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Title page

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Analysis purpose:	Post-hoc analyes		
Clinical study phase:	2	**Date:**	10 MAR 2020
Study No.:	19580	**Version:**	1.0
Author:	PPD		

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Preamble

This Statistical analyses plan is for the documentation of post-hoc analyses for publishing purposes.

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1. Annualized Bleeding rates

The number of bleeds and annalized bleeding rate is shown by treatment arm. The table differentiates the bleeds into all bleeds and spontenous bleeds. In addition, these bleeds are separated by treated and untreated bleeds. For the number of bleeds the 24 hours rule as well as the 72 hours rule as descriped in SAP sections 4.5.3 and 4.5.4 apply. Use SAS code from Kovaltry and/or Jivi as reference.

The annualized bleeding rate is defined as

$$\frac{(\#\ of\ bleeds\ in\ data\ scope\ time) \cdot 365.25}{(last\ date\ in\ data\ scope - first\ date\ in\ data\ scope + 1)}$$

The following data scopes will be analysed:

- Bleeds in 6 months before randomization. The last date of data scope is the day of randomization, the irst date in data scope is 6 months before, i.e. the time in the data scope is fixed at 183 days. This bleeds will be shown by dose initially received.
- Dose initially given: First date in that data scope is defined as first intake of the study treatment. Last date is the date of the intake of any study drug. Show bleeds for combined Part A and Part B (whole study time), as well es for Part A (last date is the end of Part A in this case) and Part B (first date is the start of Part B in this case).
- Dose actually given: show for the dose actually given the annualized bleeding rates in Part B - for patients that get escaled in Part B the last date in the data scope for a specific dose is the day the escalation into the higher dose group. For these patients the first day is the new dose group is the first date of the data scope for Part B and that escalated dose group is the day of the escalation.

Subgroup analyses will be performed by previous treatment.

2. Individual Lab plot

Show table CLIPS LB1C and figure CLIPS LB-F2 for available laboratory parameter and subjects.

3. PK/PD individual plots

Show figure CLIPS PK-F2 for available PK/PD parameter.

Title page

Multiple escalating dose study of BAY 1093884 in adults with hemophilia A or B with or without inhibitors

Bayer study drug	BAY 1093884		
Clinical study phase:	2	**Date:**	23 Jul 2018
Study No.:	19580	**Version:**	1.0
Author:	PPD		

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

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Abbreviations

AE	**Adverse event**
AESI	Adverse event of special interest
CRF	Case report form
DIR	Dose initially recived
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EU	European Union
FIX	Factor IX
FVIIa	Activated factor VII
FVIII	Factor VIII
FX	Factor X
FXa	Activated factor X
IgG2	Immunoglobulin G2
ISR	Injection site reaction
ITI	Immune tolerance induction
IV	Intravenous
LOS	Listing only set
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
OD	On demand
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per protocol set
SAE	Serious adverse event
SAF	Safety (set)
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
US	United States (of America)

1. Introduction

This SAP is based on Study Protocol version 2.0 (dated 26 JUN 2018).

Background

Hemophilia A and B are genetic bleeding disorders caused by the deficiency of Factor VIII (FVIII) or Factor IX (FIX), respectively. Persons with mild hemophilia (6% – 49% Factor level) may have excessive bleeding following dental procedures, injury or surgery, while moderate (1% to 5% factor activity) and severe (< 1% factor activity) hemophilia are typically characterized by more frequent and severe bleeding complications. Persons with severe hemophilia may experience not only bleeding after injury, trauma or surgery, but also spontaneous bleeding into joints, muscles and internal organs, including the brain. Recurrent bleeding into joints results in chronic debilitation.

The standard treatment for hemophilia A or B is replacement therapy, with intravenous (IV) administration of plasma-derived or recombinant FVIII or FIX, respectively. Some subjects treat bleeding episodes as they occur (i.e., on-demand [OD] treatment), while others treat themselves prophylactically to prevent bleeding according to the recommendations from the

World Health Organization. In recent years, prophylactic treatment has become the prevailing type of hemophilia treatment in most developed countries.

The proven clinical benefits of prophylaxis have led to a shift in treatment paradigm from OD treatment to the use of prophylaxis in many countries.

Better outcomes of prophylaxis versus OD treatment regimen are proven, but three major challenges characterize prophylactic treatment: the need for IV injections, the relatively high bleeding rate and the most significant treatment complication, the development of inhibitors.

