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Cover page of the integrated protocol

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

This protocol version is an integration of the following documents/sections:

- **Original protocol**, Version 1.0, dated 22 FEB 2018
- **Amendment no. 1** (local amendment Japan), dated 17 APR 2018
- **Amendment no. 2** (local amendment United Kingdom), dated 30 APR 2018
- **Amendment no. 3** (local amendment Japan), dated 07 JUN 2018
- **Amendment no. 4** (global)
  forming integrated protocol Version 2.0, dated 26 JUN 2018
- **Amendment no. 5** (global)
  forming integrated protocol Version 3.0, dated 12 FEB 2019
- **Amendment no. 6** (global)
  forming integrated protocol Version 4.0, dated 05 APR 2019

1. Title page

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

Test drug:	BAY 1093884		
Clinical study phase:	2	Date:	05 APR 2019
Registration:	EudraCT no. 2017-003324-67	Version no.:	4.0
Sponsor's study no.:	19580		

Sponsor: Non-US: Bayer AG, D-51368 Leverkusen, Germany

US territory: Bayer HealthCare Pharmaceuticals Inc.,
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: G PPD r

Date: 10th April 2019 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

Title	Multiple escalating dose study of BAY 1093884 in adults with hemophilia A or B with or without inhibitors
Clinical study phase	2
Study objective(s)	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 [redacted]
Test drug(s)	BAY 1093884
Name of active ingredient	Anti TFPI monoclonal antibody (immunoglobulin G2; IgG2)
Dose(s)	Once weekly doses: The dose for Cohort 1 (X dose) will be 100 mg. The dose for Cohort 2 (Y dose) will not exceed 250 mg, and for Cohort 3 (Z dose) will not exceed 400 mg. Doses for Cohort 2 and 3 (Y and Z doses) will be selected based on the safety assessments from previous cohorts and desired duration of PD response based on pharmacokinetics/pharmacodynamics (PK/PD).
Route of administration	Subcutaneous injection
Duration of treatment	Part A of 12 weeks followed by Part B of at least another 12 weeks. After completion of Part B of the Z dose cohort, all subjects will continue treatment in an extension part. The extension part will be initiated only after DMC evaluation of safety data from the 6 patients in the dose Z cohort for 6 weeks, and will continue, pending submission of safety and efficacy data to Health Authorities after 12 months from the start of the extension part, and every 12 months thereafter until Marketing Authorization.
Reference drug(s)	Not applicable.
Name of active ingredient	Not applicable.
Dose(s)	Not applicable.
Route of administration	Not applicable.
Duration of treatment	Not applicable.
Indication	Hemophilia A and B
Diagnosis and main criteria for inclusion /exclusion	Main inclusion criteria: 1. Male severe hemophilic patients with undetectable FVIII activity <1% or FIX activity <2%, with or without inhibitors (any titer) are eligible.

	Note: Subjects with a past history of inhibitors (any inhibitor titer) are eligible. 2. Age ≥18 years. 3. Documentation of ≥4 bleeding episodes (any type or location of bleeds, treated or not) within the 6 months prior to screening. 4. For subjects on prophylaxis: willingness to interrupt ongoing prophylaxis. 5. For subjects on immune tolerance induction (ITI): willingness to interrupt ongoing ITI. 6. Signed informed consent. Main exclusion criteria: 1. History of any other coagulation disorder (particularly disseminated intravascular coagulopathy or combined FVIII/FV deficiency) or platelet disorder. 2. History of diseases related to venous thromboembolic events (e.g., pulmonary embolism, deep vein thrombosis, thrombophlebitis) or thrombotic microangiopathy. 3. Risk factors for venous or arterial diseases (e.g., uncontrolled hypertension, uncontrolled diabetes). 4. History of cardiac, coronary and/or arterial peripheral atherosclerotic disease, particularly myocardial infarction, cerebrovascular accident, stroke, transient ischemic attack, congestive heart failure, angina pectoris or treatment for angina pectoris. 5. Platelet count <100,000/µL. 6. Human immunodeficiency virus (HIV) infection with a cluster of differentiation 4 (CD4+) lymphocyte count of <200/mm^3. 7. Any planned major surgical intervention. 8. Subjects with known or suspected hypersensitivity to trial product(s) or related products. 9. Subjects with known autoimmune disease or on treatment with immune-modulatory drugs. 10. Subjects with advanced liver disease (Child-Pugh Grade B and C) or with signs of liver function impairment (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels >3 × the upper limit of the normal range and/or total bilirubin >2 × the upper limit of the normal range). 11. Subjects with serum creatinine >2.0 × the upper limit of the normal range. 12. Treatment with an investigational drug within 3 months prior to screening. 13. Subjects not willing to stop prophylaxis or ITI.
Study design	Approximately 24 adult subjects (≥18 years of age) will receive treatment with BAY 1093884. **<u>For each subject, the study is structured in three parts</u>** **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 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 (bypassing agent or replacement factor) prescribed by the Investigator pre-study.

Description of the dose cohorts

Eight (8) new distinct subjects are planned to be enrolled in each of the 3 dose cohorts. 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 to obtain safety data and individual efficacy data.

