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Title page

Post-marketing investigation (PMI) to assess safety and efficacy of Jivi (BAY 94-9027) treatment in patients with hemophilia A

Jivi interventional PMI study to assess safety and efficacy

Bayer study drug	BAY 94-9027 / Damoctocog alfa pegol; Human Pegylated rFVIII; Jivi®		
Study purpose:	Post-marketing requirements		
Clinical study phase:	IV	**Date:**	14 MAR 2022
Study No.:	19764	**Version:**	2.0 (amendment)
Author:	PPD PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

Table of Contents

Table of tables

Abbreviations

ABR	Annualized bleeding rate
AE	Adverse event
ATC	Anatomical Therapeutic Chemical Classification
CRF	Case report form
DSMB	Data safety monitoring board
ED	Exposure Day
EE	Energy expenditure
EMA	European Medicines Agency
ePD	Electronic patient diary
FDA	Food and Drug Administration
ITT	Intent to treat set
IU	International Unit
IV	Intravenous
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modifiedintent to treat set
MVPA	Moderate to vigorous physical activity
N/A	Not applicable
PA	Physical activity
PEG	Polyethylene glycol
PMDA	Pharmaceuticals and Medical Devices Agency
PMI	Post-marketing investigation
PT	Preferred term
PTP	Previously treated patient
rFVIII	Recombinant coagulation factor VIII
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

Recombinant coagulation FVIII (rFVIII) is a replacement therapy in patients with Hemophilia A. Jivi (BAY 94-9027) has received marketing authorization amongst others from Food and Drug Administration (FDA), European Medicines Agency (EMA), Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. The approved indication is: Treatment and prophylaxis of bleeding (including perioperative management) in previously treated patients (PTPs) ≥ 12 years of age with hemophilia A (congenital FVIII deficiency).

Regulatory requirements necessitate to assess the safety of Jivi in a total of 200 participants with 100 exposure days (ED) including pre-licensure participants of the development program from the studies 13024 (PROTECT VIII) and 15912 (PROTECT Kids). This study will include at least 25 participants for fulfillment of the requirements and provide a pooled analysis of all clinical studies (phase III/IV).

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methods to be used in analyzing and reporting results for the assessment of safety and efficacy of Jivi in Study 19764 and the integrated analysis of this study together with studies 13024 Part A (incl. extension) and 15912 (incl. extension).

Relevant documents

- Clinical Study Protocol No. BAY 94-9027 / 19764 Version 2.0, dated 04 FEB 2020
- Integrated Clinical Study Protocol No. BAY 94-9027 / 13024, version 6.0, dated 20 JUN 2019
- Statistical Analysis Plan for study 13024, version 7.0, dated 11 SEP 2019
- Integrated Clinical Study Protocol BAY 94-9027 / 15912, version 5.0, dated 13 JUN 2017
- Statistical Analysis Plan for study 15912, version 3.0, dated 11 SEP 2019

2. Study Objectives

The objective of the study is to confirm general safety and clinical efficacy with specific focus on immunogenicity and inhibitor documentation in a routine clinical use of the product in at least additional 25 participants during 100 ED in order to fully comply with Guideline requirements of 200 participants observed for at least 100 ED including participants from pre-authorization studies.

Table 2–1: Study objectives and endpoints for study 19764

Objectives	Endpoints throughout the study
Primary	
• To assess safety of Jivi	Primary Endpoint • FVIII inhibitor development by the Nijmegen Bethesda assay Secondary Endpoints • Treatment-emergent adverse events (TEAE) • Development of treatment-emergent anti-PEG antibodies
Secondary	
• To assess clinical efficacy of Jivi	Secondary Endpoint • Annualized bleeding rate (ABR) Other pre-specified • Number of ED • Percentage of participants with 0 bleeding events during a 6-month period • Consumption • Bleeding event attributes • Incremental recovery

3. Study Design

The study will be a multicenter, single group, uncontrolled open label trial. Severe hemophilia A patients, age ≥18 years, will be enrolled and treated with prophylaxis treatment and for breakthrough bleeds for at least 100 ED, which may require 1-2 years depending on the prophylaxis regimen. Assessment of immunogenicity and safety will be performed at pre-defined ED as required by EMA FVIII Guideline.