Despite frequent and painful IV injections (and the subsequent frequent need for central venous access devices in young children), subjects on prophylaxis still bleed, with a median annualized bleeding rate of up to 6 bleeds, thus, leaving a high unmet medical need for better protection. A higher level of protection is in some cases achievable only by increasing the burden of treatment (more frequent injections), to reduce the clotting factor fluctuations that characterize replacement factors treatment (presence of peaks and troughs).

Effective treatment options are significantly lower if inhibitory antibodies against the FVIII or FIX (inhibitors) develop. The inhibitors interfere with the infused factor concentrates rendering them ineffective and requiring the use of more costly and less effective alternative hemostatic agents, defined as “bypassing agents”. The incidence of new FVIII inhibitors in subjects with severe FVIII deficiency is up to 45%. Inhibitor development is currently the most significant treatment complication seen in subjects with hemophilia. While improvements in hemostatic agents for subjects with inhibitors have resulted in decreased mortality, inhibitors are still associated with significant morbidity, including a higher rate of bleeding complications, increased disability, and a decreased quality of life.

As such, these bypassing agents are effective in most cases, but neither agent is universally effective and there is no prophylaxis option for subjects with hemophilia B and inhibitors, as NovoSeven is not licensed for prophylaxis in EU and US.

HEMLIBRA (emicizumab-kxwh) is currently approved in the US for subcutaneous routine prophylaxis in hemophilia A subjects with inhibitors, however, mimicking the action of activated FVIII (FVIIIa), it does not provide a steady state protection (variable rates of fluctuation with potential low levels at the end of the injection interval). Additionally, it carries a black box warning of thrombotic microangiopathy and thromboembolism when used with aPCC/FEIBA for the treatment of breakthrough bleeds.

There is currently no treatment available to provide constant protection against bleeding episodes, to lower burden of treatment, and to avoid risk of FVIII/FIX inhibitor development for the entire hemophilia population, regardless of the FVIII or FIX deficiency status or the presence of FVIII or FIX inhibitors.

BAY 1093884 may address all these unmet needs, representing a valid treatment option for all subjects with hemophilia.

The coagulation cascade and the role of tissue factor pathway inhibitor (TFPI)

In the cell-based model, the coagulation is initiated (the *Initiation Phase*) by the formation of a complex between the tissue factor (TF), exposed on the surface of fibroblasts as result of vessel injury, and activated factor VII (FVIIa), normally present in the circulating blood. The TF-FVIIa complex converts factor X (FX) in activated FX (FXa), which activates

prothrombin (FII) to thrombin (FIIa). In this *Amplification Phase*, due to this limited amount of thrombin, FVIII and FIX are activated and involved in the following *Propagation Phase*, where full thrombin generation takes place, enabling for clot formation.

According to this model, the TF *extrinsic pathway* is the principal cellular initiator of normal blood coagulation in vivo, and the major regulator of hemostasis and thrombogenesis, with the *intrinsic pathway* playing an amplification role.

In people with hemophilia, the TF initiated extrinsic coagulation pathway is intact, so a question may rise on why these people do bleed. The explanation is provided by the fact that the TF activity and the extrinsic pathway of blood coagulation are regulated by a specific and natural coagulation inhibitor: the tissue factor pathway inhibitor – TFPI.

In healthy individuals TFPI maintains a normal hemostatic balance (it is in fact considered a natural anticoagulant) while in people with hemophilia it further reduces the already insufficient thrombin due to the lack of FVIII or FIX.

Thus, the inhibition of TFPI through the administration of anti-TFPI antibodies (BAY 1093884) is expected to restore the hemostatic balance toward normal thrombin generation, and thus a potential mechanism to restore hemostasis in hemophilia subjects.

The product

BAY 1093884 is a human monoclonal IgG2 antibody with a novel mechanism of action based on blocking the function of endogenous TFPI.

TFPI usually consists of 3 Kunitz domains (K1, K2, K3). The primary anticoagulant properties of TFPI are mediated through the K1 and K2 domains. BAY 1093884 binds to both K1 and K2 domains, blocking TFPI inhibition of key factors (FXa via K2, and FVIIa/TF complex via K1) in the tissue factor initiated coagulation pathway. K3 binds to Protein S, which is not directly inhibiting the protease function.

BAY 1093884 has been optimized for affinity. The effect of neutralizing TFPI with BAY 1093884 has been evaluated and demonstrated in several in vitro and in vivo studies, showing prolonged efficacy compared to current bypass therapies. As a monoclonal antibody (mAb), BAY 1093884 also offers the opportunity of subcutaneous (SC) administration, while other currently available hemophilia treatments have to be administered intravenously.