At a minimum, safety/PK/PD data from 6 subjects completing 6 weeks in Cohort 1 (Dose X) are needed to open Cohort 2 (Dose Y). All available safety information will be taken into consideration. This may include data from the 2 additional subjects in the cohort who may not have reached the 6 weeks or additional data from any of the first 6 subjects who may have been dosed for longer than 6 weeks. This guideline will apply to further cohorts as well. All available safety information from ongoing subjects will be used for safety evaluation in opening the next dose cohort. This includes safety data also from the subjects who may have escalated from a previous cohort.

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

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.

Evaluation at the end of every 12 weeks period of part B and of extension

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

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 must stay on the current dose and then escalate to the next higher dose only after it is opened.
Methodology	Throughout the study, data on the occurrence of bleeds (including type of bleed [spontaneous, non-spontaneous/non-traumatic, traumatic], location [joint, muscle, skin or mucosa, internal, other], severity [mild, moderate, severe]) and treatment of bleeds (drug, dose, number of injections) will be collected. Safety data to be collected include data on adverse events (AEs, including changes in laboratory data, vital signs and findings from physical examination). PK evaluations will be made in at least 2 subjects in each cohort (PK subjects) after the first and last doses of the first 12-week period with additional samples during the 12 weeks. Sparse samples for PK will be collected from all other subjects not participating in the PK evaluation. PD samples will be collected from all subjects.
Type of control	None
Data Monitoring Committee	Yes. Based on the safety data in the respective subset of subjects, a DMC will decide on dose escalation of BAY 1093884 for the subsequent dose step. DMC will also evaluate safety of the highest dose (dose Z) after the first 6 subjects have completed the first 6 weeks of treatment, and consequently advise on the continuation of the study through the extension part. DMC will meet and decide on safety issues that may arise during the study (including the extension part).
Number of subjects	Approximately 24 hemophilia A or B subjects with or without inhibitors on OD or prophylaxis treatment will receive treatment with BAY 1093884. In particular, 8 subjects will be assigned to each cohort, but more subjects (2-4 additional subjects) may be required. If additional safety evaluation is needed, a maximum number of 40 subjects may be included.
Primary variable(s)	The frequency of drug-related AEs, SAEs, adverse events of special interest (AESIs), and clinically relevant[a] abnormal laboratory values. [a] "Clinically relevant "implies the presence of a clinical sign or symptom that requires medical action.
Time point/frame of measurement for primary variable(s)	Throughout the study, including the extension part, all subjects will be closely monitored for safety.
Plan for statistical analysis	All data will be listed and study summary tables will be provided where appropriate. Variables measured on continuous 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.

	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 level and by study medication actually received during the study parts and the corresponding visits. Safety Vital signs, AEs and laboratory data will be analyzed by descriptive statistics. All AEs will be tabulated according to the affected system organ class and preferred term, as coded by Medical Dictionary for Regulatory Activities (MedDRA). Separate descriptions will be delivered for the different dose levels. Special interest will be given to safety observations after application of rescue medication during the treatment phase with BAY 1093884. Efficacy CCI [redacted] The main focus will be the number of spontaneous bleeds requiring additional treatment. Further details of Efficacy analysis are listed in the Statistical Analysis Plan (SAP).

Protocol amendment summary of changes

Table of main changes

Section # and name	Description of change	Brief rationale
Section 2 Synopsis Section 6.1 Inclusion criteria	Inclusion criterion 1 was modified to further specify that only subjects diagnosed with severe hemophilia, with or without inhibitors, are eligible.	Criterion updated to ensure that only hemophilic patients who are diagnosed as severe are included in the study.

Typographical, grammatical, and other minor edits are not identified.

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List of abbreviations

ABR	Annualized bleeding rate
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
aTFPI	Antibody against tissue factor pathway inhibitor
aTFPI-Ab	Antibody against aTFPI
AUC	Area under the curve
BU	Bethesda unit
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CAT	Calibrated automated thrombogram
CBC	Complete blood count
CD4+	Cluster of differentiation 4
Cl	Chloride
CL	Clearance from plasma
CO_2	Bicarbonate
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
D	dose
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	Electrocardiography, -gram
eCRF	Electronic case report form
EPD	Electronic patient diary
EU	European Union
FEIBA	Factor eight inhibitor bypassing activity
FII	Prothrombin
FIIa	Thrombin
FIX	Factor IX
FV	Factor V
FVIIa	Activated factor VII
FVIII	Factor VIII
FX	Factor X
FXa	Activated factor X
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
hsCRP	High sensitive C-reactive protein
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IgG2	Immunoglobulin G2
IL-6	Interleukin 6
IMP	Investigational medicinal product

IRB	Institutional Review Board
ISR	Injection site reaction
ITI	Immune tolerance induction
IV	Intravenous
IWRS	Interactive web responding system
K	Potassium
Kx	Kunitz domain
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOS	Listing only set
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MRT	Mean residence time
Na	Sodium
NCI	National Cancer Institute
OD	On demand
PD	Pharmacodynamics
PgX	Pharmacogenetics
PK	Pharmacokinetics
PPP	Platelet-poor plasma
PPS	Per protocol set
QA	Quality assurance
QC	Quality control
rFVIIa	Recombinant activated factor VII
SAE	Serious adverse event
SAF	Safety (set)
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SUSAR	Suspected unexpected serious adverse reaction
t_{last}	Last measurable concentration
TAT	Thrombin-antithrombin complex
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGA	Thrombin generation assay
TMA	Thrombotic microangiopathy
US	United States (of America)
VTE	Venous thromboembolic event
vWF	Von Willebrand's factor
V_{ss}	Volume at steady state
V_z	Volume during terminal phase
WHO	World Health Organization

3. Introduction

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. Currently, prophylaxis starting in early childhood with the primary goal to prevent bleeding that leads to end-stage joint disease is recommended in most developed countries (1-3).

