose/regimen change in prophylaxis dosing regimen during observational period can be found in FAS-Listing 14.1.6./1.

The subgroup analysis by country for weekly prophylaxis dosing regimen showed that the highest proportion of patients in Belgium, Germany, the Netherlands, Spain were treated 3 times per week at baseline and at end of observation. However, patients in Colombia, France and Greece were most frequently treated 2 times per week at baseline and at end of observation. In Italy and Slovenia, the most frequent prophylaxis dosing regimen documented for patients was 2 times per week at baseline for both countries and 3 times per week and every other day, respectively at end of observation. In the USA the most frequently used prophylaxis treatment regimen was 3 times per week at baseline and 2 times per week at end of observation. For region Taiwan, at baseline, patients were most frequently treated 2 times per week while at end of observation, prophylaxis dosing regimens 2 times per week and 3 times per week were equally frequent (FAS-Table 14.1.6/3).

Regarding prophylaxis dosing regimen at baseline and at end of observation, majority of patients in all countries remained in the same prophylaxis dosing regimen at end of observation as at baseline. In Italy, equal proportions of patients were in the ≤2.5x/week and >2.5x/week prophylaxis dosing regimen groups at baseline but a higher proportion of patients were documented in the >2.5x/week group at end of observation. In the USA, a higher proportion of patients were documented with >2.5x/week as their weekly prophylaxis dosing regimen at baseline than at end of observation (FAS-Table 14.1.6/3).

In the subgroup analysis by age category (<12 years: N=57 and ≥12 years: N=245), results for KOVALTRY dosing frequency were in line with results for the overall population: patients were treated most frequently 3 times per week, followed by 2 times per week and every other day at baseline and at end of observation(FAS-Table 14.1.1/35 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

As in the overall population, a clear majority of patients in the <12 years (78.9%) and ≥12 years (85.7%) subgroups had no switch of prophylaxis dosing regimen from baseline to end of observation. However, 14.0% of patients <12 years old had an increase of prophylaxis dosing regimen and 7.3% of patients ≥12 years old had this switch. Very similar proportion of patients in these subgroups had a decrease of prophylaxis dosing regimen from baseline to end of observation (7.0% and 6.9%, respectively) (FAS-switcher Table 14.1.1/36 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1). In the <12 years subgroup, four patients (7.0% of 57 patients) switched from prophylaxis dosing regimen of ≤2.5x/week at baseline to >2.5x/week at the end of observation period, while only one patient (1.8% of 57 patients) switched from prophylaxis dosing regimen of >2.5x/week at baseline to ≤2.5x/week at end of observation. In the ≥12 years subgroup, seven patients (2.9% of 245 patients) switched from prophylaxis dosing regimen of ≤2.5x/week at baseline to >2.5x/week at the end of observation period and 14 patients (5.7% of 245 patients) had the reverse switch from baseline to end of observation (FAS-shift Table 14.1.1/36 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Data on weekly dose of most recent FVIII treatment prior to KOVALTRY and for KOVALTRY at end of observation by different age categories (<6 years, ≥6 - <12 years, ≥12 - <18 years and ≥18 years) are presented in Table 28 in Annex 2.

A summary of prophylaxis dose per week and the overall duration of therapy with KOVALTRY is presented in Table 13.

Table 13: KOVALTRY dose and therapy duration overall and by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Mean prescribed prophylaxis dose per kg per week [IU/kg]			
n	115	167	282
Nmiss	9	11	20
Mean	59.877	83.562	73.903
SD	25.853	45.504	40.377
Median	55.556	75.054	69.806
Min, Max	14.01, 160.00	11.90, 276.32	11.90, 276.32
Change of prescribed prophylaxis dose per kg per week from baseline to end of observation [IU/kg]			
n	120	173	293
Nmiss	4	5	9
Mean	2.688	2.290	2.453
SD	16.460	35.474	29.184
Median	0.000	0.000	0.000
Min, Max	-101.85, 60.12	-88.74, 366.67	-101.85, 366.67
Overall therapy duration with KOVALTRY [months]			
n	124	178	302
Nmiss	0	0	0
Mean	22.996	21.786	22.283
SD	10.425	12.977	11.992
Median	21.602	18.267	19.877
Min, Max	2.53, 78.98	3.22, 102.14	2.53, 102.14

FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation.
Source: FAS-Table 14.1.6/8

The median of mean prescribed weekly KOVALTRY dose for patients in the FAS was 69.806 IU/kg (n=282 patients), 55.556 IU/kg (n=115 patients) and 75.054 IU/kg (n=167 patients) for the total, ≤2.5x/week and >2.5x/week at baseline prophylaxis dosing regimens, respectively. The median overall therapy duration with KOVALTRY for patients in the FAS was 19.877 months (n=302 patients), 21.602 months (n=124 patients) and 18.267 months (n=178 patients) in these groups, respectively.

The mean change of prescribed weekly KOVALTRY dose per kg from baseline to end of observation for patients in the FAS was 2.453 IU/kg (n=293 patients), 2.688 IU/kg (n=120 patients) and 2.290 IU/kg (n= 173 patients) in the total, ≤2.5x/week and >2.5x/week at baseline prophylaxis groups, respectively.

Weekly prescribed doses at baseline and at end of observation, changes of prescribed weekly KOVALTRY dose from prior to start of KOVALTRY to baseline and to the end of observation and shift tables of these prescribed weekly KOVALTRY doses (in categories) are also presented in FAS-Table 14.1.6/8. All these data by prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.6/9.

The median of mean prescribed weekly KOVALTRY dose for patients <12 years old (n=54) and ≥12 years old (n=228) was 75.575 IU/kg (range: 29.41 to 276.32) and 66.667 IU/kg (range: 11.90 to

228.26), respectively (FAS-Table 14.1.1/76 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1). Among patients <12 years old, the median of mean prescribed weekly KOVALTRY dose for patients <6 years old was 75.054 IU/kg (range: 29.41 to 276.32) and 76.096 IU/kg (30.21 to 235.32) for patients ≥6 to <12 years old (FAS-Table 14.1.1/75 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] analyses in Annex 1).

Table 14 provides an overview of KOVALTRY dose / frequency changes and discontinuation.

Table 14: KOVALTRY dose / frequency changes and KOVALTRY discontinuation by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Number of dose / regimen changes until end of observation n(%)			
No change	75 (60.5%)	102 (57.3%)	177 (58.6%)
1 change	17 (13.7%)	21 (11.8%)	38 (12.6%)
2 changes	13 (10.5%)	12 (6.7%)	25 (8.3%)
More than 2 changes	19 (15.3%)	43 (24.2%)	62 (20.5%)
Number of regimen changes until end of observation n(%)			
No change	87 (70.2%)	112 (62.9%)	199 (65.9%)
1 change	14 (11.3%)	18 (10.1%)	32 (10.6%)
2 changes	5 (4.0%)	16 (9.0%)	21 (7.0%)
More than 2 changes	18 (14.5%)	32 (18.0%)	50 (16.6%)
Permanent discontinuation of KOVALTRY treatment n(%)			
Yes	13 (10.5%)	15 (8.4%)	28 (9.3%)
No	111 (89.5%)	163 (91.6%)	274 (90.7%)

FAS: Full Analysis Set, N: number of patients in analysis set, n: number of patients.
Source: FAS-Table 14.1.6/10

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. Regarding the subgroups, patients in the >2.5x/week baseline prophylaxis dosing regimen group had a considerably higher proportion of patients with more than 2 dose / regimen changes (24.2%) than patients in the ≤2.5x/week subgroup (15.3%). Overall in the FAS, the most frequent reasons for dose / regimen changes based on the total number of dose / regimen changes (N=575) were "increase in bleeding frequency" (15.7%), "resumption of treatment after bleeding" (14.3%), "surgical intervention" (13.4%), "bleeding" (9.7%), "adverse event" (9.4%) and "resumption of treatment after surgery" (8.5%). All other reasons were reported ≤5% of the total number of reasons (FAS-Table 14.1.6/10).

The most common three reasons ("increase in bleeding frequency", "resumption of treatment after bleeding" and "surgical intervention") were also amongst the most frequent reasons for dose / regimen changes in switcher patients, i.e., patients with an increase or decrease of prophylaxis dosing regimen from baseline to end of observation. The following reasons were more frequent reasons for dose / regimen changes in the switcher patients with a decrease of prophylaxis dosing regimen (N=93) than in those patients with an increase of prophylaxis dosing regimen (N=119) from baseline to end of observation: "adverse event" (11.8% vs. 8.4%), "increase in bleeding frequency" (26.9% vs. 17.6%), and "as a consequence of pharmacokinetics" (6.5% vs. 2.5%). The reverse was true for reasons of "bleeding" (2.2% vs. 10.1%), "surgical intervention" (8.6% vs. 11.8%), and "physician decision"

(1.1% vs. 4.2%) (FAS-Table 14.1.1/105 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

The following reasons for dose / regimen changes were more common in patients <12 years old (N=133) than in patients ≥12 years old (N=442): "surgical intervention" (16.5% vs. 12.4%), "bleeding" (15.8% vs. 7.9%), "adverse event" (11.3% vs. 8.8%), "resumption of prophylactic treatment" (6.8% vs. 4.5%) and "resolution of AE (6.0% vs. 2.9%)". In contrast, the following reasons were less frequent in patients <12 years old than in patients ≥12 years old: "increase in bleeding frequency" (9.0% vs. 17.6%), "resumption of treatment after bleeding" (10.5% vs. 15.4%) and "resumption of treatment after surgery" (6.8% vs. 9.0%) (FAS-Table 14.1.1/99 in TFL 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Only a small proportion of patients (28 patients, 9.3%) in the FAS permanently discontinued KOVALTRY treatment. The reasons for switch to another therapy in patients with permanent discontinuation of KOVALTRY treatment were "other" (12 patients, 42.9%), "physician decision" (7 patients, 25.0%), "lack of efficacy" (4 patients, 14.3%) and AE (2 patients, 7.1%). Reasons for discontinuation were missing for 3 patients (10.7%) (FAS-Table 14.1.6/10).

Information on KOVALTRY dose / regimen changes, reasons for dose / regimen changes and therapy discontinuation by prophylaxis dosing regimen at baseline and switch of regimen is presented in FAS-Table 14.1.6/11.

10.4.2 Study medications and bleeds as documented in patient diary

The median documentation period of the patient diary was 368.5 days (range: 1.00 to 789.00 days), 374.5 days (range: 36.00 to 756.00 days) and 366.0 days (range: 1.00 to 789.00 days) for the total (n=268 patients), ≤2.5x/week (n=110 patients) and >2.5x/week (n=158 patients) at baseline prophylaxis dosing regimen groups, respectively. The median documentation period of the patient diary in the subgroup of patients with complete prophylaxis documentation[23] was 368.0 days (range: 92.00 to 789.00 days; n=213 patients), 369.0 days (range: 117.00 to 751.00 days; n=89 patients) and 367 days (range: 92.00 to 789.00 days; n=124 patients) in these groups, respectively (FAS-Table 14.1.7/1). These data by prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.7/2.

The number and annualized number of injections taken by patients in different dosing regimens is presented in Table 15.

[23] The subgroup of patients with complete prophylaxis documentation of diary is defined as all patients with no time interval of 21 or more days without any documented injection. In addition a time period of at least 90 days has to be documented in the patient diary.

Table 15: Number and annualized number of injections by prophylaxis dosing regimen at baseline (FAS)

	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
n	110	158	268
Nmiss	14	20	34
Number of injections			
Mean	120.1	164.1	146.0
SD	71.9	89.6	85.4
Median	106.0	152.5	131.5
Min, Max	0, 375	0, 385	0, 385
Annualized number of injections*			
Mean	100.165	151.343	130.337
SD	33.241	39.986	45.027
Median	104.087	157.429	132.219
Min, Max	00.00, 208.14	0.00, 365.25	0.00, 365.25
Subgroup of patients with complete prophylaxis documentation of diary#			
n	89	124	213
Nmiss	0	0	0
Number of injections			
Mean	125.2	169.7	151.1
SD	72.0	81.2	80.4
Median	108.0	159.5	137.0
Min, Max	0, 375	0, 385	0, 385
Annualized number of injections*			
Mean	104.191	151.859	131.941
SD	30.628	35.761	41.070
Median	105.052	157.874	135.278
Min, Max	0.00, 208.14	0.00, 213.64	0.00, 213.64

*: The annualized number of injections was calculated as [Sum (injections) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).
#: The subgroup of patients with complete prophylaxis documentation of diary is defined as all patients with no time interval of 21 or more days without any documented injection. In addition a time period of at least 90 days has to be documented in the patient diary.
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in analysis set, Nmiss: number of patients with missing values in analysis set, SAP: Statistical Analysis Plan, SD: standard deviation
Source: FAS-Table 14.1.7/3

The median number of annualized[24] injections was 132.219 (range: 0.00 to 365.25), 104.087 (range: 0.00 to 208.14) and 157.429 (range: 0.00 to 365.25) in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. The most common reason for documented injections was "prophylactic injections" (94.4% of the total number of injections) (FAS-Table 14.1.7/5). Similar results were observed in the subgroup of patients with complete prophylaxis documentation of diary.

Data on the number of annualized injections and reasons for documented injections by prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.7/4 and FAS-Table 14.1.7/6, respectively.

[24] The annualized number of injections was calculated as [Sum (injections) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

For patients <12 years old (n=54), the median number of annualized injections was 144.488 (range: 45.66 to 213.64) and was 123.590 (range: 0.00 to 365.25) for patients ≥12 years old (n= 214). Furthermore, within patients <12 years old, the median numbers of annualized injections for patients <6 years old (n=11) and ≥6 to <12 years old (n=43) were 153.219 (range: 109.27 to 213.64) and 143.472 (range: 45.66 to 212.28), respectively (FAS-Table 14.1.1/28 and FAS-Table 14.1.1/29 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

The annualized number of reported bleeds for the FAS is summarized in Table 16.