The goal of TFPI inhibition is to restore normal levels of FXa, and thus correct the low levels of thrombin generated due to deficiency of either FVIII or FIX, independent of whether the deficiency results from ineffective production, or results from presence of inhibitory antibodies directed against either protein. TFPI inhibition targets a normal regulatory protein, and consequently is not a pro-coagulant. Thus, normal events that lead to initiation of coagulation at a site of injury are unaffected. Additionally, TFPI inhibition does not interfere with downstream mechanisms that protect from or turn off thrombin generation, thus regulation of thrombin and fibrinolysis remain intact, with a consequent favorable safety profile.

The overall nonclinical toxicology and safety profile of BAY 1093884 lends to support clinical studies with repeated administration of BAY 1093884 in subjects with hemophilia A or B with or without inhibitors.

Further details can be found in the Clinical study protocol, which contains comprehensive information on the study drug.

2. Study Objectives

Primary objective:

- To assess the safety and tolerability of multiple subcutaneous doses of BAY 1093884 in subjects with hemophilia A or B with or without inhibitors.

CCI

3. Study Design

This is an open-label Phase 2 study with multiple escalating doses of BAY 1093884 in 3 cohorts. The goal of the study is to evaluate the safety of multiple escalating doses of BAY 1093884 and identify a dose (or doses) to be used in the pivotal Phase 3 study.

The study has 2 main components - a multiple dose escalation component and a dose finding component.

Multiple-dose escalation component: Eight (8) new distinct subjects are planned to be enrolled in each of the 3 dose cohorts. Opening of the new cohort will only enroll new subjects. An initial dose of 100 mg SC has been selected for Dose X based on safety and PK/PD data from the Phase I study. Safety data from Dose X in N=6 subjects after 1x/week SC dose for 6 weeks will be the basis for opening the cohort for Dose Y. When acceptable safety and tolerability has been achieved in the first 6 subjects after 6 weeks of dosing, the cohort for Dose Y (not to exceed 250 mg) will be opened for enrollment of 8 new subjects. The opening of cohort to Dose Z (dose not to exceed 400 mg) follows the same process and will be based on safety/tolerability data from N=6 subjects given Dose Y once weekly for 6 weeks.

The DMC will review all available safety data and the proposed dose based on PK/PD prior to opening any cohort. Safety evaluation, including stopping criteria, is described in the Study Protocol.

Dose finding component: This portion of the study is designed to allow for identification of the appropriate dose(s) for the Phase 3 study. The dose selection for Phase 3 will be based on both the assessment of safety and evidence of efficacy based on bleeding control assessed over a 12 week period of dosing. In each cohort at dose level X, Y and Z the subjects will continue at that dose for at least 12 weeks and efficacy information from all 8 subjects at each dose level will be used for the assessment of efficacy (based on number of bleedings). Although acceptable safety and tolerability data of 6 weeks in at least 6 subjects at Dose X is required to open the next cohort – Dose Y, all 8 subjects at Dose X will remain at dose level X for at least 12 weeks to assess the efficacy. After 12 weeks of treatment with BAY 1093884, these patients (in dose level X or Y) will be allowed to escalate to the next dose level (if the next dose level is open), safety criteria as defined in the protocol are met, and the

patient experiences more than 2 bleeds during the first 12 weeks or more than 1 bleed at any 12 weeks interval after the first 12 weeks of dosing at a particular dose level. The safety criteria to be assessed for this portion of the study (individual dose escalation after 12 weeks of dosing in that particular dose cohort) are provided later in this section.

For each subject, the study is structured in three parts

Part A. Each subject will be treated with the allocated dose of BAY 1093884 (X mg, Y mg or Z mg) for 12 weeks. These first 12 weeks will allow for primary safety evaluations of each dose.