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 (4, 5).

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 (ABR) of up to 6 bleeds, thus, leaving a high unmet medical need for better protection (6). 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” (7). The incidence of new FVIII inhibitors in subjects with severe FVIII deficiency is up to 45%. In the SIPPET trial (Survey of Inhibitors in Plasma-Products Exposed Toddlers, “A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A”), the overall cumulative inhibitor rate for all recombinant FVIII products was 44.5% (95% confidence interval: 34.7 - 54.3) over 50 exposure days (8). 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 (9-11).

It is possible that inhibitors may be transient or resolve with high repeated doses of factor concentrates (immune tolerance induction [ITI]), but in 10–15% of hemophilia A subjects, FVIII inhibitors remain clinically significant (high titer antibodies) and cannot be managed by ITI; ITI is much less effective in managing FIX inhibitors (12).

The pharmacodynamics (PD) effect of the currently available bypassing agents (coagulation Factor VIIa (rFVIIa; e.g., NovoSeven) for hemophilia A and B, and activated prothrombin complex concentrates (aPCC; e.g., human plasma derived Factor VIII inhibitor bypassing agent [FEIBA]) for hemophilia A) can be highly variable, and dose levels do not correlate well to clinical benefit (13, 14). 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 (15).

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.

Already in 1991, in vitro evidence has demonstrated that the reduction of the inhibitory effect of TFPI is an important step for the prevention of bleeding in subjects with hemophilia (16).

Besides, anti –TFPI antibody has shown to shorten the bleeding time in rabbits with antibody-induced hemophilia A (17).

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. In vitro, the antibody exhibits high affinity binding to human TFPI (<10 pM), and is highly specific. 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.

The First in Man Phase 1 study is ongoing and is conducted in hemophilia A or B subjects (deficient in FVIII or FIX) with or without inhibitors, to evaluate safety, tolerability, and pharmacokinetics (PK) of a single-escalating dose of BAY 1093884. In this study, the single dose IV doses of 0.3 mg/kg and 1 mg/kg, SC doses of 1, 3, and 6 mg/kg were evaluated in hemophilia subjects without inhibitors. Single SC doses of 1 and 3 mg/kg were also evaluated in hemophilia subjects with inhibitors. In addition, a multiple dose cohort was also evaluated following 150 mg SC once weekly dose given for 6 weeks. Safety information is available in the current version of the IB.

All 32 subjects in the study have received the doses. Of these 32 subjects, 30 have completed the study. Two are ongoing and have follow-up visits remaining. There were no SAE, no deaths or AEs leading to discontinuation. There were no clinically significant findings in the

other safety laboratory values during the treatment and there were no clinically significant changes in vital signs and ECG.

Overall, results from the Phase 1 study support that subjects with FVIII or FIX deficiency and inhibitor subjects exhibit similar response to BAY 1093884 with regard to both PK and pharmacodynamics (PD) profile. At the highest investigated dose, complete inhibition of TFPI (defined as TFPI levels below the lower limit of quantification of the assay and corresponding to at least 82-87% of inhibition) was observed in all subjects for at least 7 days.

These results confirm that due to its mode of action, the clinical effect of BAY 1093884 is expected to be similar in all subjects, irrespective of the underlying factor deficiency or the presence of inhibitory antibodies.

The elevation in D-dimers seen in some subjects is an expected mechanistic outcome of BAY 1093884 administration, as TFPI inhibition is predicted to shift coagulation balance toward more thrombin activation, and thus production of fibrin. The goal of potentiating thrombin activation is correction of the underlying bleeding disorder, and should be safe provided that the normal compensatory mechanisms, such as fibrinolysis, are not impaired. Importantly, none of the laboratory measures in any of the subjects in this cohort suggested a shift towards uncompensated coagulation. Specifically, fibrinogen levels and platelet counts remained in normal range, and clinically meaningful changes in anti-thrombin III, protein C or FV were not observed. The laboratory studies suggest that BAY 1093884 did shift hemostatic balance towards greater thrombin generation, as intended, but that this shift was compensated by intact mechanisms of anticoagulation and fibrinolysis.

The absence of changes in vital signs, electrocardiograms (ECG), or changes in any lab values other than fibrinogen and D-dimer, confirmed in all dosed subjects the clear mechanistic effect of BAY 1093884 and the absence of any pathologic suspect or finding.

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

4. 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

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

5. 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 Sections 9.6.1.7 and 13.1.2.

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. If the next dose level is open, patients in dose level X or Y will be allowed to escalate to the next dose level after 12 weeks of treatment with BAY 1093884 if specific conditions are satisfied. First, safety criteria as defined in the protocol must be met. Second, the patient must have experienced >2 bleeds during the first 12 weeks of treatment or experienced >1 bleed during any 12-week interval after the first 12 weeks of treatment 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.