Table 16: Reported and annualized number of reported bleeds overall and by prophylaxis dosing regimen at baseline and switch of regimen (FAS)

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
n	96	131	41	110	158	268
Nmiss	11	17	6	14	20	34
Reported number of total treated bleeds						
Mean	4.4	3.5	4.5	4.6	3.5	4.0
SD	8.9	5.0	5.2	8.5	5.0	6.7
Median	1.0	1.0	2.0	1.0	1.0	1.0
Min, Max	0, 59	0, 25	0, 21	0, 59	0, 25	0, 59
Annualized number of total treated bleeds*						
Mean	4.295	3.122	3.591	4.306	3.132	3.614
SD	8.791	4.570	4.183	8.315	4.519	6.370
Median	1.021	1.124	1.764	1.114	1.112	1.112
Min, Max	0.00, 57.93	0.00, 21.49	0.00, 14.81	0.00, 57.93	0.00, 21.49	0.00, 57.93
Reported number of spontaneous bleeds						
Mean	3.1	2.3	3.1	3.2	2.3	2.7
SD	8.2	4.1	4.5	7.7	4.3	5.9
Median	0.0	0.0	1.0	1.0	0.0	1.0
Min, Max	0, 59	0, 25	0, 20	0, 59	0, 25	0, 59
Annualized number of spontaneous bleeds*						
Mean	3.065	1.923	2.318	3.004	1.966	2.392
SD	8.183	3.435	3.249	7.694	3.449	5.606
Median	0.000	0.000	0.982	0.682	0.000	0.493
Min, Max	0.00, 57.93	0.00, 19.18	0.00, 12.83	0.00, 57.93	0.00, 19.18	0.00, 57.93

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Reported number of trauma bleeds						
Mean	1.1	0.9	1.2	1.2	0.9	1.0
SD	2.7	2.2	2.0	2.7	2.1	2.3
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 17	0, 13	0, 9	0, 17	0, 13	0, 17
Annualized number of trauma bleeds*						
Mean	1.059	0.934	1.021	1.144	0.886	0.992
SD	2.715	2.341	1.918	2.674	2.224	2.418
Median	0.000	0.000	0.000	0.000	0.000	0.000
Min, Max	0.00, 17.01	0.00, 14.30	0.00, 9.11	0.00, 17.01	0.00, 14.30	0.00, 17.01
Reported number of undefined spontaneous / trauma bleeds						
Mean	0.2	0.3	0.2	0.2	0.3	0.2
SD	0.6	1.2	0.5	0.6	1.1	1.0
Median	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 4	0, 13	0, 2	0, 4	0, 13	0, 13
Annualized number of undefined spontaneous / trauma bleeds*						
Mean	0.171	0.265	0.253	0.158	0.279	0.229
SD	0.454	1.567	0.902	0.435	1.494	1.180
Median	0.000	0.000	0.000	0.000	0.000	0.000
Min, Max	0.00, 2.06	0.00, 17.52	0.00, 5.29	0.00, 2.06	0.00, 17.52	0.00, 17.52
Reported number of total joint bleeds						
Mean	3.4	2.4	3.0	3.5	2.5	2.9
SD	8.1	4.3	4.1	7.7	4.3	5.9
Median	0.5	1.0	1.0	1.0	1.0	1.0
Min, Max	0, 59	0, 25	0, 17	0, 59	0, 25	0, 59

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Annualized number of total joint bleeds*						
Mean	3.363	2.129	2.266	3.270	2.119	2.592
SD	8.054	3.694	2.975	7.582	3.594	5.602
Median	0.248	0.501	1.009	0.658	0.506	0.510
Min, Max	0.00, 57.93	0.00, 19.18	0.00, 12.83	0.00, 57.93	0.00, 19.18	0.00, 57.93

*: The annualized number of reported bleeds was calculated as (number of reported bleeds / documentation period of the patient diary in days) * 365.25 (SAP version 3.0 section 4.6, see Annex 1).
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in subgroup or analysis set, SAP: Statistical Analysis Plan, SD: standard deviation
Source: FAS-Table 14.1.7/7 and FAS-Table 14.1.7/8

The median number of annualized[25] 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) in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. The median number of annualized reported total joint bleeds was 0.510 (range: 0.00 to 57.93), 0.658 (range: 0.00 to 57.93) and 0.506 (range: 0.00 to 19.18) in these subgroups, respectively. The median number of annualized reported spontaneous bleeds was 0.493 (range: 0.00 to 57.93), 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. Similar results were observed in the subgroup of patients with complete prophylaxis documentation of diary.

On comparison of subgroups by prophylaxis dosing regimen at baseline and switch of regimen, the median number of annualized reported total treated bleeds was 1.021 (range: 0.00 to 57.93) for the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup, 1.124 (range: 0.00, 21.49) for the >2.5x/week and no switch of prophylaxis dosing regimen subgroup and 1.764 (range: 0.00 to 14.81) for the switcher of prophylaxis dosing regimen subgroup. The median number of annualized reported total joint bleeds was 0.248 (range: 0.00 to 57.93), 0.501 (range: 0.00 to 19.18) and 1.009 (range: 0.00 to 12.83) for these subgroups, respectively. The switcher of prophylaxis dosing regimen subgroup had a median of 0.982 (range: 0.00 to 12.83) annualized reported spontaneous bleeds as compared to 0.000 for the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup (range: 0.00 to 57.93) and >2.5x/week and no switch of prophylaxis dosing regimen subgroup (range: 0.00 to 19.18). There were no major differences in the median number of annualized reported trauma and undefined spontaneous / trauma bleeds among these subgroups.

A similar proportion of patients in the ≤2.5x/week (N=124) and >2.5x/week (N=178) baseline prophylaxis dosing regimen groups documented zero annualized number of total treated bleeds (33.9% vs. 34.8%) and total joint bleeds (42.7% vs. 43.8%). However, spontaneous bleeds (42.7% vs. 46.1%) and trauma bleeds (56.5% vs. 61.2%) were higher in the >2.5x/week baseline prophylaxis dosing regimen group. These data were missing for 11.3% and 11.2% of patients in these groups, respectively. In the subgroup of patients with complete prophylaxis documentation of diary, a higher proportion of patients in the >2.5x/week baseline prophylaxis dosing regimen group (N=124) had zero bleeds than the ≤2.5x/week group (N=89) for the annualized number of total treated bleeds (37.1% vs. 34.8%), spontaneous bleeds (51.6% vs. 46.1%), trauma bleeds (68.5% vs. 58.4%), and total joint bleeds (48.4% vs. 44.9%) (FAS-Table 14.1.7/7). Further information on the reported number of bleeds for all patients, for the subgroup of patients with complete prophylaxis documentation of diary and information on the reported and annualized number of bleeds in other categories can be found in FAS-Table 14.1.7/7.

On comparison of subgroups by prophylaxis dosing regimen at baseline and switch of regimen, a slightly higher proportion of patients in the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup (N=107) reported zero bleeds than the >2.5x/week and no switch of prophylaxis dosing regimen subgroup (N=148) for the annualized number of total treated bleeds (37.4% vs. 33.8%), and total joint bleeds (45.8% vs. 43.9%). However, similar proportion of patients in these subgroups reported zero spontaneous bleeds (46.7% vs. 45.9%) and trauma bleeds (60.7% vs. 60.1%). These

[25] The annualized number of reported bleeds was calculated as (number of reported bleeds / documentation period of the patient diary in days) * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

data were missing for 10.3% and 11.5% of patients in these groups, respectively. In comparison to these two subgroups, the lowest proportion of patients in the switcher of prophylaxis dosing regimen subgroup (N=47) had zero bleeds for annualized number of total treated bleeds (29.8%), spontaneous bleeds (36.2%), trauma bleeds (53.2%), and total joint bleeds (36.2%). Data for 12.8% of patients from this subgroup was missing. In the subgroup of patients with complete prophylaxis documentation of diary, a lower proportion of patients in the >2.5x/week baseline prophylaxis dosing regimen group (N=105) than the ≤2.5x/week group (N=75) documented zero annualized number of total treated bleeds (35.2% vs. 38.7%), but a higher proportion of trauma bleeds (67.6% vs. 62.7%). The proportion of patients with zero spontaneous bleeds (50.7% vs. 51.4%) and total joint bleeds (47.6% vs. 48.0%) was similar between subgroups.

Again, the lowest proportion of patients in the switcher of prophylaxis dosing regimen subgroup had zero bleeds for annualized number of total treated bleeds (33.3%), spontaneous bleeds (39.4%), trauma bleeds (57.6%), and total joint bleeds (42.4%). (FAS-Table 14.1.7/8). Further information on the reported number of bleeds for all patients, for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline and switch of regimen and information on the reported and annualized number of bleeds in other categories can be found in FAS-Table 14.1.7/8.

For patients <12 years old, the median number of annualized reported total treated bleeds in ≤2.5x/week subgroup (n=20) was higher than in the >2.5x/week subgroup (n=34) (≤2.5x/week: 3.192 [range: 0.00, 11.13;], >2.5x/week: 0.755 [range: 0.00, 8.07]). A similar tendency was observed for the number of annualized reported total joint bleeds in these patients (≤2.5x/week: 1.015 [range: 0.00, 7.06], >2.5x/week: 0.000 [range: 0.00, 4.04]). However, in patients ≥12 years old, the median number of annualized reported total treated bleeds in the ≤2.5x/week subgroup (n=90) was slightly lower than in the >2.5x/week subgroup (n=124) (≤2.5x/week: 1.070 [range: 0.00, 57.93], >2.5x/week: 1.248 [range: 0.00, 21.49]). The number of annualized**Error! Bookmark not defined.** reported total joint bleeds was comparable in both subgroups (≤2.5x/week: 0.506 [range: 0.00, 57.93], >2.5x/week: 0.541 [range: 0.00, 19.18]) (FAS-Table 14.1.1/70 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

The median number of annualized reported total treated bleeds in patients with no switch of prophylaxis dosing regimen from baseline to end of observation (n=227) was 1.077 (range: 0.00 to 57.93), 2.441 (range: 0.00 to 11.72) in patients with increase of prophylaxis dosing regimen (n=22) and 0.971 (range: 0.00 to 14.81) in patients with decrease in prophylaxis dosing regimen (n=19) during the study. The median numbers of annualized reported total joint bleeds in these subgroups were 0.496 (range: 0.00 to 57.93), 1.242 (range: 0.00 to 9.76) and 0.604 (range: 0.00 to 12.83), respectively. Similarly, the median number of annualized reported spontaneous bleeds and spontaneous joint bleeds was highest in patients with an increase of prophylaxis dosing regimen followed by patients with decrease in prophylaxis dosing regimen and no switch of prophylaxis dosing regimen. There were no major differences observed in the median number of annualized reported trauma bleeds, undefined spontaneous / trauma bleeds, and trauma joint bleeds among these subgroups (FAS-Table 14.1.1/81 in 18559_TAURUS_TGL_FA_ TFL Subgroup Analysis [FAS] in Annex 1).

Among patients <12 years old, the median number of annualized reported total treated bleeds in 11 patients <6 years old were 5.120 (range: 2.02 to 11.13) in the ≤2.5x/week subgroup (n=3) and 0.302

(range: 0.00 to 3.70) in the >2.5x/week subgroup (n=8). The median number of annualized reported total joint bleeds in these subgroups were 1.009 (range: 0.00 to 4.05) and 0.000 (range: 0.00 to 3.00), respectively. For patients ≥6 to <12 years old, the median number of annualized reported total treated bleeds in the ≤2.5x/week subgroup (n=17) was 2.986 (range: 0.00 to 9.37) and 0.898 (range: 0.00 to 8.07) in the >2.5x/week subgroup (n=26). The median number of annualized reported total joint bleeds in these subgroups were 1.020 (range: 0.00 to 7.06) and 0.000 (range: 0.00 to 4.04), respectively (FAS-Table 14.1.1/70 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

A higher proportion of patients <12 years old (N=57) was documented with zero bleeds than patients ≥12 years old (N=245) for the annualized number of total treated bleeds (38.6% vs. 33.5%), spontaneous bleeds (54.4% vs. 42.4%), and total joint bleeds (49.1% vs. 42.0%), with the exception of trauma bleeds where the proportion was lower (57.9% vs. 59.6%). These data were missing for 5.3% and 12.7% of patients in these groups, respectively. This trend was also observed in the subgroup of patients with complete prophylaxis documentation of diary in patients <12 years old (N=43) compared to patients ≥12 years old (N=170): annualized number of total treated bleeds (41.9% vs. 34.7%), spontaneous bleeds (60.5% vs. 46.5%), total joint bleeds (55.8% vs. 44.7%), and trauma bleeds (60.5% vs. 65.3%) (FAS-Table 14.1.1/75 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Among patients <12 years old, a lower proportion of patients <6 years old (N=11) were documented with zero bleeds than patients ≥6 to <12 years old (N=46) for the annualized number of total treated bleeds (36.4% vs. 39.1%) and spontaneous bleeds (45.5% vs. 56.5%), whereas the reverse was true for trauma bleeds (63.6% vs. 56.5%) and total joint bleeds (54.5% vs. 47.8%). Data for 6.5% of patients ≥6 to <12 years old was missing. A similar tendency was observed in the subgroup of patients with complete prophylaxis documentation of diary in patients <6 years old (N=10) compared to patients ≥6 to <12 years old (N=33): annualized number of total treated bleeds (30.0% vs. 45.5%),spontaneous bleeds (40.0% vs. 66.7%), and total joint bleeds (50.0% vs. 57.6%) with the exception of trauma bleeds (60.0% vs. 60.6%) where the proportion of patients was similar. (FAS-Table 14.1.1/74 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Table 17 presents change of annualized number of bleeds during observation period overall, by prophylaxis dosing regimen at baseline, and by prophylaxis dosing regimen at baseline and switch of regimen for the FAS.