The recommended starting dose is every 5 days treatment (45 IU/kg). An assessment of response to treatment will be performed at the next scheduled visit after 10-15 ED (~ 8-10 weeks). Subsequent dosing depends on need assessed by the investigator according to the following scheme and can be adjusted as needed.

Table 3–1: Recommended dose regimen

Procedure	Duration	Dose regimen		Route of administration
Screening	> 2 weeks, ≤ 8 weeks	Continuation of previous treatment		
Treatment Phase	Time to reach 10-15 ED (~ 8 to 10 weeks)	Recommended starting dose 45 IU/kg every 5 days. Dose regimen can be adjusted any time in case of bleeds		IV injection
	Time to reach 100 ED	0 bleeds during the first 8-10 weeks:	Recommended dose regimen: 60 IU/kg every 7 days	IV injection
		1 clinically relevant bleed during the first 8-10 weeks:	Continue every 5 days at dose of 60 IU/kg Or at investigator's judgement: Switch to 40 IU/kg 2x/week	
		≥ 2 clinically relevant bleeds during the first 8-10 weeks:	Change to 40 IU/kg 2x/week	

ED = exposure day, IV = intravenous
Clinically relevant: joint or muscle bleed that needs treatment

The total treatment duration is the time to reach 100 ED of Jivi. The total duration of study participation for each participant may require up to 2 years depending on the selected prophylactic regimen. When 25 participants have reached 100 ED, the study will be completed. Remaining participants may prematurely discontinue with reason 'Study terminated by sponsor' when a treatment duration of at least 6 months is reached.

4. General Statistical Considerations

4.1 General Principles

The study is not designed to test any predefined hypothesis. All analyses will be descriptive or exploratory.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum values will be calculated for metric data. Frequency tables will be generated for categorical data.

In addition to the analyses for study 19764, pooled results across the clinical phase 3/phase 4 studies will be presented. Therefore, data of study 19764 will be pooled with data from studies 13024 and 15912. CCI [redacted]

Except when mentioned otherwise, all safety analyses will present results for study 19764 and pooled results of studies 19764, 13024 Part A (incl. Part A extension) and 15912 (incl.

extension). All safety analyses will be presented for the combined Jivi treatment group and will not distinguish between different regimens or treatment frequencies.

Efficacy analyses will be done for study 19764. If presented by treatment regimen, this will refer to the regimen at Visit 3. Participants who switch their regimen after Visit 3 will be assigned to a 'Variable frequency' group. Participants who dropped out before Visit 3 will be analyzed with their baseline regimen.

In addition to the study specific efficacy analysis, pooled results from studies 19764, 13024 Part A (incl. extension), and 15912 (incl. extension) for the main efficacy endpoint, i.e. annualized bleeding rates (ABR), will be provided.

Data handling rules described in this SAP refer specifically to study 19764. Data handling will be consistent with the data handling already applied to studies 13024 Part A and 15912. More details about the data handling of studies 13024 Part A and 15912 are available in the SAPs of these studies.

The following subgroup will be analyzed for safety and pooled efficacy:

- Age group 1: <12 years vs ≥ 12 years (at enrollment)

Subgroup tables will not be displayed by study/pool but by subgroup categories instead.

In case of multiple measurements before first treatment, the last one will be analyzed as baseline measurement.

4.2 Handling of Dropouts

A participant who discontinues study participation prematurely for any reason is defined as a dropout if the participant has already been administered at least one dose of study drug.

The reasons for withdrawal will be listed in a table. Dropouts will be included in all safety analyses. They will also be included in efficacy analyses if the treatment duration is >= 3 months. The ABR will be calculated for these participants. It is assumed that a shorter treatment duration will not be sufficient to correctly estimate the ABR and would bias the results. When calculating ABRs, the end of the measuring period for a dropout is defined as the later of last available infusion record from the electronic patient diary (ePD) or the last procedure in a scheduled visit, excluding the final visit.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listings as they are recorded on the Case Report Form (CRF).