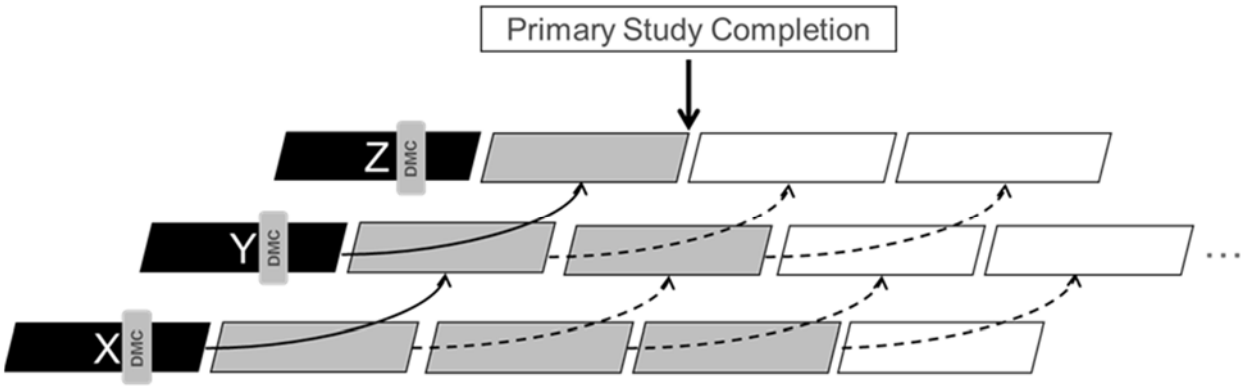
Part B. Each subject will be treated for additional periods of 12 weeks in duration. After evaluation of the number of bleeds at the end of each 12-week period, subjects can be treated with the same dose or with the next higher opened dose level. The date when the last subject in Cohort 3 (Z dose) has completed Part B, will be the database cut-off date (i.e., primary completion date).

Extension part. After completion of Part B of the Z dose cohort, and upon DMC evaluation of safety data from the first 6 patients for 6 weeks in the dose Z cohort, all subjects will be invited to continue the treatment in an extension part, at the end of their ongoing Part B period. During the extension, all subjects will be evaluated (number of bleeds) every 12 weeks and escalated to the next higher opened dose, if dose escalation criteria are fulfilled (as per Part B). The extension part will continue, pending submission of safety and efficacy data to Health Authorities after 12 months from its start and every 12 months thereafter, until Marketing Authorization.

Any bleeding event, which should occur during the study (including the extension part) and which requires additional control, will be treated with the subject's pre-assigned treatment (by-passing agent or replacement factor) prescribed by the Investigator pre-study.

Figure 1 shows a schematic overview of the study design.

Figure 1 Design overview



DMC = Data Monitoring Committee.

Black boxes:	Part A: Initial 12 weeks of treatment with BAY 1093884 (no escalation)
Grey boxes:	Part B: all subsequent groups of 12 weeks of treatment with BAY 1093884 (first escalation allowed)
White boxes:	Extension part with evaluations every 12 weeks (further escalations allowed)

Solid line arrows: Option for dose escalation, if the next higher dose is approved and the subject meets the escalation criterion (>2 bleeds in Part A).

Dotted line arrows: Option for dose escalation, if the next higher dose is approved and the subject meets the escalation criterion (>1 bleed in 12 weeks).

At least 24 adult subjects (≥18 years of age) will be enrolled. If additional safety evaluation is needed, a maximum number of 40 subjects may be included.

Eight (8) new distinct subjects are planned to be enrolled in each of the 3 dose cohorts. Opening of the new cohort will only enroll new subjects. These subjects will be treated prophylactically with the X Y or Z dose of BAY 1093884 once weekly for 12 weeks (part A). At least 1 inhibitor subject (any titer) and 2 PK subjects (willing to undergo full PK evaluations) will be enrolled in each cohort.

All subjects of each cohort will continue on the dose assigned for Part A (12 weeks) to obtain safety data and also individual efficacy data.

Individual subject dose escalation criteria in the dose finding part of the study:

In this portion of the study, the objective is to identify the appropriate dose(s) for the Phase 3 study. The dose selection for Phase 3 will be based on both the assessment of safety and evidence of efficacy based on individual bleeding control assessed over a 12 week period of dosing for each patient.

Subjects will be evaluated for the number of bleeds occurring during each part of the study. In particular, only the bleeds recorded as “spontaneous” (not related to any trauma or activity) and requiring additional treatment will be considered for the dose escalation efficacy evaluation, and are defined below as “bleeds.”

Evaluation at the end of Part A:

Subjects who present ≤2 bleeds during Part A will start Part B and continue on the same weekly dose; otherwise (if presenting >2 bleeds) subjects will escalate to the next higher opened dose cohort.

Evaluation at the end of every 12-week period of Part B and extension:

Subjects who present ≤1 bleed in 12 weeks, during Part B, or during the extension part, will continue on the same weekly dose; otherwise (if presenting >1 bleed) subjects will escalate to the next higher opened dose cohort.

Since dose Z is the highest dose, any subject on dose Z who meets the escalation criteria described above may withdraw from the study or may continue treatment to provide further safety and efficacy data. The decision on treatment continuation is at the subject’s and investigator’s discretion.

The first injection of any new or escalated dose will be given under medical supervision.