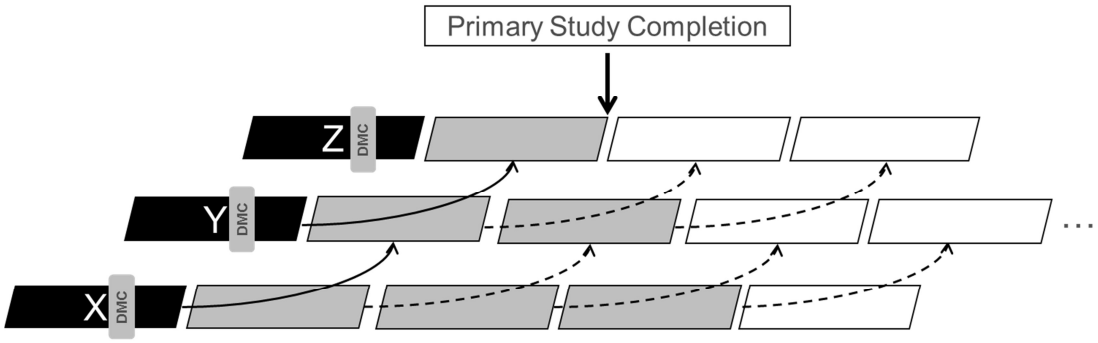
Part B. Each subject will be treated for additional periods of 12 weeks in duration. After evaluation of the number of bleeds at the end of each 12-week period, subjects can be treated with the same dose or with the next higher opened dose level. The date when the last subject in Cohort 3 (Z dose) has 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 (bypassing agent or replacement factor) prescribed by the Investigator pre-study.

Figure 5–1 shows a schematic overview of the study design.

Figure 5–1: 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 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 must stay on the current dose and then escalate to the next higher dose only after it is opened.

Dose selection for cohorts:

Results from studies on hemophilia animal models support the development of clinical studies with repeated administration of BAY 1093884 in subjects with hemophilia A or B with or without inhibitors.

Results from the Phase 1 study support that subjects with FVIII or FIX deficiency and inhibitor subjects exhibit similar response to BAY 1093884 with regard to both PK and pharmacodynamics (PD) profile.

Considering the results from these studies, the dose for Cohort 1 (X dose) will be 100 mg, for Cohort 2 (Y dose) will not exceed 250 mg and the dose for Cohort 3 (Z dose) will not exceed 400 mg. Doses for Cohort 2 and 3 (Y and Z doses) will be selected based on the safety assessments from previous cohorts, PK/PD model and the criteria described in detail in Section 7.4.1.1, together with the criteria for evaluating safety rules.

Throughout the study, the safety rules for an occurrence of a single drug-related SAE (SAR) related to study drug, or two severe or clinically significant AEs considered to be at least possibly related to study drug will be followed. In the event that a subject is suspended from the dosing of BAY 1093884, dosing will not resume until a full review is done by DMC and the risk-benefit is deemed acceptable for that patient. During suspension of dosing, the subject will be treated with his previous hemophilia treatment and any other event will be

treated in accordance with the local standard of care. If dosing resumes following DMC review, the subject should return to the clinic for their next sequential scheduled visit to restart study drug.

Data Monitoring Committee

A DMC will regularly review key safety data and give recommendations on:

- Dose escalation (opening the next dose cohort);
- Opening of the Extension Part

In addition, the DMC will meet on an *ad hoc* basis as appropriate to ensure subject safety oversight in the trial.

The DMC may recommend modifying or stopping the study early due to safety concerns at any time, based on these periodic and *ad hoc* data reviews.

The full description of DMC review is provided in Sections 9.6.1.7 and 13.1.2, and in the DMC charter.

Justification of study design

At the highest dose investigated in the Phase 1 study, complete inhibition of TFPI (defined as TFPI levels below the lower limit of quantification of the assay and corresponding to at least 82-87% of inhibition) was observed in all subjects for at least 7 days.

These data support the rationale for this open-label Phase 2 study, with the aim to evaluate the safety and explore the efficacy of multiple escalating doses of BAY 1093884 in 3 cohorts.

The Phase I study utilized weight-based dosing. The proposed study will use fixed doses. Like most monoclonal antibodies, BAY 1093889 is expected to distribute predominately to the blood plasma and extracellular fluids due to its large molecular weight (18). Preliminary estimations of the volume of distribution at steady-state (V_{ss}, calculated as [dose/AUC]*MRT after IV administration) are in the range of 0.05 to 0.08 L/kg, corresponding to absolute volumes of approximately 3.5 to 5.6 L for a 70 kg individual, and support this expectation. Although blood volume is increased in obese and decreased in underweight individuals when compared to normal weight individuals, these changes are less than proportional with the change in body weight (18). As a consequence, body composition and the presence of excess body weight are of less importance for an antibody when compared to small molecules. Physiologically-based pharmacokinetic (PBPK) modelling was used to predict the variability of PK parameters (AUC, C_{max} and C_{min}) and free TFPI levels following a body-weight normalized dose (1 mg/kg) and a flat dose (70 mg) in a population of virtual male individuals with an age range between 18 and 45 years and a weight range between 50 and 110 kg. The flat dosing resulted in slightly lower inter-individual variabilities in BAY 1093884 PK parameters and free TFPI concentrations. Based on general physiological considerations of the distribution properties of antibodies and predictions of the BAY 1093884 PBPK model, it is justified to administer BAY 1093884 in a fixed dose regimen in this dose escalation study.