Table 17: Change of annualized number of bleeds during observation period overall, by prophylaxis dosing regimen at baseline, and by prophylaxis dosing regimen at baseline and switch of regimen (FAS)

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Difference of annualized number of total treated bleeds during observation period and annualized number of bleeds prior to study entry*						
n	96	131	41	110	158	268
Nmiss	11	17	6	14	20	34
Mean	-0.018	0.175	-0.653	0.106	-0.109	-0.021
SD	9.567	5.029	4.748	9.034	5.051	6.952
Median	0.000	0.000	0.000	0.000	0.000	0.000
Min, Max	-36.00, 57.93	-20.07, 15.49	-16.00, 8.83	-36.00, 57.93	-20.07, 15.49	-36.00, 57.93
Difference of annualized number of total joint bleeds during observation period and annualized number of joint bleeds prior to study entry#						
n	96	131	41	110	158	268
Nmiss	11	17	6	14	20	34
Mean	-0.054	0.129	-1.539	-0.093	-0.260	-0.192
SD	8.554	4.341	7.902	8.085	5.565	6.701
Median	0.000	0.000	0.000	0.000	0.000	0.000
Min, Max	-26.99, 57.93	-20.00, 14.74	-44.98, 6.77	-26.99, 57.93	-44.98, 14.74	-44.98, 57.93

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Difference of annualized number of total treated bleeds during observation period and annualized number of bleeds prior to initiation of KOVALTRY[**]						
n	90	120	38	103	145	248
Nmiss	17	28	9	21	33	54
Mean	0.073	0.602	-1.301	0.177	0.077	0.118
SD	6.636	4.440	10.846	6.376	6.757	6.589
Median	0.000	0.000	0.252	0.000	0.000	0.000
Min, Max	-26.74, 25.41	-14.37, 16.74	-60.93, 7.13	-26.74, 25.41	-60.93, 16.74	-60.93, 25.41
Difference of annualized number of total joint bleeds during observation period and annualized number of joint bleeds prior to initiation of KOVALTRY[##]						
n	90	121	38	103	146	249
Nmiss	17	27	9	21	32	53
Mean	-0.189	0.244	-1.375	-0.194	-0.136	-0.160
SD	5.288	4.490	8.229	5.090	5.782	5.495
Median	0.000	0.000	0.002	0.000	0.000	0.000
Min, Max	-28.80, 16.53	-20.00, 17.18	-44.98, 4.93	-28.80, 16.53	-44.98, 17.18	-44.98, 17.18

[*]: Annualized number of total treated bleeds during observation period - annualized number of bleeds prior to study entry
[#]: Annualized number of total joint bleeds during observation period - annualized number of joint bleeds prior to study entry
[**]: Annualized number of total treated bleeds during observation period - annualized number of bleeds prior to initiation of KOVALTRY
[##]: Annualized number of total joint bleeds during observation period - annualized number of joint bleeds prior to initiation of KOVALTRY
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in subgroup or analysis set, SD: standard deviation
Source: FAS-Table 14.1.7/9 and FAS-Table 14.1.7/10

There was no drastic change in annualized number of total treated bleeds and total joint bleeds during the observation period compared to prior to study entry or prior to initiation of KOVALTRY in any of the subgroups (by prophylaxis dosing regimen at baseline / by prophylaxis dosing regimen at baseline and switch of regimen). The mean changes differed between the subgroups however, this difference was not reflected in the median changes.

Further data in change of annualized number of bleeds during observation period for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline and by prophylaxis dosing regimen at baseline and switch of regimen in the FAS can be found in FAS-Table 14.1.7/9 and FAS-Table 14.1.7/10, respectively.

Data on the number and annualized number of injections for bleeds for all patients and for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline can be found in FAS-Table 14.1.7/11 and FAS Table 14.1.7/13, respectively. These data by prophylaxis dosing regimen at baseline and switch of regimen in the FAS can be found in FAS-Table 14.1.7/12 and FAS-Table 14.1.7/14, respectively.

The data analyzed for total dose of KOVALTRY for bleeds for all patients in the FAS and for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline can be found in FAS-Table 14.1.7/15. These data by prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.7/16.

Data for total and annualized doses for surgery for the subgroup of patients with at least one KOVALTRY injection for surgery documented in the patient diary by prophylaxis dosing regimen at baseline in the FAS are provided in FAS-Table 14.1.7/17. These data By prophylaxis dosing regimen at baseline and switch of regimen are presented in FAS-Table 14.1.7/18. A listing for injections for surgery is provided in FAS-Listing 14.1.7/1.

The number and annualized number of injections for prophylaxis for all patients in the FAS and for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline is presented in FAS-Table 14.1.7/19. Data on the dose for prophylaxis for all patients in the FAS and for the subgroup of patients with complete prophylaxis documentation of diary by prophylaxis dosing regimen at baseline are presented in FAS-Table 14.1.7/21. These data are also presented by prophylaxis dosing regimen at baseline and switch of regimen for (annualized) number of injections and dose for prophylaxis in FAS-Table 14.1.7/20, FAS-Table and 14.1.7/22, respectively.

Understandably, a higher proportion of patients from the ≤2.5x/week baseline prophylaxis dosing regimen group documented 2x/week prophylaxis dosing regimen in patient diary compared to the >2.5x/week group (55.6% vs 17.4%). The reverse was true for documentation of 3x/week prophylaxis dosing regimen (9.7% vs. 62.4%). This data was missing for 11.3% and 11.2% of patients from these groups, respectively. Similar results were also observed among subgroup of patients with complete prophylaxis documentation of diary (FAS-Table 14.1.7/23).

The total annualized factor consumption for the FAS is summarized in Table 18.

Table 18: Total annualized dose for prophylaxis and total annualized factor consumption overall, by prophylaxis dosing regimen at baseline, and by prophylaxis dosing regimen at baseline and switch of regimen (FAS)

	≤2.5x/week and no switch of prophylaxis dosing regimen N=107	>2.5x/week and no switch of prophylaxis dosing regimen N=148	Switcher of prophylaxis dosing regimen N=47	≤2.5x/week N=124	>2.5x/week N=178	Total N=302
Annualized total dose per kg for prophylaxis (IU/kg)*						
n	96	130	40	110	156	266
Nmiss	11	18	7	14	22	36
Mean	3215.877	4570.149	3732.527	3205.825	4484.000	3955.431
SD	1550.865	2248.017	2612.189	1552.477	2385.488	2171.983
Median	3369.351	4041.084	3441.205	3352.814	3974.755	3704.713
Min, Max	0.00, 10330.80	1187.62, 16866.06	0.00, 13527.01	0.00, 10330.80	0.00, 16866.06	0.00, 16866.06
Total annualized factor consumption (IU/kg/year)**						
n	96	130	40	110	156	266
Nmiss	11	18	7	14	22	36
Mean	3488.788	4821.282	4032.466	3492.214	4736.189	4221.763
SD	1661.461	2287.035	2608.192	1644.899	2419.370	2216.592
Median	3448.000	4350.086	3685.949	3383.774	4307.538	3923.002
Min, Max	0.00, 10606.88	1429.96, 16866.06	0.00, 13527.01	0.00, 10606.88	0.00, 16866.06	0.00, 16866.06

*: [Sum (doses per kg for prophylaxis) / documentation period of the patient diary in days] * 365.25
**: [Sum (all doses per kg) / documentation period of the patient diary in days] * 365.25
FAS: Full Analysis Set, Max: maximum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: : number of patients with missing values in subgroup or analysis set, SD: standard deviation.
Source: FAS-Table 14.1.7/21, FAS-Table 14.1.7/22, FAS-Table 14.1.7/23 and FAS-Table 14.1.7/24

The median total annualized[26] 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. The median annualized[27] total dose per kg for prophylaxis for these subgroups was 3704.713 IU/kg, 3352.814 IU/kg, and 3974.755 IU/kg, respectively.

[26] The annualized factor consumption for prophylaxis, bleeds and other events was calculated as [Sum (all doses per kg) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

[27] The annualized total dose per kg for prophylaxis was calculated as [Sum (doses per kg for prophylaxis) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

For the subgroups by prophylaxis dosing regimen at baseline and switch of regimen, the median total annualized factor consumption for prophylaxis, bleeds and other events was 3448.000 IU/kg/year for the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup, 4350.086 IU/kg/year for the >2.5x/week and no switch of prophylaxis dosing regimen subgroup, and 3685.949 IU/kg/year for the switcher of prophylaxis dosing regimen subgroup. The median annualized total dose per kg for prophylaxis for these subgroups was 3369.351 IU/kg, 4041.084 IU/kg, and 3441.205 IU/kg, respectively.

Further data on prophylaxis regimen as documented in the diary per 30 day time intervals and overall total dose and annualized total dose for prophylaxis, bleeds and other events are presented in FAS-Table 14.1.7/23. These data for treatment dose and frequency by prophylaxis dosing regimen at baseline and switch of regimen are given in FAS-Table 14.1.7/24.

A listing with details of injections documented in patient diary (at or after initial visit and before end of observation) by patients in each participating country is provided in Listing 14.1.1/1 to 14.1.1/12 and can be found in Annex 1 as a stand-alone document.

The median total annualized factor consumption for prophylaxis, bleeds and other events for patients with no switch of prophylaxis dosing regimen (n=226) was higher than for either of the switcher groups, i.e. increase (n=21) or decrease (n=19) of prophylaxis dosing regimen from baseline to end of observation: 3943.740 IU/kg/year (range: 0.00 to 16866.06) vs. 3682.454 IU/kg/year (range: 0.00 to 13527.01) or 3779.602 IU/kg/year (range: 0.00 to 11025.26) (FAS-Table 14.1.1/81 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1). A similar trend was observed on comparison of median annualized total dose per kg for prophylaxis within these subgroups: 3759.523 IU/kg (range: 0.00 to 16866.06) for patients with no switch of prophylaxis dosing regimen vs. 3402.116 IU/kg (range: 0.00 to 13527.01) for patients with increase of prophylaxis dosing regimen and 3480.294 IU/kg (range: 0.00 to 11025.26) for patients with decrease of prophylaxis dosing regimen from baseline to end of observation (FAS-Table 14.1.1/58 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1)..

For patients <12 years old (n=54), the median total annualized factor consumption for prophylaxis, bleeds and other events was 4117.615 IU/kg/year (range: 2141.14 to 16866.06) and it was 3777.307 IU/kg/year (range: 0.00 to 11910.33) for patients ≥12 years old (n=212) (FAS-Table 14.1.1/75 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1). Specifically for patients <12 years old, the median total annualized factor consumption for prophylaxis, bleeds and other events: 5535.391 IU/kg/year (range: 2978.23 to 16866.06) for patients <6 years old (n=11) and 3953.473 IU/kg/year (range: 2141.14 to 13527.01) for patients ≥6 to <12years old (n=43) (FAS-Table 14.1.1/74 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

The median annualized total dose per kg for prophylaxis for patients <12 years old and patients ≥12 years old was 3843.604 IU/kg (range: 2141.14 to 16866.06) and 3610.693 IU/kg (range: 0.00 to 11910.33), respectively (FAS-Table 14.1.1/52 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1). For patients <6 years old and patients ≥6 to <12years old, the median annualized total dose per kg for prophylaxis was 4258.919 IU/kg (range: 2546.83 to 16866.06) and 3841.462 IU/kg (range: 2141.14 to 13527.01), respectively (FAS-Table 14.1.1/51 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

Data on prophylaxis dosing regimen, joint bleeds and target joints prior to KOVALTRY treatment and with KOVALTRY at end of observation by age categories (<6 years, ≥6 - <12 years, ≥12 - <18 years and ≥18 years) are presented in Table 29 in Annex 2.

10.4.3 PK Assessment and findings

Data for von Willebrand factor prior to KOVALTRY, at baseline and at end of observation was not documented for the vast majority of patients (>90.0%) in the FAS, presented in FAS-Table 14.1.5/1 by prophylaxis dosing regimen at baseline. These data by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.5/2.

PK assessments performed during most recent FVIII therapy prior to prophylaxis with KOVALTRY was not documented for 81.5% of patients, was documented for 17.5% of patients, and was missing for 1.0% of patients in the FAS. The number of PK assessments performed since start of KOVALTRY treatment was not documented for 55.6% in the FAS. Similarly, for the majority of patients the number of PK assessments with one stage assay and with chromogenic assay performed since start of KOVALTRY treatment was not documented for 64.6% and 91.1%, respectively. 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 (FAS-Table 14.1.5/3). Other PK assessments since start of KOVALTRY were not performed for the majority of patients: FVIII C activity assessments (56.3%), FVIII half-life assessments (87.7%), 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%). For all these parameters, a higher proportion of patients in the >2.5x/week baseline prophylaxis dosing regimen group were documented with assessments than in the ≤2.5x/week group (FAS-Table 14.1.5/3). These data by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.5/4.

A listing of PK assessments and findings is provided in FAS-Listing 14.1.5/1.

For patients <12 years old (N=57), 19.3% of patients had 1 and 3.5% of patients had 2 assessments performed for the FVIII half-life assessments since start of KOVALTRY. These assessments for patients ≥12 years old (N=245) were performed in 9.0% and 0.8% of patients, respectively. One AUC and clearance assessment since start of KOVALTRY was performed for 0.8% and 2.0% of patients ≥12 years old, respectively and two assessments were performed for 0.4% of patients each. For patients <12 years old, 1 AUC and clearance assessment was performed in 1.8% and 3.5% of patients, respectively and none of the patients had 2 of these assessments (FAS-Table 14.1.1/29 in 18559_TAURUS_TGL_FA_v1.0_FAS_PK_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

10.4.4 Inhibitor measurements

In the SAF, none of the patients for which data on inhibitor assessments were available had a positive test result. A total of 159 patients (50.8%) had a negative test result and data were not available for 154 patients (49.2%) (SAF-Table 14.1.5/1). A listing of inhibitor measurements is provided in SAF-Listing 14.1.5/1.

10.4.5 Target joints

For all patients in the FAS, the number of target joints at baseline was documented. The mean (± SD) number of target joints for these patients at baseline was 1.0 ± 1.8 (median: 0.0, range: 0 – 15). In total for patients in the FAS at baseline 175 patients (57.9%), 57 patients (18.9%) and 70 patients (23.2%) had 0, 1 and 2 or more target joints, respectively. The number of target joints at the end of observation was documented for 262 of 302 patients in the FAS. The mean (±SD) number of target joints for these patients at the end of observation was 0.7 ± 1.4 (median: 0.0, range: 0 – 8). In total, for patients in the FAS; 181 patients (59.9%), 38 patients (12.6%) and 43 patients (14.2%) had 0, 1 and 2 or more target joints, respectively. Data on the number of target joints for 13.2% of total patients were missing at the end of observation (FAS-Table 14.1.8/1). The number of target joints and proportion of patients with target joints at baseline and at end of observation were comparable between the ≤2.5x/week and >2.5x/week prophylaxis dosing regimen groups at baseline.