If a subject qualifies for dose escalation based on the number of bleeds, but the next higher dose cohort has not been opened, the subject should stay on the current dose and then escalate to the next higher dose only after it is opened.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

Primary completion

The primary completion event for this study is when the last subject in Cohort 3 has completed 24 weeks of treatment (end of Part B).

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

All data (efficacy, safety, PK/ PD, and demographic data) will be listed and study summary tables will be provided where appropriate. Variables measured on metrical scales will be summarized using descriptive statistics that will include: the number of non-missing observations, the arithmetic mean, the sample standard deviation, the median, the minimum and maximum, as well as the first and third quartiles where appropriate. Frequency tables will be provided for variables measured on ordinal or nominal scales. Tables will display the number and percentage of subjects falling within a particular category.

Data will be displayed by dose cohort and by study medication actually received during the respective study parts and their visits.

Data will be displayed by period of time. This includes:

- Part A: The first 12 weeks of treatment of each subject.
- Part B: The additional 12-week periods of treatment after Part A. Each subject will be analyzed in the dose cohort he was assigned to (data of dose escalated subjects will be not included).

In general, data will be displayed as measured at each scheduled time point, individual values will be presented in listings.

4.2 Handling of Dropouts

In this study, all efforts must be taken to engage patients to comply with all study procedures and to continue to be followed until the end of the study.

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has received at least 1 dose of BAY 1093884. A subject is regarded a “screening failure” if he terminates the study for any reason (e.g., failure to satisfy the selection criteria) prior to the time point used for the definition of “dropout” .

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

The number of subjects who prematurely discontinue the study during the treatment phase or during the post-treatment observation phase for any reason, as well as the reasons for premature discontinuation of study, will be displayed by dose cohort and dose actually recived. Baseline characteristics will be displayed by premature discontinuation (yes/no) from study.

Subjects who drop from the study after first administration of study treatment will be included in a listing in addition to the inclusion into the SAF.

4.3 Handling of Missing Data

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

General rules

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

- **Efficacy Variables**
  If the details of a bleed are missing (e.g., type of bleed spontaneous, non-spontaneous/non-traumatic or traumatic), the bleed will be counted for all categories of bleeds, but not for the corresponding subgroup of bleeds.

  Each subject's bleeding period start date will be needed to allocate the bleedings to the respective period. If dates for bleeds and injections of rescue medication are both missing then these bleeds cannot be counted. If the bleed date is missing, but the injection date is available, injection date will be used.
- **AE Variables**
  For the purpose of treatment-emergent flags, missing AE start day will be imputed as the 15th of the month. However, if the AE start day is missing, but the AE starts suring the same month or on the same day as the first dose, but the AE start time is missing, the AE start day (and time in the second case) will be taken from first dose start day (and time). If both day and month of AE start date are missing, day and month will be imputed as the date of the first dose.

4.4 Interim Analyses and Data Monitoring

An independent Data Monitoring Committee will review safety data according to the DMC charter. No alpha adjustment is required. No interim efficacy analysis is planned.

After all subjects still participating in the study have completed Part A and at least one 12-week Part B period (primary completion) of the study, all dose levels will be assessed including clinical safety, routine safety laboratory, hemostasis and thrombosis markers as per PK/PD assessment and clinical efficacy.

4.5 Data Rules

All bleed and infusion data will be reported and imported into SAS. If an infusion is given for a bleed and the bleed information is not provided, the infusion date will be used as the bleed date. All bleeds include spontaneous bleeds and trauma. An untreated bleed is a bleed with no corresponding infusion for the bleed. Bleeds occurring before start of treatment with study medication will not be counted. Bleeds will be counted if at least one of the following information on bleed is available: parts of the date of bleed (as long as the information is sufficient that the bleed fits in the treatment period), given severity or response to treatment of bleed, type of bleed or information on treatment or reason for treatment.

4.5.1 Baseline values

Baseline values for vital sign measures and laboratory values are planned to be taken at Visit 2 before administration of study drug. If these values are not available, values taken before first administration of study drug will be considered (e.g., values taken on Visit 1). In case of

more than one available value before first administration of study drug, the non-missing value closest to Visit 2 will be taken.

4.5.2 Annualized bleed rate

Regarding the definition on the annualized bleed rate (see section 6.2.1) the following datetime will be used:

For annualized bleed rate for Part A, the first datetime of Part A will be the datetime of the first administration of study drug (Visit 2 – Start of BAY 1093884 treatment at the respective dose). The last datetime of Part A will be 1 minute before the datetime of the Visit 6 administration of study drug (the first administration of study drug in Part B). For subjects who discontinue the study during Part A, the last datetime of Part A is the datetime of the later of last visit and last administration of study drug.