Data from the Phase 1 study has been used to build a PK/PD model to allow for initial selection of the starting dose (dose X) and it will be further refined with available data generated from the multiple dose levels in this study to select the doses for the subsequent dose levels. The model will be used to project doses that will result in certain duration of

TFPI inhibition and improvement in parameters measured with the thrombin generation assay (TGA) following weekly SC administration. For this projection, to safely evaluate the potential accumulation following multiple administration of BAY 1093884, the lower dose X will provide preliminary safety information, while is not expected to result in meaningful control of bleeding episodes over 7 days. The following Y dose is expected to provide both safety and efficacy data over the 7 days after BAY 1093884 administration. The last dose, Z, is supposed to provide additional efficacy information and safety margin, without exceeding the highest evaluated dose in the Phase 1 study.

The reason to start with 100 mg dose is that this dose is expected to result in 3-5 days of TFPI inhibition. In addition, all subjects have been exposed to 100 mg or more in the Phase 1 study, where the safety of this dose has been established. In fact, single doses of 1 mg/kg (68 - 91 mg), 3 mg/kg (213 - 270 mg) and 6 mg/kg (401 - 510 mg) have been administered in the Phase 1 study.

The rationale to include in the study both subjects treated on demand and subjects on prophylaxis who present at least 4 bleeding episodes in the previous 6 months is to ensure enrollment of subjects with high unmet need (at least 8 bleeds per year). It is well known that the annualized bleeding rate in subjects on prophylaxis is between 1 and 3 for non-inhibitor subjects (19, 20) and approximately 5 for inhibitor subjects (21).

Subjects treated on demand with previously assigned products will switch to prophylaxis with BAY 1093884, which is expected to lead to similar or lower bleeding rates. Subjects previously treated prophylactically may benefit from the study drug because of their high bleeding rate (despite frequent regular injections). In any case, any occurring bleed that will need additional control will be treated with their pre-study treatment (with already proven response) and subjects will be always allowed to continue the study or to interrupt it, based on their response to treatment and treatment satisfaction.

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).

Communication plan

A communication plan is in place to outline how the safety data and dose escalation decision will be communicated to all investigator sites.

Routine updates via email, newsletter, or teleconference will be provided to the investigators throughout the course of the study to facilitate communication of new safety data from treated patients from the ongoing studies. DMC recommendations, including dose escalation decision, will be communicated to the investigators in a timely manner.

6. Study population

6.1 Inclusion criteria

1. Male severe hemophilic patients with undetectable FVIII activity <1% or FIX activity <2%, with or without inhibitors (any titer) are eligible.

   Note: Subjects with a past history of inhibitors (any inhibitor titer) are eligible.

2. Age ≥18 years.
3. Documentation of ≥4 bleeding episodes (any type or location of bleeds, treated or not) within the 6 months prior to screening.
4. For subjects on prophylaxis: Willingness to interrupt ongoing prophylaxis.
5. For subjects on ITI: willingness to interrupt ongoing ITI
6. Signed informed consent.

6.2 Exclusion criteria

1. History of any other coagulation disorder (particularly disseminated intravascular coagulopathy or combined FVIII/FV deficiency) or platelet disorder.
2. History of diseases related to venous thromboembolic events (e.g., pulmonary embolism, deep vein thrombosis, thrombophlebitis) or thrombotic microangiopathy.
3. Risk factors for venous or arterial diseases (e.g., uncontrolled hypertension, uncontrolled diabetes).
4. History of cardiac, coronary and/or arterial peripheral atherosclerotic disease, particularly myocardial infarction, cerebrovascular accident, stroke, transient ischemic attack, congestive heart failure, angina pectoris or treatment for angina pectoris.
5. Platelet count <100,000/µL.
6. Human immunodeficiency virus (HIV) infection with a cluster of differentiation 4 (CD4+) lymphocyte count of <200/mm^3.
7. Any planned major surgical intervention.
8. Subjects with known or suspected hypersensitivity to trial product(s) or related products.
9. Subjects with known autoimmune disease or on treatment with immune-modulatory drugs.
10. Subjects with advanced liver disease (Child-Pugh Grade B and C) or with signs of liver function impairment (e.g., alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels >3 × the upper limit of the normal range and/or total bilirubin >2 × the upper limit of the normal range).
11. Subjects with serum creatinine >2.0 × the upper limit of the normal range.
12. Treatment with an investigational drug within 3 months prior to screening visit.
13. Subjects not willing to stop prophylaxis or ITI.

6.3 Withdrawal of subjects from study

6.3.1 Withdrawal

Withdrawal criteria

Subjects *must* be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and even without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Development of an inhibitory antibody to BAY 1093884 that neutralizes the activity sufficiently to interfere with effective treatment.
- Failure to comply with scheduled appointments for study-related testing or with Electronic Patient Diary (EPD) data entry to an extent that compromises collection of critical data
- Significant concurrent illness or deterioration in the subject's condition, including laboratory values that the investigator deems to be incompatible with the subject's continued safe participation in the study.