The majority of patients had the same number of target joints at baseline and at end of observation: 0 target joints in 136 patients (45.0%), 1 target joint in 25 patients, (8.3%), 2 or more target joints in 35 patients (11.6%). A total of 23 patients (7.6%) and 22 patients (7.3%) with 1 target joint and 2 or more target joints at baseline, respectively, were reported with 0 target joints at end of observation. Ten patients (3.3%) with 0 target joints at baseline were reported with 1 target joint at end of observation. Other switches from 0 or 1 target joints at baseline to 2 or more target joints at end of observation and 2 or more target joints at baseline to 1 target joint at end of observation were documented in few patients (≤2.0%). Comparable results for shift of number of target joints from baseline to end of observation were observed between the ≤2.5x/week and >2.5x/week prophylaxis dosing regimen groups at baseline (FAS-Table 14.1.8/1).

Data on the location of target joints by age category at both baseline and end of observation are provided in FAS-Table 14.1.8/1.

The number and location of target joints at baseline and at the end of observation and shift table of number of target joints from baseline to end of observation by prophylaxis dosing regimen at baseline and switch of regimen is presented FAS-Table 14.1.8/2.

Results for the SAF were in line with the FAS (SAF-Table 14.1.6/1).

In the subgroup analysis by age category, a higher proportion of patients <12 years old (N=57) than ≥12 years old (N=245) had 0 target joints (86.0% vs. 51.4%). In contrast, lower proportions of patients <12 years old than ≥12 years old had 1 target joint (10.5% vs. 20.8%) or 2 or more target joints (3.5% vs. 27.8%) at baseline. This tendency was also maintained at end of observation: a higher proportion of patients <12 years old than ≥12 years old had 0 target joints (78.9% vs. 55.5%), while lower proportions of patients <12 years old than ≥12 years old had 1 target joint (8.8% vs. 13.5%) or 2 or more target joints (5.3% vs. 16.3%). Thus, overall younger patients presented lower numbers of target joints. In line with results for the overall FAS, however, the majority of patients had the same number of target joints at baseline and at end of observation in both subgroups, <12 years and ≥12 years. In the subgroup of patients <12 years, 2 patients (3.5%) shifted from 1 target joint at baseline to 0 target

joints at end of observation. In the subgroup of patients ≥12 years, 21 patients (8.6%) shifted from 1 target joint at baseline to 0 target joints at end of observation, and 22 patients (9.0%) and 3 patients (1.2%) shifted from 2 or more target joints at baseline to 0 and 1 target joint at end of observation, respectively. Few patients had a shift from 0 or 1 target joints at baseline to 1 or 2 or more target joints at end of observation (FAS-Table 14.1.1/6 in 18559_TAURUS_TGL_FA_v1.0_FAS_target_joints_20210415.docx, see TFL Subgroup Analysis [FAS] in Annex 1).

10.4.6 Hemo-SAT

Adult patients (>17 years of age; Hemo-SAT A) and parents/caregivers for children (Hemo-SAT P) completed the Hemo-SAT questionnaire at the start and end of study. Patients or parents/caregivers answered 34 items in the Hemo-SAT questionnaires pertaining to the following six dimensions: ease and convenience, efficacy, burden, specialist/nurse, center/hospital, and general satisfaction. Subscores and total score ranged from 0 (lowest dissatisfaction) to 100 (highest dissatisfaction). The results for the Hemo-SAT A total score at baseline, a year and two years after the baseline visit and at last post-baseline assessment is provided in Table 19.

Table 19: Hemo-SAT A total score overall and by prophylaxis dosing regimen at baseline (FAS)

Visit:	Baseline*			One year after baseline*			Two years after baseline*			Last post-baseline assessment* (≥300 days after baseline)		
Total score	**≤2.5x/ week N=94**	**>2.5x/ week N=124**	**Total N=218**	**≤2.5x/ week N=94**	**>2.5x/ week N=124**	**Total N=218**	**≤2.5x/ week N=94**	**>2.5x/ week N=124**	**Total N=218**	**≤2.5x/ week N=94**	**>2.5x/ week N=124**	**Total N=218**
n	76	95	171	43	44	87	18	14	32	62	64	126
Nmiss	18	29	47	51	80	131	76	110	186	32	60	92
Mean	13.474	13.317	13.387	13.672	11.882	12.767	15.276	9.322	12.671	13.704	11.514	12.591
SD	10.518	8.520	9.431	13.033	7.860	10.708	11.309	7.002	9.985	11.884	7.953	10.100
Median	10.662	11.765	11.029	8.824	11.765	10.294	13.235	7.537	12.322	10.662	11.397	11.029
Min,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,	0.00,
Max	45.59	40.44	45.59	47.06	37.50	47.06	42.19	22.79	42.19	47.06	40.44	47.06

*FAS subgroup of adult patients with at least one documented Hemo-SAT questionnaire at analysis timepoints.
Baseline questionnaire assessment is defined as up to 30 days after initial visit, one year assessment as between 300 and 420 days after initial visit, two-year assessment as between 660 and 780 days after initial visit. Subscores and total score range from 0 (lowest dissatisfaction) to 100 (highest dissatisfaction).
FAS: Full Analysis Set, Hemo-SAT A: Hemophilia treatment satisfaction questionnaire filled out by adults, Max: maximum, Min: minimum, n: number of patients, N: number of patients from analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation
Source: FAS-Table 14.1.9/1

The median total score for Hemo-SAT A from 171 patients at baseline in the FAS was 11.029 (range: 0.00 to 45.59), 10.294 (range: 0.00 to 47.06) from 87 patients one year after baseline and 12.322 (range: 0.00 to 42.19) from 32 patients two years after baseline. At the last post-baseline assessment the median total score for Hemo-SAT A from 126 patients was 11.029 (range: 0.00 to 47.06). Thus, the satisfaction level among patients in the FAS at one and two years after initial visit did not change drastically.

Regarding the prophylaxis dosing regimen groups at baseline, the mean (±SD) change in total score for Hemo-SAT A one year after baseline in the ≤2.5x/week (n=38 patients) and >2.5x/week (n=43 patients) dosing regimen groups was 1.182 (7.783) and -0.277 (8.005), respectively. The mean change two years after baseline was 1.487 (8.729) and 0.888 (5.497) in the ≤2.5x/week (n=18 patients) and >2.5x/week (n=12 patients) dosing regimen groups, respectively (FAS-Table 14.1.9/1). However, results should be interpreted with caution due to few documented Hemo-SAT A questionnaires at the latter timepoint in both the prophylaxis dosing regimen groups.

Results for all 6 dimensions of the questionnaire are provided in FAS-Table 14.1.9/1.

Data for Hemo-Sat A questionnaire by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.9/2.

Considering data for Hemo-SAT A questionnaire by switch of dosing regimen from baseline to end of observation for adult patients with at least one documented Hemo-SAT questionnaire at analysis timepoints: the median total score for Hemo-SAT A at baseline for patients with no switch of prophylaxis dosing regimen (n=147) was 11.029 (range: 0.00 to 45.59), 12.500 (range: 0.00 to 30.88) for patients with an increase in prophylaxis dosing regimen (n=15) and 11.765 (2.21 to 19.12) for patients with a decrease in prophylaxis dosing regimen (n=9). These values at last post-baseline assessment (≥300 days after baseline) for these subgroups were 10.662 (range: 0.00 to 42.19; n=104 patients), 12.132 (range: 0.00 to 47.06; n=14 patients) and 10.662 (range: 2.21 to 19.12; n=8 patients), respectively. The mean (±SD) change in total score for Hemo-SAT A at this time point was -0.207 (7.501) for patients with no switch of prophylaxis dosing regimen (n= 99), 3.125 (7.340) for patients with an increase in prophylaxis dosing regimen (n=12) and -0.315 (2.396) for patients with a decrease in prophylaxis dosing regimen (n=7). Less than 7 patients in the switcher subgroups filled in Hemo-SAT A questionnaires at one year and two years post baseline (FAS-Table 14.1.1/12 in 18559_TAURUS_TGL_FA_v1.0_FAS_Hemosat_20210415.docx, see TFL Subgroup Analysis [FAS] in Annex 1). Due to few patients in the switcher subgroups, these results should be interpreted cautiously.

The Hemo-SAT P total score at baseline, a year and two years after the baseline visit and at last post-baseline assessment is provided in Table 20.

Table 20: Hemo-SAT P total score overall and by prophylaxis dosing regimen at baseline (FAS)

Visit:	Baseline*			One year after baseline*			Two years after baseline*			Last post-baseline assessment* (≥300 days after baseline)		
Total score	**≤2.5x/ week N=27**	**>2.5x/ week N=59**	**Total N=86**	**≤2.5x/ week N=27**	**>2.5x/ week N=59**	**Total N=86**	**≤2.5x/ week N=27**	**>2.5x/ week N=59**	**Total N=86**	**≤2.5x/ week N=27**	**>2.5x/ week N=59**	**Total N=86**
n	26	54	80	10	25	35	8	6	14	18	35	53
Nmiss	1	5	6	17	34	51	19	53	72	9	24	33
Mean	12.956	14.550	14.032	12.817	13.006	12.952	8.661	14.905	11.337	9.660	12.897	11.798
SD	9.499	12.079	11.270	11.242	9.985	10.190	4.851	9.452	7.571	9.273	9.416	9.406
Median	10.000	11.071	10.000	10.000	10.714	10.714	9.643	11.786	9.643	5.357	10.714	9.286
Min,	0.00,	0.00,	0.00,	2.86,	0.00,	0.00,	1.43,	6.43,	1.43,	0.71,	0.00,	0.00,
Max	37.86	47.86	47.86	36.03	30.71	36.03	15.00	30.15	30.15	36.03	30.71	36.03

*FAS subgroup of patients with at least one documented parent Hemo-SAT questionnaire at analysis timepoints.
Baseline questionnaire assessment is defined as up to 30 days after initial visit, one year assessment as between 300 and 420 days after initial visit, two-year assessment as between 660 and 780 days after initial visit. Subscores and total score range from 0 (lowest dissatisfaction) to 100 (highest dissatisfaction).
FAS: Full Analysis Set, Hemo-SAT P: Hemophilia treatment satisfaction questionnaire filled out by parents/caregivers, Max: maximum, Min: minimum, n: number of patients, N: number of patients from analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation
Source: FAS-Table 14.1.9/3

The median total score at baseline visit from 80 Hemo-SAT P questionnaires was 10.0 (range: 0.00 to 47.86). At one year after baseline the median total score from 35 Hemo-SAT P questionnaires was 10.714 (range: 0.00 to 36.03), at two years after baseline the total median score for 14 patients was 9.643 (range: 1.43 to 30.15) and 9.286 (range: 0.00 to 36.03) at the last post-baseline assessments from 53 parents/caregivers. Thus, the satisfaction level among patients in the FAS at one and two years after initial visit remained stable.

Regarding the prophylaxis dosing regimen groups at baseline, the mean (±SD) change in total score for Hemo-SAT P one year after baseline in the ≤2.5x/week (n=9 patients) and >2.5x/week (n=23 patients) dosing regimen groups was 2.687 (10.877) and -0.304 (12.435), respectively. The mean change two years after baseline was -2.589 (6.434) and -3.522 (7.888) in the ≤2.5x/week (n= 8 patients) and >2.5x/week (n=3 patients) dosing regimen groups, respectively (FAS-Table 14.1.9/3).However, these results should be interpreted with caution due to very few documented questionnaires in both the prophylaxis dosing regimen groups.

Results for all 6 dimensions of the questionnaire are provided in FAS-Table 14.1.9/3. Data for Hemo-SAT P questionnaire by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.9/4.

Considering data for Hemo-SAT P questionnaire by switch of dosing regimen from baseline to end of observation for patients with at least one documented parent Hemo-SAT questionnaire at analysis timepoints: the median total score for Hemo-SAT P at baseline for patients with no switch of prophylaxis dosing regimen (n=69) was 10.000 (range: 0.00 to 47.86), 10.000 (range: 5.00 to 27.86) for patients with an increase in prophylaxis dosing regimen (n=5) and 18.214 (2.86 to 30.71) for patients with a decrease in prophylaxis dosing regimen (n=6). These values at last post-baseline assessment (≥300 days after baseline) for these subgroups were 10.000 (range: 0.00 to 36.03; n=42 patients), 5.000 (range: 0.71 to 21.43; n=5 patients) and 9.643 (range: 2.86 to 30.15; n=6 patients), respectively. The mean(±SD) change in total score for Hemo-SAT P at this time point was 0.945 (10.553) for patients with no switch of prophylaxis dosing regimen (n=36), -6.286 (9.694) for patients with an increase in prophylaxis dosing regimen (n=5) and -3.785 (12.127) for patients with a decrease in prophylaxis dosing regimen (n=6). Between 0 and 5 patients in the switcher subgroups filled in Hemo-SAT P questionnaires at one year and two years post baseline (FAS-Table 14.1.1/35 in 18559_TAURUS_TGL_FA_v1.0_FAS_Hemosat_20210415.docx, see TFL Subgroup Analysis [FAS] in Annex 1). However, due to very few patients in the switcher subgroups, these results should be interpreted cautiously.

10.4.7 Veritas

The prophylactic treatment adherence scale consisted of 24 questions on following six subscales: time, dose, plan, remember, skip, communicate. Patients who self-infuse or the parent/caregiver completed the questionnaire at baseline, six months, one year and two years after baseline. Total score ranged from 24 to 120 where 24 equaled most adherent.

Table 21 presents the VERITAS-PRO total score at baseline, half year, one year and two years after baseline.