For annualized bleed rate for each 12-week Part B period, the first datetime of the Part B period will be the datetime of the first administration of study drug in Part B (Visit 6) in case of first Part B period, or the datetime of the administration of study drug of Visit 7 or any subsequent 12-week visit. The last datetime of Part B will be 1 minute before the datetime of the administration of study drug of Visit 7 or the following subsequent 12-week visit. For subjects who discontinue the study during Part B, the last datetime of Part B is the datetime of the later of last visit and last administration of study drug.

For annualized bleed rate for period on dose initially recived (DIR), the first datetime on DIR will be the datetime of the first administration of study drug (Visit 2 – Start of BAY 1093884 treatment at the respective dose). The last datetime on DIR will be 1 minute before the datetime of the administration of the next higher dose of study drug (Visit 6 or Visit 7). For subjects who discontinue prior to administration of the next higher dose or never met the dose-escalation criteria, the last datetime on DIR is the datetime of the later of last visit and last administration of study drug.

4.5.3 24 hours rule

Count no more than 1 bleed in a calendar day. If there is more than 1 bleed in a calendar day, to determine the bleed that gets counted, give priority to treated bleeds, spontaneous or trauma bleeds, then joint bleeds. Otherwise, count the first bleed in the day. Severity and treatment response will come from this selected bleed. Bleed site will be aggregated over all bleeds from that day. Regardless of which bleed is selected, the time of the first bleed in the day will be used. All other infusions in the day for treating bleeds will be considered follow-up infusions.

If more than one prophylaxis injection is given on a calendar day, the data of all prophylaxis injection will be combined to one injection and the time will be taken from the first prophylaxis injection of that day.

4.5.4 72 hours rule

Do not count a spontaneous joint/muscle bleed if it occurs within 72 hours of a bleed (or infusion for that bleed) at the same site. For a bleed to be affected by this rule, all sites listed on the bleed must also be specified in the previous bleed. If the current and previous bleeds are both skin/mucosa bleeds, this rule does not apply. Such infusions for bleeds will be considered to be follow-up infusions.

Joint bleeds can occur in more that 1 joint site. For each joint bleed, count all sites (combining left and right). For the table showing the Joint Site frequency, sum counts over all sites.

4.6 Blind 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 subjects 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 set(s) (see section 4.6).

The statistical analysis sets are defined as follows:

Safety analysis set (SAF)

All subjects with at least one intake of study drug.

Per protocol set (PPS)

All SAF subjects who completed Part A and Part B of the study with no major protocol deviations.

Pharmacokinetic Analysis Set (PK set)

All SAF subjects with evaluable PK profiles.

Subjects who were assigned to treatment but did not receive study medication will not be included in the SAF. As the number of these excluded subjects is anticipated to be negligible, if at all any exist in this design, an “all assigned treatment analysis set” will not be generated.

Subjects who do not belong to SAF will not be included into statistical considerations. These subjects are classified as ‘listing only set’ (LOS). Number of screening failures and dropouts will be tabulated.

6. Statistical Methodology

The efficacy analyses will be based on the PPS and sensitivity analyses will be based on the SAF as appropriate.

The primary analysis population for the safety analysis will be the SAF.

6.1 Population characteristics

6.1.1 Demography and baseline characteristics

Demographic and baseline data will be evaluated descriptively for the SAF as well as for the PPS and PK set, by treatment groups and overall. No statistical tests will be performed to compare these characteristics across treatment groups.

Descriptive statistics (such as mean, standard deviation, median, quartiles, minimum and maximum) will be provided for continuous variables such as

- age at Screening,
- body weight,
- body height.

Counts and (appropriate) percentages will be provided for categorical variables such as

- year of birth,
- sex,
- race/ethnicity.

Reasons for exclusion from analysis populations will be summarized.

6.1.2 Medical history

Medical history data will be evaluated by frequency tables, showing the number and percentage of subjects with medical history findings (i.e., previous diagnoses, diseases or surgeries) that started before signing of the informed consent and that are considered relevant for the subject's study eligibility using MedDRA Primary System Organ Class / Prefered Term.