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

At the time of discontinuation, the subject should be scheduled to perform the procedures and evaluations required at the final study visit.

Subjects *may* be withdrawn from the study if any of the following occurs:

- Violation of eligibility criteria;
- Withdrawal of a subject at the specific request of the Sponsor;
- Withdrawal of a subject at the Investigator's request. As examples: If the Investigator considers that the subject's health is compromised by remaining in the study or if a subject on the highest dose (without possibility for dose escalation) presents excessive uncontrolled bleeding; or the subject is not sufficiently cooperative;
- Withdrawal of a subject from the study if the subject is lost to follow-up.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure."

Re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is not allowed – with the following exceptions:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in-/exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).

Thus, participation of an initial "screening failure" subject at a later time point even if he meets all selection criteria upon re-screening is not acceptable.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. In addition, the subject must re-sign the informed consent form during re-screening, even if it was not changed after the subject's previous screening. If a subject is re-screened, he will be assigned a new subject number.

Dropout

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.

General procedures

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 subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Completer

A subject is defined as completer if he has completed at least Part A, a minimum of one Part B, and has performed a final visit.

6.3.2 Replacement

If fewer than 6 subjects per cohort will complete 6 weeks, additional subjects will be recruited to achieve the target sample size of 6 subjects for DMC review. Subjects may be replaced only if they have not withdrawn from the study for drug-related safety concerns.

If inhibitor subjects with less than 24 weeks of treatment or PK subjects with less than 12 weeks of treatment drop out, additional subjects will be recruited to ensure that at least 2 PK subjects (with complete PK evaluations) and at least 1 evaluable inhibitor subject are included in each dose cohort.

6.4 Subject identification

Upon enrollment, each subject will receive a unique subject number. Screening procedures will be performed and eligibility for the study confirmed. Once assigned to a subject the unique subject number must not be used for another subject within this study.

The subject number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

7. Treatments

7.1 Treatments to be administered

7.1.1 Prophylaxis treatment with BAY 1093884

Table 7–1 displays the treatment administered during the study.

Table 7–1 Prophylaxis treatment with BAY 1093884

Cohort	No. of subjects to be treated	Dose of BAY 1093884	Route	Frequency of administration
Dose X	8	100 mg per dose	subcutaneous	every 7 days ± 1 day
Dose Y	8 + escalated subjects	Y mg per dose	subcutaneous	every 7 days ± 1 day
Dose Z	8 + escalated subjects	Z mg per dose	subcutaneous	every 7 days ± 1 day

Prophylaxis infusions (either with BAY 1093884 or any other pre-assigned treatment) in addition to the planned weekly infusions (e.g., before certain physical activities like sports) are not allowed.

The dose range will be 100 mg (X dose) to ≤400 mg (Z dose). The Y and Z doses will be defined based on the safety of the preceding dose level and PK/PD model.

In all cohorts and for each escalated dose, the first injection of every BAY 1093884 dose level will be administered under medical supervision with a post-dose observation period of 30-60 minutes.

To allow for appropriate PD evaluations, the following wash-out times of FVIII, FIX products and FEIBA must be observed (Table 7–2).

Table 7–2 Wash-out times prior to the first BAY 1093884 injection

Product	Wash-out Times	
FVIII	72 h	(3 days)
EHL FVIII	120 h	(5 days)
FIX	96 h	(4 days)
EHL FIX	480 h	(20 days)
Emicizumab	30 days	(30 days)
rFVIIa	24 h	(1 day)
FEIBA	96 h	(4 days)

EHL = Extended half-life, FEIBA = Factor eight inhibitor bypassing activity, FIX = Factor XIV, FVIII = Factor VIII, rFVIIa = Recombinant activated factor VII

Dose cohorts will be opened subsequently, based on an initial safety review (by the Sponsor and a Data Monitoring Committee [DMC]) of the data from the first 6 subjects with at least 6 weeks of dosing in the respective cohort.

All subjects in Cohort 1 and 2 will continue on their initial dose for 12 weeks (Part A) to obtain safety data and efficacy data. Thereafter, in Part B, subjects will remain on this dose, unless they meet the dose escalation criteria as specified in Section 5. No dose escalation is possible for subjects in Cohort 3 who are allocated to the highest dose. All subjects in Cohort

3 will be treated with this dose for at least 24 weeks (Part A and Part B) and then continue the study in the extension part.

During the extension part, subjects will continue treatment with BAY 1093884 either on their current dose or escalate to the next higher opened dose (dose Y for subjects currently on dose X, dose Z for subjects currently on dose Y), after safety and efficacy evaluations every 12 weeks (including DMC evaluation, where appropriate), if dose escalation criteria are met. The extension part will be initiated only after DMC evaluation of safety data from the 6 patients in the dose Z cohort for 6 weeks, and continued pending submission of safety and efficacy data to Health Authorities after 12 months from the start of the extension part, and every 12 months thereafter until Marketing Authorization.

For further details, see Section 5.