Table 21: VERITAS PRO total score overall and by prophylaxis dosing regimen at baseline, half year, one year and two years after baseline (FAS)

Visit:	Baseline*			Half year after baseline*			One year after baseline*			Two years after baseline*		
Total score	≤2.5x/ week N=119	>2.5x/ week N=169	Total N=288	≤2.5x/ week N=119	>2.5x/ week N=169	Total N=288	≤2.5x/ week N=119	>2.5x/ week N=169	Total N=288	≤2.5x/ week N=119	>2.5x/ week N=169	Total N=288
n	108	156	264	80	95	175	68	96	164	27	24	51
Nmiss	11	13	24	39	74	113	51	73	124	92	145	237
Mean	38.185	37.927	38.033	37.671	38.175	37.945	36.392	37.670	37.140	37.259	33.750	35.608
SD	10.837	11.211	11.039	10.593	12.174	11.449	11.089	11.131	11.097	11.448	8.115	10.078
Median	35.00	35.00	35.00	36.00	36.00	36.00	33.50	35.00	34.00	33.00	33.00	33.00
Min,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,	24.00,
Max	78.00	69.00	78.00	72.00	80.00	80.00	71.00	78.00	78.00	69.00	56.00	69.00

*: FAS subgroup of patients with at least one documented VERITAS PRO questionnaire at analysis timepoints.
Baseline questionnaire assessment is defined as up to 30 days after initial visit, six months assessment as between 120 and 240 days, one year assessment as between 300 and 420 days, two-year assessment as between 660 and 780 days after initial visit. Subscores range from 4 (most adherent) to 20 (least adherent). Total score ranges from 24 (most adherent) to 120 (least adherent).
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients from analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation, VERITAS-PRO: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis
Source: Table 14.1.10/1

The median total score from 264 VERITAS-PRO questionnaires in the FAS at baseline was 35.0 (range: 24.0 to 78.0). The adherence level among patients in the FAS at half year, one year and two years after initial visit remained relatively stable; median total scores at these time points were 36.0 (range: 24.0 to 80.0, n=175 patients), 34.0 (range: 24.0 to 78.0, n=164 patients) and 33.0 (range: 24.0 to 69.0, n=51 patients).

No major differences were observed between the subgroups by baseline prophylaxis dosing regimen. The mean (±SD) change in total score for VERITAS questionnaires half year after baseline in the ≤2.5x/week (n=72 patients) and >2.5x/week (n=89 patients) dosing regimen groups was 0.111 (6.780) and -0.929304 (6.470), respectively. The mean change for VERITAS questionnaires one year after baseline was -0.844 (8.483) in the ≤2.5x/week (n= 60 patients) and -1.004 (7.529) in the >2.5x/week (n=89 patients) dosing regimen groups, and two years after baseline was 0.480 (6.407) in 25 patients and -2.857 (5.756) in 21 patients for these groups, respectively (FAS-Table 14.1.10/1). As few patients completed the VERITAS-PRO questionnaire the end of the study, the results have to be interpreted with caution.

VERITAS-PRO total score at last post-baseline assessment is presented in Table 22.

Table 22: VERITAS PRO total score overall and by prophylaxis dosing regimen at last post-baseline assessment (FAS)

Visit:	**Last post-baseline assessment* (≥300 days after baseline)**		
Total score	**≤2.5x/ week N=119**	**>2.5x/ week N=169**	**Total N=288**
n	88	119	207
Nmiss	31	50	81
Mean	36.598	37.398	37.058
SD	11.240	10.878	11.014
Median	33.00	35.00	34.00
Min, Max	27.00, 69.00	24.00, 78.00	24.00, 78.00

*FAS subgroup of patients with documented VERITAS PRO questionnaire at analysis timepoints. Baseline questionnaire assessment is defined as up to 30 days after initial visit, six months assessment as between 120 and 240 days, one year assessment as between 300 and 420 days, two-year assessment as between 660 and 780 days after initial visit. Subscores range from 4 (most adherent) to 20 (least adherent). Total score ranges from 24 (most adherent) to 120 (least adherent).
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients from analysis set, Nmiss: number of patients with missing values in analysis set, SD: standard deviation, VERITAS-PRO: Validated Hemophilia Regimen Treatment Adherence Scale-Prophylaxis Source: Table 14.1.10/1

The median total score from 207 VERITAS questionnaires in the FAS at last post-baseline assessment was 34.0 (range: 24.0 to 78.0).

Results for all 6 subscales are provided in FAS-Table 14.1.10/1. Data for VERITAS-PRO questionnaire by prophylaxis dosing regimen at baseline and switch of regimen are provided in FAS-Table 14.1.10/2.

The median total score for adherence to prophylaxis regimen at baseline for patients with no switch of prophylaxis dosing regimen (n=225) was 35.000 (range: 24.00 to 78.00), 37.000 (range: 24.00 to 74.00) for patients with an increase in prophylaxis dosing regimen (n=23) and 29.000 (range:24.00 to 56.00) for patients with a decrease in prophylaxis dosing regimen (n=16). These values at last post-baseline assessment (≥300 days after baseline) for these subgroups were 35.000 (range: 24.00 to 78.00; n=170 patients), 32.500 (range: 24.00 to 74.00; n=22 patients) and 30.000 (26.00 to 57.00; n=15 patients), respectively. The mean (±SD) change in total score for VERITAS-PRO at this time

point was -0.785 (8.037) for patients with no switch of prophylaxis dosing regimen (n=155), -2.825 (7.412) for patients with an increase in prophylaxis dosing regimen (n=21) and 2.308 (4.644) for patients with a decrease in prophylaxis dosing regimen (n=13) (FAS-Table 14.1.1/12 in 18559_TAURUS_TGL_FA_v1.0_FAS_VERITAS_PRO_20210415.docx, see TFL Subgroup Analysis [FAS] in Annex 1). Other than a slight improvement in adherence for patients with an increase in prophylaxis dosing regimen, in the other two subgroups no stark differences in the adherence to prophylaxis regimen were observed from baseline to last post-baseline assessment. However, due to few patients in the switcher subgroups, these results should be interpreted cautiously.

10.5 Other analyses

In addition to the subgroup analyses by prophylaxis dosing regimen at baseline described above, further subgroups analyses were performed. These include:

- FVIII level at diagnosis (FAS and SAF)
- Prophylaxis dosing regimen at baseline x FVIII level at diagnosis (FAS and SAF)
- Pretreatment with KOVALTRY (FAS and SAF)
- Age category 1 (FAS and SAF)
- Age category 2 (FAS)
- Mean prescribed weekly prophylaxis dose 1 and 2 (FAS)
- Completion of one year of observational period (FAS)
- Completion of two years of observational period (FAS)
- Prophylaxis dosing regimen at baseline and age (FAS)
- Switch of dosing regimen from baseline to end of observation (FAS)
- Age group at initiation of prophylaxis therapy (FAS)
- Most recent FVIII product used prior to start of KOVALTRY (FAS)
- Most recent FVIII regimen used prior to start of KOVALTRY (FAS)
- Premature discontinuation of study (FAS)
- History of inhibitor (FAS)
- Target joints at baseline (FAS)
- Surgery during study (FAS)
- Adherence at baseline based on VERITAS-PRO (FAS)
- Historical bleeding information prior to study start (FAS)
- Historical bleeding information prior to KOVALTRY (FAS).

Results for subgroup analyses for the FAS can be found in the specific FAS TFLs for subgroup analyses, see Annex 1. Results for subgroup analyses for the SAF are presented in the SAF TFLs, see Annex 1.

10.6 Adverse events/adverse reactions

10.6.1 Adverse Events

Summary of adverse events

Of the 313 patients in SAF, 96 patients (30.7%) experienced an AE. All reported AEs were TEAEs (SAF-Table 14.1.7/2 and SAF-Table 14.1.7/3). Patient-based incidences for TEAEs by age category were: 6 of 12 patients in the < 6 years group, 17 of 46 patients in the ≥ 6 to < 12 years group, 14 of 54 patients in the ≥ 12 to < 18 years group, and 59 of 201 patients in the ≥ 18years group (SAF-Table 14.1.7/3). In 31 patients (9.9%) serious AEs were observed. Three patients (1.0%) had a drug-related TEAE. Two patients each (0.6%) had fatal TEAEs and TEAEs leading to discontinuation of KOVALTRY treatment. A listing of AEs, drug-related AEs, AEs leading to discontinuation of KOVALTRY treatment and fatal AEs can be found in SAF-Listings 14.1.7/1, 14.1.7/2, 14.1.7/3, and 14.1.7/4, respectively. No AEs or TEAEs related to the inhibitor development or positive inhibitor measurement were observed (SAF-Listing 14.1.7/5).

An overview of the TEAEs in KOVALTRY-treated patients is presented in Table 23.

Table 23: Overview of TEAEs (SAF)

	Total N=313 n (%)
TEAEs	
Number of patients with any TEAE	96 (30.7%)
Number of patients with serious TEAE	31 (9.9%)
Number of patients with drug-related TEAE	3 (1.0%)
Number of patients with serious drug-related TEAE	0 (0.0%)
Number of patients with fatal TEAE	2 (0.6%)
Number of patients with TEAE leading to discontinuation of KOVALTRY treatment	2 (0.6%)
Number of patients with TEAE related to inhibitor development	0 (0.0%)

Treatment-emergent: Any event arising or worsening after start of KOVALTRY until 7 days after last intake.
n: number of patients, N: number of patients from analysis set, SAF: Safety Analysis Set, TEAE: Treatment Emergent Adverse Event
Source: SAF-Table 14.1.7/1

Table 24 lists patient-based incidences of TEAEs (cut-off >0.5% of patients) by MedDRA SOC and PT.

Table 24: Patient based incidences of TEAEs (cut-off >0.5% of patients) by SOC and PT (SAF)

MedDRA SOC PT	Total N=313 n (%)
Number of patients with any TEAE	96 (30.7%)
Blood and lymphatic system disorders	2 (0.6%)
Congenital, familial and genetic disorders	2 (0.6%)
Ear and labyrinth	2 (0.6%)

MedDRA SOC **PT**	**Total** **N=313** **n (%)**
Gastrointestinal disorders	16 (5.1%)
Abdominal pain upper	2 (0.6%)
Toothache	2 (0.6%)
General disorders and administration site conditions	9 (2.9%)
Medical device site irritation	2 (0.6%)
Pyrexia	2 (0.6%)
Hepatobiliary disorders	2 (0.6%)
Infections and infestations	14 (4.5%)
Appendicitis	2 (0.6%)
Influenza	2 (0.6%)
Vascular device infection	2 (0.6%)
Injury, poisoning and procedural complications	34 (10.9%)
Contusion	2 (0.6%)
Fall	12 (3.8%)
Humerus fracture	2 (0.6%)
Injury	4 (1.3%)
Joint injury	2 (0.6%)
Ligament sprain	5 (1.6%)
Limb injury	2 (0.6%)
Radius fracture	2 (0.6%)
Investigations	6 (1.9%)
Weight increased	3 (1.0%)
Metabolism and nutrition disorders	3 (1.0%)
Musculoskeletal and connective tissue disorders	34 (10.9%)
Arthralgia	17 (5.4%)
Arthritis	2 (0.6%)
Haemarthrosis	5 (1.6%)
Osteoarthritis	2 (0.6%)
Pain in extremity	3 (1.0%)
Nervous system disorders	7 (2.2%)
Headache	2 (0.6%)
Psychiatric disorders	2 (0.6%)
Renal and urinary disorders	4 (1.3%)
Respiratory, thoracic and mediastinal disorders	3 (1.0%)
Cough	3 (1.0%)
Skin and subcutaneous tissue disorders	4 (1.3%)
Acne	2 (0.6%)
Surgical and medical procedures	6 (1.9%)
Synoviorthesis	2 (0.6%)
Vascular disorders	2 (0.6%)
Hypertension	2 (0.6%)

Treatment-emergent: Any event arising or worsening after start of KOVALTRY until 7 days after last intake.
MedDRA: Medical Dictionary for Regulatory Activities, n: number of patients, N: number of patients in analysis set, PT: Preferred Term, SAF: Safety Analysis Set, SOC: System Organ Class, TEAE: Treatment Emergent Adverse Event.
Source: SAF-Table 14.1.7/3

Among 313 patients in the SAF, the most frequent TEAEs at SOC level were injury, poisoning and procedural complications and musculoskeletal and connective tissue disorders (34 patients each, 10.9%), gastrointestinal disorders (16 patients, 5.1%) and infections and infestations (14 patients,

4.5%). At PT level, the most common AEs were arthralgia (17 patients, 5.4%), fall (12 patients, 3.8%), ligament sprain and haemarthrosis (5 patients each, 1.6%), injury (4 patients, 1.3%), weight increased, pain in extremity and cough (3 patients each, 1.0%). All other PTs were documented for either one or two patients. In the SAF, the most common AEs were the same as the TEAEs at SOC and PT level (SAF-Table 14.1.7/2).

Deaths, serious adverse events and other significant adverse events

All serious adverse events

An overview of patient-based incidences of SAEs (cut-off >0.5% of patients) at MedDRA SOC and PT level is given in Table 25.

Table 25: Patient based incidences of serious AEs (cut-off >0.5% of patients) by SOC and PT (SAF)

MedDRA SOC PT	Total N=313 n (%)
Number of patients with any serious AE	31 (9.9%)
Congenital, familial and genetic disorders	2 (0.6%)
Gastrointestinal disorders	7 (2.2%)
Hepatobiliary disorders	2 (0.6%)
Infections and infestations	6 (1.9%)
Appendicitis	2 (0.6%)
Influenza	2 (0.6%)
Vascular device infection	2 (0.6%)
Injury, poisoning and procedural complications	6 (1.9%)
Fall	2 (0.6%)
Humerus fracture	2 (0.6%)
Musculoskeletal and connective tissue disorders	4 (1.3%)
Haemarthrosis	4 (1.3%)
Nervous system disorders	2 (0.6%)
Renal and urinary disorders	3 (1.0%)
Surgical and medical procedures	3 (1.0%)

AE: Adverse Event, MedDRA: Medical Dictionary for Regulatory Activities, n: number of patients, N: number of patients in analysis set, PT: Preferred Term, SAF: Safety Analysis Set, SOC: System Organ Class.
Source: SAF-Table 14.1.7/4

A total of 31 patients (9.9%) in SAF experienced SAEs. The most common SAEs at SOC level were gastrointestinal disorders in 7 patients (2.2%), infections and infestations and injury, poisoning and procedural complications in 6 patients each (1.9%). At PT level, haemarthrosis was most frequent with 4 patients (1.3%), followed by appendicitis, influenza, vascular device infection, fall and humerus fracture with 2 patients each (0.6%). All other PTs were recorded for single patients only.