General rules

When appropriate, the following imputation rules will be implemented so as not to exclude participants from statistical analyses due to missing or incomplete data:

- **Missing time of infusions**

If an in-hospital infusion has a missing time, the time of the pre-infusion FVIII level measurement plus 1 minute will be used. If this time is also missing, 10:00 will be substituted.

- **Missing or incomplete adverse event (AE) start date**

If first study treatment falls within imputation range, incomplete start date is imputed as first day of treatment. Otherwise, it is imputed to the earliest date of the imputation interval.

Empty start date is not imputed. Incomplete stop date is always imputed as the latest date of the imputation interval. Empty stop date is not imputed and presumed to be ongoing.

- **Missing or incomplete concomitant medication start and end date**

If first study treatment falls within imputation range, incomplete start date is imputed as first day of treatment. Otherwise, it is imputed to the earliest date of the imputation interval. Empty start date is not imputed. Incomplete stop date is always imputed as the latest date of the imputation interval. Empty stop date is not imputed and presumed to be ongoing.

Partially missing dates of medications categorized as 'PRIOR FVIII THERAPY' will not be imputed. All these medications will be considered prior medications.

Additional descriptive analyses in the presence of missing data

The number of participants who prematurely discontinue the study for any reason, as well as the time point and reasons for premature discontinuation of study, will be reported. The number of missing FVIII inhibitor and anti-drug or anti-PEG antibody measurements will be provided.

4.4 Interim Analyses and Data Monitoring

An optional interim analysis might be performed, if needed for regulatory submission or publication purposes, after all participants have been treated for 6 months for assessment of the main safety (inhibitor development) and efficacy endpoints.

The scope of the interim analysis will depend on its purpose and will be defined in an SAP supplement, if needed.

There will be no Data Safety Monitoring Board (DSMB) for this study.

4.5 Data Rules

The following derivation rules will be applied to this study:

Counting of bleeds:

- 'All bleeds' will include all bleeds, regardless of treated or untreated (untreated bleeds will only be available from study 19764)
- A bleed will be counted as treated bleed if either the flag variable from the diary indicates that the bleed was treated or there is a matching infusion for this bleed (regardless of product used).

ABR:

$$Annualized\ number\ of\ bleeds = \frac{\#\ of\ bleeds * 365.25 * 24 * 60}{period}$$

Period is defined as the number of minutes calculated from the date and time of the beginning of the evaluation period and the date and time of the end of the evaluation period.

Evaluation periods for study 19764:

- Main efficacy period: Time from injection at visit 3 to end of treatment
- Complete study: Time from first injection at visit 2 to end of treatment

End of treatment is defined as date of latest infusion plus 7 days or end of study, whatever is earlier.

24-hour rule:

All bleeds that occur during the same calendar day will be considered as one bleed. Priority will be determined according to the following order:

- - spontaneous bleed
- - joint bleed
- - treated bleed
- - earliest bleed

The analyzed bleed will be the one with the highest priority. It will get the following derived characteristics:

- - combination of all types and locations
- - highest treated status (i.e. treated if at least one bleed on that day is treated)
- - worst assessment of hemostasis

All other bleeds on the same calendar day will not be considered for analysis but only listed.

72-hour rule:

A spontaneous joint or spontaneous muscle bleed will not be counted if it occurs within 72 hours of a bleed (or infusion for that bleed) at the same site. For a spontaneous bleed to be affected by this rule, all sites listed on the bleed must also be specified in the previous bleeds during a 72 hour time frame. Infusions for such bleeds will be considered to be follow-up infusions. If the current and previous bleeds are both skin/mucosa bleeds, this rule does not apply. The rule operates with date/time and bleed locations adjusted by 24-hour rule. Bleeds eliminated by 24-hr rule are not considered.

Joint bleed:

Joint bleeds can occur in more than 1 joint site. When counting sites for the joint bleeds, all sites will be counted. Data reflecting joint site frequencies will include the frequencies over all sites.