7.1.2 Treatment of bleeds

The occurrence of bleeds of different cause, severity and site is a typical characteristic of subjects with hemophilia, being the clinical manifestation of the disease itself.

Bleeds will be classified into the following types:

- **Spontaneous:** Not attributable to any trauma or activity
- **Non-spontaneous/non-traumatic:** Not related to a trauma, but due to activity (walk, run, sport, gym, etc.)
- **Traumatic:** Related to an identified trauma

Throughout the study, all bleeds will be recorded, but only the bleeds recorded as "spontaneous" (not related to any trauma or activity) and "requiring additional treatment" will constitute the base for the efficacy evaluation.

All bleeds occurring in subjects receiving prophylactic treatment with BAY 1093884 after Visit 2 ("Start of treatment with BAY 1093884") which require additional treatment will be treated according to the subject's pre-study treatment as outlined in Section 8.1. Given the potential additive effect of BAY 1093884 and concomitant medication, it is recommended to treat the bleeds with the lowest approved doses of the prescribed replacement factor or bypassing agent, and repeat the dose, if additional doses will be needed, at the investigator's judgment.

For the same reason, the investigator must carefully consider the intensity and the location of a trauma for which bleeding has not yet occurred before the preventive use of a replacement factor or a bypassing agent during treatment with BAY 1093884. Careful oversight of bleed treatment by the Investigators will ensure the patients' safety.

If a bleed occurs on a day of the planned injection of BAY 1093884, the subject should treat the bleed with his usual medication and administer the scheduled prophylactic injection of BAY 1093884. The injection schedule with BAY 1093884 will not be affected by the treatment of bleeds.

7.1.3 Treatment for PK/PD assessments

PK assessment using dense sampling will be done in a subset of 2 subjects (PK subjects) after the first administration and after the last administration of BAY 1093884 during Part A of each dose cohort (X mg, Y mg, or Z mg). Sparse PK samples will also be collected from the all other subjects in the study.

The wash-out times for FVIII, FIX products and FEIBA as listed in Section 7.1, Table 7–2, must be observed prior the first injection of BAY 1093884.

For PK subjects: Blood samples will be drawn pre-dose and 4 h (Visits 2.1 and 6.1, respectively), 24 h (Day 1; Visits 2.2 and 6.2, respectively), 96 h (Day 4; Visits 2.3 and 6.3, respectively) and 168 h (Day 7; Visits 3.1 and 6.4, respectively) post-dose after the first and the last dose in the first 12-week period. Further PK samples will be collected during the visits at Weeks 3 and 6. After the first 12-week period, at each planned visit in the hospital, one sparse PK sample will be drawn in all subjects (including non-PK subjects) regardless of the wash-out time for bypassing agents or replacement factors (if taken for the treatment of bleed). At all these visits, subjects should come to the site prior to the scheduled BAY 1093884 injection.

For non-PK subjects: The wash-out times for FVIII, FIX products and FEIBA as listed in Section 7.1, Table 7–2, must be observed prior the first injection of BAY 1093884. Following the collection of the baseline sample, one sparse PK sample will be drawn at each planned site visit regardless of the wash-out of bypassing or replacement agents (if taken for treatment of bleed). Sparse PK samples will also be drawn regardless of study drug intake, except for Visit 6, Visit 7 and the Every 12-week Visit, when the subject should come to the site prior to the scheduled BAY 1093884 injection.

PD assessments will be done in all subjects as outlined in Section 9.

7.1.4 Treatment for minor and major surgery

In the event a subject requires an unplanned minor surgery during the interventional part of the study, the treatment schedule with BAY 1093884 will not be affected. As for the treatment of bleeds (see Section 7.1.2), the subject's pre-study hemophilia treatment can be administered, as required. It may be tailored to the subject's individual response.

The appropriate treatment of minor surgery is left to the discretion of the treating physician and/or local clinical practice.

Minor surgery is defined as any surgical procedure that does not meet the definition of major (see below), and may include (but is not restricted to) dental extractions, incision and drainage of an abscess, or excisions.

Major surgery is defined as any surgical or invasive procedure (elective or emergent) in which the overall bleeding risk may be excessive, would require a general anesthetic in an individual without a bleeding disorder, penetrates or exposes a major body cavity, could result in substantial impairment of physical or physiological functions, or requires special anatomic knowledge or manipulative skill (e.g., tonsillectomy, laparotomy, thoracotomy, joint replacement).

If major surgery is required during the subject's first 24 weeks of treatment (i.e., during Part A and B), the subject will be withdrawn from the study. If major surgery is required

after the first 24 weeks, the subject may use his own hemophilia medication and prophylaxis treatment with BAY 1093884 will be interrupted. In this case, following surgery, the subject may re-enter the study and restart prophylaxis with BAY 1093884 after discussion with the sponsor.