In the SAF, three patients (≥ 18 years) were documented with any drug-related AE. At PT level, nausea, arthralgia, and pruritus were observed in one patient each (0.4%), but none of these events were serious (SAF Table 14.1.7/5 and SAF Table 14.1.7/6). A listing of drug-related AEs can be found in SAF-Listing 14.1.7/2.

Death

Two fatal AEs were observed in this study. One patient was a PPD male diagnosed with osmotic demyelination syndrome on PPD 2018 and fatality occurred on PPD 2018. The other patient was

a PPD male diagnosed with pancreatic carcinoma metastatic on PPD 2019 and died on PPD 2019. The causality of both AEs was not related to the treatment of this study. (SAF-Table 14.1.7/7, SAF-Listing 14.1.7/4).

Other significant adverse events

Of the 313 patients in the SAF, three adult patients (1.0%) experienced a drug-related AEs (PTs: nausea, arthralgia, pruritus) (SAF-Table 14.1.7/5). The events of nausea and pruritus in these two patients led to discontinuation of KOVALTRY treatment (SAF-Table 14.1.7/8, SAF-Listing 14.1.7/3).

No AEs related to the development of an inhibitor or positive inhibitor measurement were observed (SAF-Listing 14.1.7/5).

10.6.2 Other safety analyses

Data regarding surgeries since initiation of KOVALTRY was missing for 256 out of 313 patients (81.8%) in the SAF. Of the patients with information on surgeries, 46 patients (14.7%) had one surgery, 8 patients (2.6%) had two surgeries and three patients (1.0%) had three surgeries. The majority of patients (33 patients, 10.5%) had one minor surgery, whereas four patients (1.3%) and three patients (1.0%) had two and three minor surgeries, respectively. A total of 17 patients (5.4%) had a major surgery and two patients (0.6%) had two major surgeries (SAF-Table 14.1.7/9). Of 71 surgeries documented during the study, 61 surgeries (85.9%) were elective and 10 surgeries (14.1%) were emergency. No complications were reported and FVIII infusions were received during 67 surgeries (94.4%) FVIII infusions were received whereas it was not given during three surgeries (4.2%) and was not documented for one surgery (1.4%) (SAF-Table 14.1.7/9). A listing of surgeries since initiation of KOVALTRY treatment can be found in SAF-Listing 14.1.7/6.

11. Discussion

11.1 Key results

This study was a multinational, open label, prospective, non-interventional, single arm Phase 4 study (database hard lock date: 01 MAR 2021).

A total of 318 patients were enrolled in the study with the **FAS and SAF** comprising 302 (95.0%) and 313 (98.4%) patients, respectively. In the FAS and SAF, 37.1% of patients each had 2 follow-up visits followed by 27.8% and 27.5%, respectively, with 3 follow-up visits. The mean observation period for the final analysis was 451.4 days for the FAS and 446.5 days for the SAF. For the majority of patients the main reason for end of observation was “regular end of study” (FAS: 71.5% of patients, SAF: 69.3%). The most common main reasons for not completing the study were “switch to other therapy” (11.9% and 11.5%, respectively) and “premature termination by Sponsor due to COVID-19 pandemic” (9.3% and 8.9%, respectively).

All patients of this study were male and the majority of them were PPD with a median age of PPD in the FAS.

The primary objective of this study was to investigate weekly prophylaxis dosing regimens of KOVALTRY used in standard clinical practice to treat patients with Hemophilia A. 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.

Results are presented for the overall population and for subgroups by prophylaxis dosing regimen at baseline (i.e. ≤2.5x/week and >2.5x/week) and / or by prophylaxis dosing regimen at baseline and switch of prophylaxis dosing regimen from baseline to end of observation (i.e. ≤2.5x/week and no switch of prophylaxis dosing regimen, >2.5x/week and no switch of prophylaxis dosing regimen, and switcher of prophylaxis dosing regimen). Switcher and no switch patients were defined based on the prophylaxis dosing regimen at end of observation compared to that at baseline (initial visit): "No switch of prophylaxis dosing regimen", if last prescribed dosing frequency during observational period = prescribed dosing frequency at initial visit; "Increase of prophylaxis dosing frequency", if last prescribed dosing frequency during observational period > prescribed dosing frequency at initial visit and "Decrease of prophylaxis dosing frequency", if last prescribed dosing frequency during observational period < prescribed dosing frequency at initial visit.

In the FAS, total, ≤2.5x/week and >2.5x/week groups, the majority of the patients 84.4%, 79.0% and 88.2%, respectively, had a 0% to <1% **FVIII level at diagnosis**. The median length of continuous regular **prophylaxis treatment prior to their entry** into this study was 10.0 years (range: 0.00 to 49.00 years). The mean age to initiate prophylaxis therapy was 13.2 years (median PPD range: PPD With regard to the subgroups by prophylaxis dosing regimen at baseline, the median length of continuous regular prophylaxis treatment prior to study entry was longer in the >2.5/week group than in the ≤2.5x/week group (12.0 vs. 8.0 years). On comparison of mean age at initiation of prophylaxis therapy in the subgroups by prophylaxis dosing regimen at baseline, patients in the >2.5/week group were younger (11.3 years) than in the ≤2.5x/week group (16.3 years).

The mean (±SD) **number of bleeds in the last 6 months and 12 months**[28] **prior to baseline** in the FAS was 1.7 ± 3.5 bleeds (median: 0.0 bleeds, n=302 patients) and 3.4 ± 7.0 bleeds (median: 0.0 bleeds), respectively. The number of joint bleeds for these time points was slightly lower. Only 13 patients in the FAS had on demand treatment as most recent FVIII treatment prior to KOVALTRY. These patients had a mean number of 2.9 ± 5.6 bleeds (median: 1.0) and 2.8 ± 5.6 joint bleeds (median: 2.0) in the last 6 months prior to baseline.

All of the 302 patients in the FAS had **prior FVIII treatment documented** with majority (75.5%) treated with KOGENATE FS/Bayer. The median duration of the most recent FVIII treatment prior to KOVALTRY initiation was 6.546 years. The **mean total weekly dose** of this most recent FVIII treatment prior to KOVALTRY was 71.409 IU/kg. Most patients received regular prophylaxis (95.7%). 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%). Among the patients with regular prophylaxis, the most common **dosing frequencies** were 3 times per week (42.9%), 2 times per week (30.1%) and every other day (17.0%). Of the total patients in the FAS, 46.7% of patients had **pretreatment with KOVALTRY** more than three months before initial visit, 35.8% of patients had pretreatment with KOVALTRY up to three months before initial visit, and in 17.5% of patients KOVALTRY treatment start was at or after baseline. With regard to the subgroups by prophylaxis dosing regimen at baseline, patients in the ≤2.5x/week group had a

[28] Number of (joint) bleeds in the last 12 months (annualized) is calculated by number of (joint) bleeds in the last 6 months * 2 (SAP version 3.0 section 4.6, see Annex 1).

shorter treatment duration than patients in the >2.5x/week group. Mean weekly doses of the most recent FVIII treatment were also lower in the ≤2.5x/week group than in the >2.5x/week group.

In the SAF a total of 147 of 313 patients (47.0%) had **prior diseases**, 132 patients (42.2%) had **concomitant diseases** and 147 patients (47.0%) had any **concomitant medication**. No major differences were observed between subgroups by prophylaxis dosing regimen at baseline within medical history and concomitant medication and results for the FAS were in line with the SAF.

The most common **reason for the initial switch to KOVALTRY** in the FAS was "physician's decision" (65.6%, 71.8%, 61.2% in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively). The other common reasons were "prior FVIII product discontinued or about to be discontinued" (16.6%, 10.5% and 20.8%, respectively) and "patient decision" (12.3%, 14.5% and 10.7%, respectively). The same three reasons were also documented as most common reasons for all subgroups in the subgroup analysis by prophylaxis dosing regimen at baseline and switch of regimen. The most frequent **reasons for selection of initial dose/dosing frequency** of KOVALTRY in the FAS 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%). These reasons were also frequently reported for subgroups by prophylaxis dosing regimen at baseline and for subgroups by prophylaxis dosing regimen at baseline and switch of regimen for selection of initial dose / dosing frequency of KOVALTRY.

Overall in the FAS **at baseline**, patients were **most frequently treated** 3 times per week (43.4%), followed by 2 times per week (34.8%) and every other day (12.9%). At this time point, 124 patients (41.1%, 95% CI: 35.5% - 46.8%) were on a ≤2.5x/week prophylaxis dosing regimen and 178 patients (58.9%, 95% CI: 53.2% - 64.5%) on a >2.5x/week prophylaxis dosing regimen. The **most common dosing regimens** were 2 times per week (84.7%) and every week (10.5%) in the ≤2.5x/week and 3 times per week (73.6%) and every other day (21.9%) in the >2.5x/week baseline prophylaxis dosing regimen subgroups. **At the end of observation** overall in the FAS, patients were **most frequently treated** 3 times per week (41.4%), followed by 2 times per week (35.1%) and every other day (12.6%). At this time point, 128 patients (42.4%, 95% CI: 36.7% - 48.2%) were on a ≤2.5x/week prophylaxis dosing regimen and 174 patients (57.6%, 95% CI: 51.8% - 63.3%) on a >2.5x/week prophylaxis dosing regimen. The most common dosing regimens were 2 times per week (75.8%) and every week (8.9%) in the ≤2.5x/week and 3 times per week (65.2%) and every other day (20.8%) in the >2.5x/week baseline prophylaxis dosing regimen subgroups.

Of 124 patients (100%) who were on a ≤2.5x/week prophylaxis dosing regimen at baseline, 113 patients (91.1%) remained in the same regimen category at end of observation, while 11 patients (8.9%) switched to >2.5x/week. Of 178 patients (100%) who were on a >2.5x/week prophylaxis dosing regimen at baseline, 163 patients (91.6%) remained in the same regimen category at end of observation, while 15 patients (8.4%) switched to ≤2.5x/week. Most patients (84.4% of 302 patients) had no switch of **prophylaxis dosing regimen**, 26 patients (8.6%) had an increase of prophylaxis dosing frequency and 21 patients (7.0%) had a decrease of prophylaxis dosing frequency. Of the 26 switcher patients with an increase of prophylaxis dosing frequency from baseline to end of observation, 16 patients were in the ≤2.5x/week group at baseline. Of these, 5 patients remained in the ≤2.5x/week group at end of observation, in spite of the increased prophylaxis dosing frequency, while 11 patients changed to >2.5x/week group at end of observation. The other 10 patients with an increase of prophylaxis dosing frequency remained in >2.5x/week group at end of observation. Of the

21 switcher patients with a decrease of prophylaxis dosing frequency from baseline to end of observation, 20 patients were in the >2.5x/week group at baseline. Of these, 5 patients remained in the >2.5x/week group at end of observation, in spite of the decreased dosing frequency, while 15 patients changed to ≤2.5x/week group at end of observation. The other patient with a decrease of prophylaxis dosing frequency remained in the ≤2.5x/week group at end of observation.

The analysis of **weekly prophylaxis dosing regimen by country** showed that the most frequent prophylaxis regimen at baseline and end of observation in Belgium, Germany, the Netherlands, Spain, Colombia, France and Greece was 3 times per week or 2 times per week. However, in Italy, Slovenia and the USA the weekly prophylaxis dosing regimen was different at baseline and at end of observation. For region Taiwan, at baseline, patients were most frequently treated 2 times per week while at end of observation, prophylaxis dosing regimens 2 times per week and 3 times per week were equally frequent. Regarding prophylaxis dosing regimen at baseline and at end of observation, majority of patients in all countries remained in the same prophylaxis dosing regimen at end of observation as at baseline. In the subgroup analysis by age category (<12 years: N=57 and ≥12 years: N=245), results for KOVALTRY dosing frequency were in line with results for the overall population: patients were treated most frequently 3 times per week, followed by 2 times per week and every other day at baseline and at end of observation.

The median of **mean prescribed weekly KOVALTRY dose** for patients in the FAS was 69.806 IU/kg (n=282 patients), 55.556 IU/kg (n=115 patients) and 75.054 IU/kg (n=167 patients) for the total, ≤2.5x/week and >2.5x/week at baseline prophylaxis dosing regimens, respectively. The median of mean prescribed weekly KOVALTRY dose for patients <12 years old (n=54) and ≥12 years old (n=228) was 75.575 IU/kg and 66.667 IU/kg, respectively.

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. Regarding the subgroups, patients in the >2.5x/week baseline prophylaxis dosing regimen group had a considerably higher proportion of patients with more than 2 dose / regimen changes (24.2%) than patients in the ≤2.5x/week subgroup (15.3%). Overall in the FAS, the most frequent reasons for dose / regimen changes based on the total number of dose / regimen changes (N=575) were "increase in bleeding frequency" (15.7%), "resumption of treatment after bleeding" (14.3%), "surgical intervention" (13.4%), "bleeding" (9.7%), "adverse event"(9.4%) and "resumption of treatment after surgery" (8.5%). All other reasons were reported ≤5% of the total number of reasons. Only a small proportion of patients (28 patients, 9.3%) in the FAS permanently **discontinued KOVALTRY** treatment.

The median number of **annualized**[29] **injections** was 132.219 (range: 0.00 to 365.25), 104.087 (range: 0.00 to 208.14) and 157.429 (range: 0.00 to 365.25) in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. For patients <12 years old (n=54), the median number of annualized injections was 144.488 (range: 45.66 to 213.64) and was 123.590 (range: 0.00 to 365.25) for patients ≥12 years old (n= 214).