6.1.3 Disease history

The following baseline characteristics of the disease history will be evaluated descriptively for the SAF as well as for the PPS, by treatment groups and overall in addition:

- Date of hemophilia diagnosis
- Start of therapy
- Current FVIII or FIX products (product, dose and frequency of administration)
- Current by-passing agents (product, dose and frequency of administration)
- Number of exposure days
- Type of FVIII of FIX gene mutation (from history)
- Family history of hemophilia
- FVIII or FIX level and type of assay
- Family and personal history of past inhibitor formation
- Current inhibitor level
- Current ITI status
- Number and type of bleeds in the past 6 months

- Presence and location of target joints

6.1.4 Medication history

Medication history data including include prior and current FVIII/FIX products and bypassing agents used for hemophilia treatment as well as a history of other prior and current medications will be evaluated descriptively for the SAF as well as for the PPS, both overall and by treatment groups. This includes:

- Medication trade name and dose (including food supplements)
- Reason for medication
- Start date and end date

6.2 Efficacy

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All endpoints will be summarized by descriptive statistics.

The responder variables (number of subjects in each 12-week Part B period with ≤1 spontaneous bleed requiring treatment, number of subjects without spontaneous bleeds requiring treatment in addition to BAY 1093884, number of subjects in Part A with ≤2 spontaneous bleeds requiring treatment in addition to BAY 1093884)will be estimated together with 90% confidence intervals based on exact method (Clopper-Pearson).

For the analysis on each 12-week Part B period, only subjects who were not escalated are taken into account. It should be noted that this kind of analysis must be interpreted carefully, as the restriction is based on post-baseline events.

The variables number of subjects without spontaneous bleeds requiring treatment in addition to BAY 1093884, total number of spontaneous bleeds requiring treatment in addition to BAY 1093884 and number of muscle, joint, target joint, spontaneous, non-spontaneous/non-traumatic, traumatic and all bleeds (requiring treatment in addition to BAY 1093884) will be descriptively analysed on Part A, on each 12-week Part B period and on combination of these. For the analyses which are based on Part B, only subjects who were not escalated are taken

into account. It should be noted that this kind of analysis must be interpreted carefully, as the restriction is based on post-baseline events.

6.2.1 Additional analyses

All analyses mentioned above will additionally be performed by dose actually recived. It should again be noted that these analyses must be interpreted carefully, as only the dose actually recived in Part A can be assumed to be independent of the efficacy. For all other parts the dose actually recived depends on post-baseline events.

In addition to the number of bleed endpoints already mentioned, annualized bleed rates will be provided and analyzed. It should be mentioned that the parts of the study have a planned length of three months, and that a subject being initially assigned to the highest dose will have a planned follow-up of 6 months until the primary completion. Thus for an annualization an extrapolation is needed which makes the interpretation of this endpoint in a literal sense imprecise. However, the annualized bleed rate is considered useful and will be included, as this type of endpoint accounts for the possible different follow-up length of subjects (including drop-outs).

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The annualized bleed rate will be derived as follows:

Annualized bleed rate for Part A is defined as

$$\frac{(\#of\ bleeds\ in\ Part\ A) \cdot {}^{365.25}/_{(\text{last datetime in Part A} - \text{ first datetime in Part A})}}{60 \cdot 60 \cdot 24}$$

Annualized bleed rate for each 12-week Part B period is defined as

$$\frac{(\#of\ bleeds\ in\ Part\ B) \cdot {}^{365.25}/_{(\text{last datetime in Part B} - \text{ first datetime in Part B})}}{60 \cdot 60 \cdot 24}$$

Annualized bleed rate for period on dose initially recived (DIR) is defined as

$$\frac{(\#of\ bleeds\ in\ period\ on\ DIR) \cdot {}^{365.25}/_{(\text{last datetime on DIR} - \text{ first datetime on DIR})}}{60 \cdot 60 \cdot 24}$$

6.2.2 Subgroup analysis

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- [redacted]
- [redacted]
- [redacted]

6.3 Pharmacokinetics/pharmacodynamics

All PK analyses will be based on the PK set.

Descriptive statistics for PK data will be presented as n, geometric mean, geometric standard deviation, geometric coefficient of variation, arithmetic mean, standard deviation (SD), median, minimum, and maximum.

The changes in PK parameters across the dose range studied may be assessed by comparisons of the above variables at each dose level. BAY 1093884 plasma concentrations will be plotted as a function of time for each subject according to dose.

Plots of summary data for each dose (geometric mean and arithmetic mean plasma concentrations at each time point) will also be presented on both linear and logarithmic scales. BAY 1093884 plasma levels may also be plotted to evaluate the correlation of plasma levels with safety and other endpoints.

PD parameters will be analyzed descriptively and with statistical models as appropriate.