Incremental recovery:

FVIII levels measured by the chromogenic assay will be analyzed.

Incremental recovery is calculated as shown below:

Incremental recovery = (post-infusion FVIII level – pre-infusion FVIII level) * weight / dose (in IU)

The most recent weight measurement at time of blood sampling will be used for calculation.

If a FVIII level value is below the lower limit of quantification (LLOQ), a data point with the value of one-half the LLOQ will be substituted.

Participants with positive FVIII inhibitor or any positive anti-drug antibody measurement during study will be excluded from recovery analyses. Results of these participants will be listed.

A validity flag for incremental recovery values will be created. All incremental recoveries will be considered valid except when the following conditions apply:

- Pre-infusion FVIII level is equal to or higher than the post-infusion FVIII level
- Post-infusion FVIII value is below the LLOQ
- The time from previous study drug infusion to the pre-infusion FVIII level measurement is less than 72 hours (i.e. protocol defined wash-out period of 72 hours was not kept)

If an incremental recovery is flagged as not valid, then the corresponding pre-infusion, post-infusion and incremental recovery value will not be considered in tables displaying summary statistics of incremental recovery values and FVIII levels. FVIII levels that are not valid for calculation of incremental recovery will be listed.

Medical history groupings:

'Medical history of HIV' will be defined as the occurrence of at least one of the medical history preferred terms 'HIV infection', 'HIV disease', and 'HIV test positive'.

'Medical history of hepatitis C' is given if at least one of the preferred terms 'Hepatitis C', 'Chronic hepatitis C', 'Hepatitis C virus test positive', 'Hepatitis C antibody positive', 'Hepatitis C infection', 'Hepatitis C chronic' is reported in the medical history data.

'Medical history of arthropathy' will be defined as the occurrence of at least one of the medical history preferred terms 'Arthropathy' and 'Haemophilic arthropathy'.

Compliance:

Compliance of each patient will be calculated as:

Compliance (%) based on prophylaxis infusion count = 100 * number of actual prophylaxis infusions / number of expected prophylaxis infusion

Compliance (%) based on total infusion count = 100 * number of actual infusions / number of expected prophylaxis infusion

Number of expected prophylaxis infusions: Number of prescribed infusions per week / 7 * period of prescribed frequency (days)

Treatment administration:

Documented infusions with other FVIII products or with a dose of 0 IU will be excluded. Infusions with a missing dose will be counted for number of infusions and exposure days but will be excluded from other treatment administration analyses.

4.6 Blind Review/Validity review

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of participants to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis sets (see section 4.6).

Safety analysis set (SAF)

A participant will be included in the SAF if he received at least 1 infusion of study drug.

Intent to treat set (ITT)

A participant will be included in the ITT if he received at least 1 infusion of study drug and has any injection/bleeding data available.

Modified Intent-to-treat set (mITT)

A participant will be included in the mITT if he received at least 1 infusion of study drug and has injection/bleeding data for at least 3 months available.

A participant of study 13024 or study 15912 will only be included in the mITT if he entered the extension phase of the study.

6. Statistical Methodology

6.1 Population characteristics

All tables will be provided for the SAF and the mITT.

Demographics will include age, ethnicity, race, weight, height and BMI.

Baseline characteristics will include age at first treatment, type of first treatment regimen, type of FVIII gene mutation, family history of hemophilia, family history of inhibitor, presence of target joint, frequencies for specific target joints, previous FVIII treatment type, prior hemophilia treatment drug, medical history of concomitant diseases (e.g. HIV, hepatitis C, arthropathy, hypertension).

Summary statistics will be provided for number of bleeds and number of joint bleeds during the last 12 months prior to study and will be stratified by previous treatment type.

Descriptive statistics will be provided for the baseline activity level and previous dosing frequencies and dosages of study 19764.