[29] The annualized number of injections was calculated as [Sum (injections) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

The median number of **annualized**[30] **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) in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. The median number of **annualized reported joint bleeds documented in patient diary** was 0.510 (range: 0.00 to 57.93), 0.658 (range: 0.00 to 57.93) and 0.506 (range: 0.00 to 19.18) in these subgroups, respectively. There were no major differences in the median number of **annualized reported total treated bleeds**, trauma and undefined spontaneous / trauma bleeds among the subgroups by prophylaxis dosing regimen at baseline, while the median number was lower in the >2.5x/week baseline prophylaxis dosing regimen group than in the ≤2.5x/week group. A similar proportion of patients in the ≤2.5x/week (N=124) and >2.5x/week (N=178) baseline prophylaxis dosing regimen groups documented zero annualized number of total treated bleeds (33.9% vs. 34.8%) and total joint bleeds (42.7% vs. 43.8%). However, spontaneous bleeds (42.7% vs. 46.1%) and trauma bleeds (56.5% vs. 61.2%) were higher in the >2.5x/week baseline prophylaxis dosing regimen group. These data were missing for 11.3% and 11.2% of patients in these groups, respectively. On comparison of **subgroups by prophylaxis dosing regimen at baseline and switch of regimen**, the median number of annualized reported total treated bleeds was 1.021 (range: 0.00 to 57.93) for the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup, 1.124 (range: 0.00, 21.49) for the >2.5x/week and no switch of prophylaxis dosing regimen subgroup and 1.764 (range: 0.00 to 14.81) for the switcher of prophylaxis dosing regimen subgroup. The median number of annualized reported total joint bleeds was 0.248 (range: 0.00 to 57.93), 0.501 (range: 0.00 to 19.18) and 1.009 (range: 0.00 to 12.83) for these subgroups, respectively. In these subgroups, a slightly higher proportion of patients in the ≤2.5x/week and no switch of prophylaxis dosing regimen subgroup (N=107) reported zero bleeds than the >2.5x/week and no switch of prophylaxis dosing regimen subgroup (N=148) for the annualized number of total treated bleeds (37.4% vs. 33.8%) and total joint bleeds (45.8% vs. 43.9%). However, similar proportion of patients in these subgroups reported zero spontaneous bleeds (46.7% vs. 45.9%), trauma bleeds (60.7% vs. 60.1%). These data were missing for 10.3% and 11.5% of patients in these groups, respectively. In comparison to these two subgroups, the lowest proportion of patients in the switcher of prophylaxis dosing regimen subgroup (N=47) had zero bleeds for annualized number of total treated bleeds (29.8%), spontaneous bleeds (36.2%), trauma bleeds (53.2%), and total joint bleeds (36.2%). Data for 12.8% of patients from this subgroup was missing. **For patients <12 years old**, the median number of annualized reported total treated bleeds in ≤2.5x/week subgroup (n=20) was higher than in the >2.5x/week subgroup (n=34) (≤2.5x/week: 3.192 [range: 0.00, 11.13;], >2.5x/week: 0.755 [range: 0.00, 8.07]). A similar tendency was observed for the number of annualized reported total joint bleeds in these patients. (≤2.5x/week: 1.015 [range: 0.00, 7.06], >2.5x/week: 0.000 [range: 0.00, 4.04]). However, in **patients ≥12 years old**, the median number of annualized reported total treated bleeds in the ≤2.5x/week subgroup (n=90) group was slightly lower than in >2.5x/week subgroup (n=124) (≤2.5x/week: 1.070 [range: 0.00, 57.93], >2.5x/week: 1.248 [range: 0.00, 21.49]). The number of annualized reported total joint bleeds was comparable in both subgroups (≤2.5x/week: 0.506 [range: 0.00, 57.93], >2.5x/week: 0.541 [range: 0.00, 19.18]). A higher proportion of patients <12 years old (N=57) were documented with zero bleeds than patients ≥12 years old (N=245) for the annualized number of total treated bleeds (38.6% vs. 33.5%), spontaneous bleeds (54.4% vs. 42.4%), and total joint bleeds (49.1% vs. 42.0%), with the exception of trauma bleeds where the proportion was lower (57.9% vs. 59.6%). These data were missing for 5.3% and 12.7% of patients in these groups,

[30] The annualized number of reported (joint) bleeds was calculated as (number of reported (joint) bleeds / documentation period of the patient diary in days) * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

respectively. There was no drastic **change in annualized number of total treated bleeds and total joint bleeds** during the observation period compared to prior to study entry or prior to initiation of KOVALTRY in any of the subgroups (by prophylaxis dosing regimen at baseline / by prophylaxis dosing regimen at baseline and switch of regimen).

The median **total annualized**[31] **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. The median **annualized**[32] **total dose per kg for prophylaxis** for these subgroups was 3704.713 IU/kg, 3352.814 IU/kg and 3974.755 IU/kg, respectively. The median total annualized factor consumption for prophylaxis, bleeds and other events for patients with no **switch of prophylaxis dosing regimen** (n=226) was higher than for either of the switcher groups, i.e. increase (n=21) or decrease (n=19) of prophylaxis dosing regimen from baseline to end of observation: 3943.740 IU/kg/year (range: 0.00 to 16866.06) vs. 3682.454 IU/kg/year (range: 0.00 to 13527.01) or 3779.602 IU/kg/year (range: 0.00 to 11025.26). A similar trend was observed on comparison of median annualized total dose per kg for prophylaxis within these subgroups. For **patients <12 years old** (n=54), the median total annualized factor consumption for prophylaxis, bleeds and other events was 4117.615 IU/kg/year (range: 2141.14 to 16866.06) and it was 3777.307 IU/kg/year (range: 0.00 to 11910.33) for **patients ≥12 years old** (n=212). The median annualized total dose per kg for prophylaxis for patients <12 years old and patients ≥12 years old was 3843.604 IU/kg (range: 2141.14 to 16866.06) and 3610.693 IU/kg (range: 0.00 to 11910.33), respectively.

Data **for von Willebrand factor** prior to KOVALTRY, at baseline and at end of observation was not documented for the vast majority of patients (>90.0%) in the FAS. The number of **PK assessments** performed since start of KOVALTRY treatment was not documented for 55.6% of patients in the FAS. Similarly, for the majority of patients the number of PK assessments with one stage assay and with chromogenic assay performed since start of KOVALTRY treatment was not documented for 64.6% and 91.1%, respectively. 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. Other PK assessments since start of KOVALTRY were not performed for the majority of patients: FVIII C activity assessments (56.3%), FVIII half-life assessments (87.7%), 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%).

Target joints were documented for all 302 patients (100%) in the FAS at baseline but data for 40 patients (13.2%) was missing at the end of observation. The mean (± SD) number of target joints for patients in the FAS at baseline and at end of observation was 1.0 ± 1.8 (median: 0.0, range: 0 – 15) and 0.7 ± 1.4 (median: 0.0, range: 0 – 8), respectively. The number of target joints and proportion of patients with target joints at baseline and at end of observation were comparable between the ≤2.5x/week and >2.5x/week prophylaxis dosing regimen groups at baseline. The majority of patients

[31] The annualized factor consumption for prophylaxis, bleeds and other events was calculated as [Sum (all doses per kg) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

[32] The annualized total dose per kg for prophylaxis was calculated as [Sum (doses per kg for prophylaxis) / documentation period of the patient diary in days] * 365.25 (SAP version 3.0 section 4.6, see Annex 1).

had the same number of target joints at baseline and at end of observation: 0 target joints in 136 patients (45.0%), 1 target joint in 25 patients, (8.3%), 2 or more target joints in 35 patients (11.6%). In the subgroup analysis by age category, a higher proportion of patients <12 years old (N=57) than ≥12 years old (N=245) had 0 target joints (86.0% vs. 51.4%). In contrast, lower proportions of patients <12 years old than ≥12 years old had 1 target joint (10.5% vs. 20.8%) or 2 or more target joints (3.5% vs. 27.8%) at baseline. This tendency was also maintained at end of observation: a higher proportion of patients <12 years old than ≥12 years old had 0 target joints (78.9% vs. 55.5%), while lower proportions of patients <12 years old than ≥12 years old had 1 target joint (8.8% vs. 13.5%) and or 2 or more target joints (5.3% vs. 16.3%). Thus, overall younger patients presented lower numbers of target joints. In line with results for the overall FAS, however, the majority of patients had the same number of target joints at baseline and at end of observation in both subgroups, <12 years and ≥12 years. In the subgroup of patients <12 years, 2 patients (3.5%) shifted from 1 target joint at baseline to 0 target joints at end of observation. In the subgroup of patients ≥12 years, 21 patients (8.6%) shifted from 1 target joint at baseline to 0 target joints at end of observation, and 22 patients (9.0%) and 3 patients (1.2%) shifted from 2 or more target joints at baseline to 0 and 1 target joint at end of observation, respectively. Few patients had a shift from 0 or 1 target joints at baseline to 1 or 2 or more target joints at end of observation.

The median total score for **Hemo-SAT A** from 171 patients at baseline in the FAS was 11.029 (range: 0.00 to 45.59), 10.294 (range: 0.00 to 47.06) from 87 patients one year after baseline and 12.322 (range: 0.00 to 42.19) from 32 patients two years after baseline. At the last post-baseline assessment the median total score for Hemo-SAT A from 126 patients was 11.029 (range: 0.00 to 47.06). Thus, the satisfaction level among patients in the FAS at one and two years after initial visit did not change drastically. The median total score at baseline visit from 80 **Hemo-SAT P** questionnaires was 10.0 (range: 0.00 to 47.86). At one year after baseline the median total score from 35 Hemo-SAT P questionnaires was 10.714 (range: 0.00 to 36.03), at two years after baseline the total median score for 14 patients was 9.643 (range: 1.43 to 30.15) and 9.286 (range: 0.00 to 36.03) at the last post-baseline assessments from 53 parents/caregivers. Thus, the satisfaction level among patients in the FAS at one and two years after initial visit remained stable. However, results should be interpreted with caution due to few documented Hemo-SAT A and Hemo-SAT P questionnaires at the latter timepoint in both the prophylaxis dosing regimen groups.

The median total score from 264 **VERITAS-PRO** questionnaires in the FAS at baseline was 35.0 (range: 24.0 to 78.0). The adherence level among patients in the FAS at half year, one year and two years after initial visit remained relatively stable; median total scores at these time points were 36.0 (range: 24.0 to 80.0, n=175 patients), 34.0 (range: 24.0 to 78.0, n=164 patients) and 33.0 (range: 24.0 to 69.0, n=51 patients). No major differences were observed between the subgroups by baseline prophylaxis dosing regimen. As few patients completed the VERITAS-PRO questionnaire the end of the study, the results have to be interpreted with caution.

Of the 313 patients in SAF, 96 patients (30.7%) experienced an **AE**. **All reported AEs were TEAEs**. Patient-based incidences for TEAEs by age category were: 6 of 12 patients in the < 6 years group, 17 of 46 patients in the ≥ 6 to < 12 years group, 14 of 54 patients in the ≥ 12 to < 18 years group, and 59 of 201 patients in the ≥ 18years group.

Among 313 patients in the SAF, the **most frequent AEs and TEAEs** at SOC level were injury, poisoning and procedural complications and musculoskeletal and connective tissue disorders (34 patients each, 10.9%), gastrointestinal disorders (16 patients, 5.1%) and infections and infestations (14 patients, 4.5%). At PT level, the most common AEs were arthralgia (17 patients, 5.4%), fall

(12 patients, 3.8%), ligament sprain and haemarthrosis (5 patients each, 1.6%), injury (4 patients, 1.3%), weight increased, pain in extremity and cough (3 patients each, 1.0%).

A total of 31 patients (9.9%) in SAF experienced SAEs. The **most common SAEs** at SOC level were gastrointestinal disorders in 7 patients (2.2%), infections and infestations and injury, poisoning and procedural complications in 6 patients each (1.9%). At PT level, haemarthrosis was most frequent with 4 patients (1.3%), followed by appendicitis, influenza, vascular device infection, fall and humerus fracture with 2 patients each (0.6%).

In the SAF, three patients (≥ 18 years) were documented with any **drug-related AE**. At 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.

11.2 Limitations

This prospective, open label, non-interventional, single arm Phase 4 study provided an opportunity to collect real-life data on safety and effectiveness in children and adults with moderate to severe Hemophilia A (≤5% FVIII:C) who were treated with KOVALTRY. However, this study was a single arm study without a comparison group. Further, 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). Additionally, adherence to treatment is prone to be biased by adherence to documentation.

11.3 Interpretation

The primary objective of this study was to investigate weekly prophylaxis dosing regimens of KOVALTRY used in standard clinical practice to treat patients with Hemophilia A.

The report presents data the for the final analysis of the study. As a consequence of the COVID-19 pandemic, the study sponsor decided to close the study prematurely in all countries, except Italy. This decision had no impact on the safety, physical or mental well-being of the study participants. The impact on the primary objective was considered to be minor since all patients were to be included in the analysis. The actual observation period of the prematurely discontinued patients was considered to be long enough to allow a meaningful interpretation of the statistical results (refer to Bayer NTF dated 15 JUN 2020, Annex 1).

A total of 318 patients were enrolled in the study with the FAS and SAF comprising 302 (95.0%), and 313 (98.4%) patients respectively. All patients of this study were male and the majority of them were PPD with a median age of PPD years in the FAS. In the analyses of the FAS by prophylaxis dosing regimen at baseline, 124 of 302 patients had a dosing regimen of ≤2.5x/week at baseline and 178 patients had a dosing regimen of >2.5x/week at baseline. Patients with a dosing regimen ≤2.5x/week were older than patients with a dosing regimen >2.5/week. Analyses were also performed by prophylaxis dosing regimen at baseline and switch of regimen (i.e., last prescribed dosing frequency during observation period = prescribed dosing frequency at initial visit). In the FAS, 107 of 302 patients had a dosing regimen of ≤2.5x/week at baseline and no switch of prophylaxis

dosing regimen, 148 patients had a dosing regimen of >2.5x/week at baseline and no switch of prophylaxis dosing regimen while 47 patients switched prophylaxis dosing regimen from baseline to end of observation.

In the FAS, the median length of continuous regular prophylaxis treatment prior to entry into this study was 10.0 years (range: 0.00 to 49.00 years). All of the 302 patients in the FAS had prior FVIII treatment documented with majority (75.5%) treated with KOGENATE FS/Bayer. The mean total weekly dose of this most recent FVIII treatment prior to KOVALTRY was 71.409 IU/kg. 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%).