6.4 Safety

In accordance with the primary objective of the study, which is the assessment of the safety and tolerability of multiple subcutaneous doses of BAY 1093884 in subjects with hemophilia A or B with or without inhibitors, the primary variables of the study are the following:

- Incidences of drug-related AEs, SAEs, adverse events of special interest (AESIs), and clinically relevant abnormal laboratory values.

Hypersensitivity reactions, thromboembolic and thrombotic microangiopathic events are defined as AESIs.

In addition, the following safety variables are also of particular interest:

- Incidences of injection site reactions (ISRs)
- Incidences of binding and neutralizing antibodies against BAY 1093884

6.4.1 Adverse events

The investigator has to record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent form and the end of the follow-up phase. The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For each AE, the number and percentage of subjects who experienced at least 1 occurrence of the given event will be tabulated according to the affected primary system organ class (SOC) and preferred term (PT) by dose cohort and dose actually recived. A total column will be included in all safety summaries.

Frequency tables, showing an overall summary of number of subjects with drug-related AEs, SAEs and AESIs will be given, and will include the following information:

- maximum intensity for any AE,
- AE related deaths,
- AE resulting in permanent discontinuation of study drug,

- treatment emergent AE.

AEs will be considered treatment-emergent if they begin after the first administration of study drug and they do not start after more than 30 days after the last administration. Determination of whether or not an event is treatment-emergent will be derived after the missing or incomplete AE start date is imputed. Inhibitors will be defined as treatment-emergent if they develop after first study drug application. Imputation rules for missing and incomplete AE start are described in section 4.3.

The severity or intensity of an AE should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. If no exact matching code is available in NCI CTCAE version 5.0, the following guidance should be used:

- CTCAE grade 1: Mild
- CTCAE grade 2: Moderate
- CTCAE grade 3: Severe and/or disabling AE
- CTCAE grade 4: life-threatening and/or intervention needed
- CTCAE grade 5: resulting in death (fatal)

A similar table showing overall summary information of AEs during screening will be given.

In addition, frequency tables will summarize the number of subjects with injection site reactions.

Similar to 6.2, frequency tables will summarize the number of subjects with

- any event during Part A,
- any event during each 12-week Part B period
- any event during combination of these periods.

This will also include tabulation by dose actually received.

6.4.2 Vital signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) obtained at Visit 1 (Screening), Visit 2 (before and 30-60 minutes after study drug administration), Visit 3, Visit 4, Visit 5, Visit 6 (before and 30-60 minutes after study drug administration), Visit 7 or any subsequent 12-week visit (before and 30-60 minutes after study drug administration) as well as during Final visit and Early termination visit will be displayed by means of descriptive statistics and change from baseline.

6.4.3 Laboratory parameter

Only centrally analyzed blood samples will be considered for analysis.

Central laboratory parameters at Visit 1 (Screening), Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 or any subsequent 12-week visit as well as during Final visit and Early termination visit will be displayed by means of descriptive statistics and change from baseline.

High/low abnormalities and incidences of clinically relevant abnormal laboratory values by laboratory parameter will be presented, including variousCBC, platelet, and serum chemistry parameters.

The values of antibodies against BAY 1093884 at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, each Visit 7 as well as during Final visit and Early termination visit will be displayed by means of descriptive statistics and change from baseline.

Incidences of binding and neutralizing antibodies against BAY 1093884 will be presented.

6.4.4 Subgroup analysis

An overall summary of number of subjects with drug-related AEs, SAEs and AESIs, incidences of clinically relevant abnormal laboratory and incidences of binding and neutralizing antibodies against BAY 1093884 will be given by the following subgroups:

- Type of hemophilia (hemophilia A, hemophilia B)
- Inhibitor status (with/without inhibitors)
- Previous treatment (on demand, on prophylaxis)

6.4.5 Pregnancies

Any reported pregnancy on any female participant will be displayed.

Any reported pregnancy occurring in partners of study subjects during the subject's participation in this study will be displayed.

7. Document history and changes in the planned statistical analysis

- First draft of SAP on 18-Jul-2018
- Final version of the SAP on 23-Jul-2018

8. References

9. Appendix

9.1 Determination of sample size

CCI [redacted] no formal determination of sample size was done.

Considering that this is a Phase 2 study for a rare disease, a sample size of 24 is a reasonable number to evaluate the safety of a multiple escalating dose of a new drug. Having the safety data of 8 subjects per cohort, a firm clinical understanding of the drug can be obtained (4 subjects per cohort have been evaluated for the single dose escalation in the first-in-man study). All safety parameters will be analyzed by descriptive statistics only, no hypothesis tests will be performed. The same holds true for the efficacy analysis. Therefore, no sample size calculation applies for this study

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