Medical history, concomitant medication use

Medical history data as coded by MedDRA will be summarized by primary system organ class (SOC) and preferred term (PT). Prior and concomitant medications as coded by WHO-

DD will be summarized by ATC class and subclass. Medications taken before start of study drug will be considered prior medications, medications taken within the treatment period will be considered concomitant medications.

New concomitant medications that started after first treatment and belong to the ATC subclasses 'ANTIHEMORRHAGICS', 'BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS', and 'ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS' will be presented by ATC subclass and standardized medication name. Factor VIII medications will be identified and grouped. A listing of new concomitant medications stratified by 'Antihemorrhagics', 'Blood substitutes and perfusion solutions', and 'Antiinflammatory and antirheumatic products' will be provided for study 19764.

Exposure and treatment duration

Number of EDs and time in study will be analyzed by summary statistics. Number of EDs will be categorized into < 50 ED vs >= 50 - < 100 ED vs >= 100 ED. One ED is defined as a calendar day during which at least one infusion is taken by the participant.

Compliance

Summary statistics for compliance (%) and time between prophylaxis injections (days) will be presented. Calculation of compliance is described in section 4.5.

Compliance will be categorized into < 95%, >= 95% - <= 105%, > 105%.

6.2 Efficacy

The secondary objective of the study is to assess clinical efficacy. Unless otherwise mentioned, all efficacy analyses will be performed on the mITT population with a treatment period of at least 3 months. A comprehensive efficacy analysis will be done for study 19764. In addition, pooled results will be provided for the ABR.

The following descriptions refer to the analysis for the individual study data of 19764.

ABR:

The ABR is the main efficacy endpoint of the secondary objective.

- ABRs will be presented for all bleeds, joint bleeds, spontaneous bleeds, , and trauma bleeds
- Results for the main efficacy period (Visit 3 to end of study) will be displayed by treatment regimen as described in section 4.1
- Results for the complete study period (baseline to end of study) will be shown for the combined prophylaxis group

Other efficacy endpoints

Unless otherwise mentioned, results will be presented for complete study periods.

- Percentages of participants with 0 bleeds, 0 joint bleeds, 0 spontaneous bleeds, during the following treatment periods:
    - Last 6 months
    - Last year

- Treatment administration (overall, prophylaxis, treatment of bleeds): number of infusions (all and per year), consumption (IU, IU/kg, IU/kg/year, IU/kg/infusion, IU/year, IU/infusion)
- Reason for infusion
- Bleeding attributes: type, location, intensity, number of infusions to control, response to treatment
- FVIII levels pre- and post-infusion and incremental recovery: Results will be displayed by visit and overall (means per participant across visits)
- Pre- and post-infusion FVIII levels which are invalid for the calculation of recovery will be listed
- Bleeds into pre-existing target joints (annualized number, proportion of participants with 0 such bleeds) for the complete study period as well as the main efficacy period (starting with Visit 3)
- All untreated bleeds of study 19764 will be listed.
- Dosing regimens at baseline, Visit 3, and end of study will be compared in shift tables
- All dosing frequencies, planned doses, and reasons for dose modifications will be listed

Pooled efficacy analysis:

Pooled ABRs will be presented for the combined prophylaxis group and complete study periods. Only subjects who participated in the extension periods will be included in the analysis. Participants from study 13024 who only received on-demand treatment will be excluded from the pooled efficacy analysis because on-demand treatment was not applied in the other studies and pooling of on-demand and prophylaxis participants is not meaningful for efficacy endpoints. Participants who switched from on-demand treatment in the main study to prophylaxis in the extension part of study 13024 will be included in the prophylaxis group with their prophylaxis treatment period. The on-demand main study part of these participants will not be included in the analysis. Results will be dispayed by age group.

Sensitivity analyses:

- Estimates and 95% confidence intervals from a negative binomial regression model will be presented for the ABRs of all bleeds, different lengths of evaluation periods will be addressed via an offset variable
- A subject listing including number and kind of bleeds and time in study will be provided for participants excluded from the mITT set

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6.3 Pharmacokinetics/pharmacodynamics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

6.4 Safety

All safety analyses will be performed on the SAF. MedDRA codes of studies 13024 and 15912 will be updated by the MedDRA version used for study 19764. An AE will be considered treatment-emergent if it starts after first injection and not later than 7 days after last injection of Jivi.