At baseline 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 and the most common reason for the initial switch to KOVALTRY in the FAS was "physician's decision". The most frequent reason for selection of initial dose/dosing frequency of KOVALTRY was "current treatment regimen". Thus, it can be expected that physicians' role and the ongoing treatment regimen play an important role in determining the initial switch to KOVALTRY and the prophylaxis dosing regimen at baseline, respectively. From baseline to end of observation overall in the FAS, patients were most frequently treated 3 times per week, followed by 2 times per week and every other day. Analyses of weekly prophylaxis dosing regimen 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.

The median of mean prescribed weekly KOVALTRY dose for patients in the FAS was 69.806 IU/kg, 55.556 IU/kg and 75.054 IU/kg for the total, ≤2.5x/week and >2.5x/week at baseline prophylaxis dosing regimens, respectively. The median of mean prescribed weekly KOVALTRY dose for patients <12 years old and ≥12 years old was 75.575 IU/kg and 66.667 IU/kg, respectively.

The majority of patients in the FAS had no dose / regimen changes until the end of observation. Overall, there were 575 dose / regimen changes in the FAS. The most frequent reasons were related to bleeding (increase in bleeding frequency [15.7% of dose / regimen changes], bleeding [9.7%] and resumption of treatment after bleeding [14.3%]), surgery (surgical intervention [13.4%] and resumption of treatment after surgery [8.5%]) and adverse event (9.4%).

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) in the total, ≤2.5x/week and >2.5x/week baseline prophylaxis dosing regimen groups, respectively. The median number of annualized reported joint bleeds documented in patient diary was 0.510 (range: 0.00 to 57.93), 0.658 (range: 0.00 to 57.93) and 0.506 (range: 0.00 to 19.18) in these subgroups, 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. For patients <12 years old, the median number of annualized reported total treated and total joint bleeds in ≤2.5x/week subgroup was higher than in the >2.5x/week subgroup. However, in patients ≥12 years old, the median number of annualized reported total treated and total joint bleeds in the ≤2.5x/week subgroup group was slightly lower than in >2.5x/week subgroup.

The median total annualized factor consumption for prophylaxis, bleeds and other events and the median annualized total dose per kg for prophylaxis was higher for patients with no switch of prophylaxis dosing regimen than for either of the switcher groups i.e. increase or decrease of prophylaxis dosing regimen from baseline to end of observation. For patients <12 years old, the median total annualized factor consumption for prophylaxis and the median annualized total dose per kg for prophylaxis was higher than for patients ≥12 years old.

The majority of patients had the same number of target joints at baseline and at end of observation. The number of target joints and proportion of patients with target joints at baseline and at end of observation were comparable between the ≤2.5x/week and >2.5x/week prophylaxis dosing regimen groups at baseline. In the subgroup analysis by age category, a higher proportion of patients <12 years old than ≥12 years old had 0 target joints while, lower proportions of patients <12 years old than ≥12 years old had 1 target or 2 or more target joints at baseline. This tendency was also maintained at end of observation. Thus, overall, younger patients presented lower numbers of target joints. In line with results for the overall FAS, however, the majority of patients in both subgroups had the same number of target joints at baseline and at end of observation.

Hemo-SAT and VERITAS-PRO questionnaires were used to assess patients' treatment satisfaction and adherence with KOVALTRY, respectively. 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 later time points in both the prophylaxis dosing regimen groups.

During the period of the study, 30.7% of patients experienced an AE and 9.9% experienced a SAE. Only three patients had any as drug-related AE, none of them being serious. Two patients discontinued the study because of drug-related AEs (nausea, pruritus). No new and unexpected AE has been detected. 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. Overall, based on currently available data, the benefit-risk analysis for KOVALTRY for its indications in hemophilia A is considered favorable.

11.4 Generalizability

The eligibility criteria for this study were selected to allow for a broad representation of patients within the study. The study enrolled 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 is representative of real world. The vast majority of the study participants were previously treated with Kogenate or Helixate (same molecules). Previously untreated hemophilia A patients were 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, previously untreated patients (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. In addition, the study

allowed the enrollment of a heterogeneous patient population with regard to demographic and disease characteristics and, thus, the patient population in this study is assumed to reflect the real-life situation in patients with Hemophilia A who are treated with KOVALTRY. Patients were treated according to daily practice conditions. The observational design of the study allowed to collect real-life data, without influencing the physicians' treatment decisions.

12. Other information

Not applicable

13. Conclusion

This non-interventional Phase 4 study aimed to investigate weekly prophylaxis dosing regimens of KOVALTRY used in standard clinical practice to treat patients with Hemophilia A.

Data analyzed in this final analysis indicate that prophylaxis treatment regimens before and after initiation of KOVALTRY remained stable (i.e. patients remained in the same regimen category, ≤2.5x/week and >2.5x/week, even after changes in the prophylaxis dosing regimen) 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.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 26: List of stand-alone documents

Document Name	Final version and date (if available)*
18559_TAURUS_Investigator_List	
18559_TAURUS_IEC_IRB_Approvals_20200113	13 JAN 2020
18559_TAURUS_DMP_v1.0	13 OCT 2016
18559_TAURUS_MRP_v4.0_2020-01-16	16 JAN 2020
18859_TAURUS_QRP_V2.0_20200318	18 MAR 2020
18559_TAURUS_VDR_FA_v1.0_2021-02-24	24 FEB 2021
18559_TAURUS_FQRR_V1.0_20210122_clean	22 JAN 2021
18559_KV1601_TAURUS_Protocol_Version 4.1_27 Sep 2019	27 SEP 2019
SAP version 3.0	25 JUN 2020
18559_TAURUS_NTF_COVID-19 study country closure	15 JUN 2020
TFL Main Results (FAS): 18559_TAURUS_TGL_FA_v1.0_FAS_main_results_20210413	13 APR 2021
TFL Subgroup Analysis (FAS) 18559_TAURUS_TGL_FA_v1.0_FAS_disposition_demo_20210413 18559_TAURUS_TGL_FA_v1.0_FAS_hemophilia_history_20210414 18559_TAURUS_TGL_FA_v1.0_FAS_Hemosat_20210415 18559_TAURUS_TGL_FA_v1.0_FAS_main_results_20210413 18559_TAURUS_TGL_FA_v1.0_FAS_medical_history_20210414 18559_TAURUS_TGL_FA_v1.0_FAS_PK_20210414 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_2_20210416 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_3_20210416	13 – 16 APR 2021

Document Name	**Final version and date (if available)***
18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_4_20210416 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414 18559_TAURUS_TGL_FA_v1.0_FAS_target_joints_20210415 18559_TAURUS_TGL_FA_v1.0_FAS_VERITAS_PRO_20210415	
TFL (SAF): 18559_TAURUS_TGL_FA_v1.0_SAF_20210413	13 APR 2021
18559_TAURUS_TGL_FA_v1.0_Listings_20210413	13 APR 2021
18559_TAURUS_NTF_COVID-19 study country closure	15 JUN 2020

Annex 2: Additional information

Table 27: FVIII treatment prior to KOVALTRY treatment and at end of observation by age categories (FAS)

	<6 years N=11	≥6 - <12 years N=46	≥12 - <18 years N=53	≥18 years N=192	Total N=302	<6 years N=11	≥6 - <12 years N=46	≥12 - <18 years N=53	≥18 years N=192	Total N=302
	Prior to KOVALTRY					End of Observation				
On-demand treatment, n (%)	0 (0.0%)	3 (6.5%)	1 (1.9%)	9 (4.7%)	13 (4.3%)	Not applicable				
Regular prophylaxis, n (%)	11 (100.0%)	43 (93.5%)	52 (98.1%)	183 (95.3%)	289 (95.7%)	All patients in the study were in prophylaxis (100%)				

FAS: Full Analysis Set, n: number of patients, N: number of patients in subgroup or analysis set, TFL: Tables, Figures and Listings.
Source: FAS-Table 14.1.1/3 in TFL Main Results, see Annex 1. FAS-Table 14.1.1 / 28 in 18559_TAURUS_TGL_FA_v1.0_FAS_hemophilia_history_20210414.docx, see TFL Subgroup Analysis [FAS] in Annex 1.

Table 28: Weekly dose of most recent FVIII treatment prior to KOVALTRY and of KOVALTRY at end of observation by age categories (FAS)

	<6 years N=11	**≥6 - <12 years N=46**	**≥12 - <18 years N=53**	**≥18 years N=192**	**Total N=302**	**<6 years N=11**	**≥6 - <12 years N=46**	**≥12 - <18 years N=53**	**≥18 years N=192**	**Total N=302**
	Prior to KOVALTRY					**End of Observation**				
	Total weekly dose of most recent FVIII treatment prior to KOVALTRY, IU/kg					**Weekly prescribed dose at end of observation, IU/kg**				
n	11	42	51	176	280	11	45	52	185	293
Nmiss	0	4	2	16	22	0	1	1	7	9
Mean (SD)	108.152 (82.582)	80.761 (50.584)	62.992 (46.273)	69.320 (32.288)	71.409 (41.716)	100.619 (76.986)	88.010 (42.151)	77.495 (43.233)	72.177 (47.098)	76.620 (47.427)
Median	83.333	72.479	49.180	69.376	66.667	75.000	76.923	64.867	68.966	70.588
Min, Max	29.41, 315.79	30.00, 333.33	7.87, 249.11	11.90, 175.00	7.87, 333.33	29.41, 276.32	28.57, 195.12	20.16, 184.21	10.99, 466.67	10.99, 466.67

FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients in subgroup or analysis set, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in subgroup or analysis set, SD: standard deviation, TFLs: Tables, Figures and Listings
Source: FAS-Table 14.1.1 / 28 in 18559_TAURUS_TGL_FA_v1.0_FAS_hemophilia_history_20210414.docx
FAS-Table 14.1.1 / 75 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414
For sources see TFL Subgroup Analysis [FAS] in Annex 1.

Table 29: Prophylaxis dosing regimen, joint bleeds and target joints prior to KOVALTRY treatment and with KOVALTRY at end of observation by age categories (FAS)

	<6 years N=11	≥6 - <12 years N=43	≥12 - <18 years N=52	≥18 years N=183	Total N=289	<6 years N=11	≥6 - <12 years N=46	≥12 - <18 years N=53	≥18 years N=192	Total N=302
	Prior to KOVALTRY[a]					End of Observation				
	Dose frequency for most recent prophylaxis FVIII treatment prior to KOVALTRY					Weekly prophylaxis dosing regimen at end of observation[b]				
Missing, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
≤2.5x/week, n(%)	3 (27.3%)	15 (34.9%)	17 (32.7%)	72 (39.3%)	107 (37.0%)	3 (27.3%)	14 (30.4%)	23 (43.4%)	88 (45.8%)	128 (42.4%)
>2.5x/week, n(%)	8 (72.7%)	28 (65.1%)	35 (67.3%)	110 (60.1%)	181 (62.6%)	8 (72.7%)	32 (69.6%)	30 (56.6%)	104 (54.2%)	174 (57.6%)
	Number of joint bleeds in the last 12 months prior to start with KOVALTRY[c]					Annualized number of total joint bleeds[d]				
n	11	41	47	168	267	11	43	45	169	268
Nmiss	0	2	5	15	22	0	3	8	23	34
Mean (SD)	1.3 (3.6)	1.0 (1.7)	1.0 (2.7)	3.1 (7.6)	2.3 (6.3)	0.872 (1.388)	1.255 (1.738)	1.918 (3.124)	3.223 (6.729)	2.592 (5.602)
Median	0.0	0.0	0.0	0.0	0.0	0.000	0.000	0.971	0.495	0.510

	<6 years N=11	≥6 - <12 years N=43	≥12 - <18 years N=52	≥18 years N=183	Total N=289	<6 years N=11	≥6 - <12 years N=46	≥12 - <18 years N=53	≥18 years N=192	Total N=302
	Prior to KOVALTRY[a]					**End of Observation**				
Min, Max	0, 12	0, 6	0, 16	0, 58	0, 58	0.00, 4.05	0.00, 7.06	0.00, 13.93	0.00, 57.93	0.00, 57.93
	Number of target joints at start of KOVALTRY treatment					**Number of target joints at end of observation**				
n	11	45	50	184	290	11	42	38	171	262
Nmiss	0	1	3	8	12	0	4	15	21	40
Mean (SD)	0.5 (1.2)	0.2 (0.8)	0.1 (0.3)	1.6 (2.7)	1.1 (2.3)	0.4 (1.2)	0.3 (0.9)	0.1 (0.3)	0.9 (1.6)	0.7 (1.4)
Median	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 4	0, 5	0, 1	0, 23	0, 23	0, 4	0, 5	0, 1	0, 8	0, 8

a: Subgroup of patients with regular prophylaxis schedule for most recent FVIII treatment prior to KOVALTRY.
b: Is defined as the last documented regimen change or if no change is documented then regimen at baseline.
c: Number of (joint) bleeds in the last 12 months is calculated by number of (joint) bleeds in the last 6 months * 2.
d: The annualized number of reported bleeds was calculated as (number of reported bleeds / documentation period of the patient diary in days) * 365.25 (SAP version 3.0 section 4.6, see Annex 1).
FAS: Full Analysis Set, Max: maximum, Min: minimum, n: number of patients, N: number of patients in subgroup or analysis set, Nmiss: number of patients with missing values in subgroup or analysis set, SAP: Statistical Analysis Plan, SD: standard deviation, TFLs: Tables, Figures and Listings
Source: FAS-Table 14.1.1 / 5, FAS-Table 14.1.1 / 28 in 18559_TAURUS_TGL_FA_v1.0_FAS_hemophilia_history_20210414.docx
FAS-Table 14.1.1 / 33 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_investigator_20210414
FAS-Table 14.1.1 / 74 in 18559_TAURUS_TGL_FA_v1.0_FAS_study_medication_diary_1_20210416.docx
FAS-Table 14.1.1 / 5 in 18559_TAURUS_TGL_FA_v1.0_FAS_target_joints_20210415.docx
For sources see TFL Subgroup Analysis [FAS] in Annex 1.

Annex 3: Signature Pages

A. Electronic Signature

Signature Page

This protocol is electronically signed in the study management system

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	Version 1.0, 12 JUL 2021
IMPACT study number	18559
Study type / Study phase	Phase IV PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS15459
Medicinal product	KOVALTRY (Octocog alfa)
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Signatories

- PPD
-
-
-
-
-
-