Overview tables displaying all AEs, all pre-treatment AEs and all treatment emergent adverse events (TEAEs) will be created. All subsequent tables will be presented by MedDRA preferred term (PT) and system organ class (SOC). Serious AEs, TEAEs, serious TEAEs, drug-related TEAEs, serious drug-related TEAEs, TEAEs of special interest, TEAEs causing discontinuation of study drug, TEAEs by maximum intensity, drug-related TEAEs by maximum intensity, non-serious TEAEs, and AEs leading to death will be presented.

Overview tables, all TEAEs, serious TEAEs, drug-related TEAEs and serious drug-related TEAEs will be displayed by subgroups.

Factor VIII inhibitor, PEG antibody and BAY 94-9027 antibody results

Frequency tables will be provided for the number of participants with confirmed inhibitors and anti-drug and anti-PEG antibodies. The status during study will be displayed by pre-treatment status. Proportion of participants with positive measurements at the end of the observation period will be displayed based on the number of participants with positive status during study.

Inhibitors will be classified as being either low titer (≥0.6 BU/mL and ≤5 BU/mL) or high titer (>5 BU) based upon persistence of an inhibitor.

Antibody incidences at screening/baseline as well as new antibody incidences after start of treatment will be presented.

Subject listings will be provided for all participants from study 19764 with at least one positive FVIII inhibitor measurement/BAY 94-9027 antibody measurement/PEG antibody measurement/PEG IgM antibody measurement showing all FVIII inhibitor/BAY 94-9027 antibody/PEG antibody/PEG IgM antibody (respectively) laboratory measurements as well as FVIII recovery results of these participants, including the number of ED before the measurement dates and the date of the last injection before measurement dates.

All measurement results for inhibitors including repeated measurements in case of positive results will be displayed by time point and presented in subject listings.

Clinical laboratory

Number of participants with treatment emergent high and low laboratory abnormalities will be displayed in frequency tables by laboratory category.

Summary statistics for all laboratory values at baseline and individual last visit will be presented. Changes from baseline at last visit will be provided, if applicable.

Shift tables for urinalysis parameters will be shown.

In addition, summary statistics for all laboratory values and changes from baseline by visit will be displayed for study 19764.

Laboratory results will not be displayed by subgroups.

Vital signs

Summary statistics including changes from baseline will be presented for vital signs (systolic blood pressure, diastolic blood pressure, heart rate, temperature) by visit for study 19764.

Vital signs will not be stratified by subgroups.

COVID-19 pandemic

Subjects affected by the COVID-19 pandemic related study disruptions and important protocol deviations associated with the COVID-19 pandemic will be listed.

7. Document history and changes in the planned statistical analysis

This SAP is based on the protocol Version 2.0 dated 04 FEB 2020.

SAP Version	Date	Change	Rationale
1	03 SEP 2019	Not applicable	Original version
2	14 MAR 2022	Data display	Safety results will be displayed for study 19764 and pooled, instead of by study and pooled. By-study display for 13024 and 15912 would be a repetition of already available results.
		Scope of efficacy analyses.	Main focus was changed from the pooled efficacy to the individual study efficacy analysis. Only ABRs will presented across studies. Reason for including pooled results is the requirement to provide pooled safety data to the authority. Pooled efficacy results are not required. Also, there are differences in study design which would impact pooled efficacy outcomes.
		Number of subgroups reduced	Results will only be stratified by age < 12 years vs >= 12 years. Other subgroup analyses are only of interest for publication purposes and will be as post-hoc analyses.
		Adaption of data rules	Minor changes in descriptions for consistency with standard macros and standard approaches applied. Details for validity of recovery results were specified.
		All bleeds will be analyzed	Treated bleeds will not be analyzed separately due to the low number of such bleeds.Analyzing all bleeds is considered conservative.
		CCI [redacted]	CCI [redacted]

8. References

Not applicable.