7.2 Identity of study treatment

Code name: BAY 1093884

Manufacturer of drug product:

Bayer AG
Muellerstrasse 178
D-13353 Berlin
Germany

Manufacturer of the Investigational Medicinal Product (IMP):

Fisher Clinical Services GmbH
Steinbuehlweg 69
CH - 4123 Allschwil
Switzerland

Final release of the IMP – EU, International and Emerging Markets:

Bayer AG
Muellerstrasse 178
13353 Berlin
Germany

Importation and final release (US and Canada):

Bayer HealthCare LLC, Berkeley, California (CA)
800 Dwight Way
Berkeley, CA
USA

Dosage form: Ready-to-use liquid for subcutaneous injection

Strength: BAY 1093884 will be provided in vials containing either 100 mg/mL or 150 mg/mL

Description: 10 mL colorless glass vials containing either 1.6 mL of BAY 1093884 at a concentration of 100 mg/mL or 1.8 mL of BAY 1093884 at a concentration of 150 mg/mL

Storage: 2°C - 8°C

Until dispensed to the subjects, the study medication will be stored in a securely locked area, accessible to authorized personnel only.

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.3 Treatment assignment

Enrollment will start with recruitment into Cohort 1, followed by enrollment into Cohorts 2 and 3, according to the decisions of the DMC.

An interactive web responding system (IWRS) will be used to assign at least 1 inhibitor subject and 2 PK subjects to each cohort.

7.4 Dosage and administration

The dose selections for this study are based on the results of the Phase 1 study or are extrapolated from experience with BAY 1093884 in the Phase 1 study.

Except for injections administered at study visits, subjects will self-inject the study drug by themselves in their home, or will be injected by caregivers at home or other facility near to subject's home, or by the investigator or delegate. Subjects/caregivers will receive detailed information regarding the administration of the study medication.

The potential side effects associated with subcutaneous injections and of BAY 1093884 are detailed in the core informed consent, and will be updated as needed. All subjects/caregivers are expected to review this information at the time of study enrollment. Study site personnel should review the following topics with the subjects/caregivers: subcutaneous injection practices and needle disposal, how to use and store the medication, how to respond to the potential side effects of BAY 1093884, provide instructions on when and how to contact the treatment center for questions or concerns, and how to obtain emergency medical care if required.

7.4.1 Selection of doses in the study

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

A DMC will review key safety data from the first 6 subjects after 6 weeks of dosing in each cohort before recommending opening a cohort at a higher dose. Any available data from subjects continuing in the study will also be included in the DMC review.

The sponsor will provide dose recommendations based on the PK/PD model and safety evaluation, taking into consideration the criteria described in Section 7.4.1.1. The DMC will be asked to recommend next dosing cohort using the criteria specified in this section, and may review the safety data anytime during the course of the study per the criteria described in this section.

In the event that a subject is suspended from the dosing of BAY 1093884, dosing will not resume until a full review is done by DMC and the risk-benefit is deemed acceptable for that patient. During suspension of dosing, the subject will be treated with his previous hemophilia

treatment and any other event will be treated in accordance with the local standard of care. If dosing resumes following DMC review, the subject should return to the clinic for their next sequential scheduled visit to restart study drug.

7.4.1.1 PK/PD criteria for dose recommendation

The selection of doses for the multiple dose escalation is based on several considerations.

Hemophilia animal models suggest that complete inhibition of TFPI is required to restore hemostasis. PK/PD modeling using data from the first in man study suggests that TFPI inhibition can be maintained at or above 100 μg/L concentration of BAY 1093884.

Data from the first-in-man study has been used to build a PK/PD model to allow for initial selection of the starting dose (dose X). The model will be refined with data generated from the completed dose levels in this study to select the doses for the subsequent dose levels for this study. The model will be used to project doses that will result in certain duration of TFPI inhibition and improvement in TGA parameters following weekly SC administration. Assuming that improvement in TGA parameters can be achieved with only partial TFPI inhibition, the following criteria will be considered for selecting dose Y and Z for the Cohort 2 and 3, keeping in mind that the desired frequency for prophylaxis is SC administration once weekly:

Cohort 1 (dose X)

A dose that would result in at least 3-5 days of PD effect (i.e., improvement in thrombin generation parameters or TFPI complete inhibition) over a 7-day period has been selected for this cohort. This dose is not expected to be completely ineffective based on the current understanding of the changes in mechanistic and PD markers. Current projections based on the PK/PD model suggest that a dose of 100 mg once per week will results in 3-5 days of PD effect. Therefore, a dose of 100 mg has been chosen for the Cohort 1.

Cohort 2 (dose Y)

A dose that would result in at least 7 days of PD effect (e.g., improvement in thrombin generation parameters or TFPI complete inhibition) over a 7-day period will be selected for this cohort. The dose for this cohort will not exceed 250 mg (2.5-fold higher than the dose for Cohort 1).

Cohort 3 (dose Z)

A dose that achieves higher anti-TFPI mAb levels at steady state compared to Y-dose to establish a margin of safety. This dose should also result in at least 7 days of PD effect (e.g., TGA improvement or TFPI complete inhibition) over a 7-day period. This dose level will not exceed 400 mg dose. This dose is less than the dose of 6 mg/kg that was given in a cohort of the Phase 1 single dose escalation study and did not have any SAE or AE leading to discontinuation.

A DMC will review key safety data and dose recommendation before recommending escalation to the next dosing cohort.

At a minimum, safety/PK/PD data from 6 subjects completing 6 weeks in Cohort 1 (Dose X) are needed to open Cohort 2 (Dose Y). All available safety information will be taken into consideration. This may include data from the 2 additional subjects in the cohort who may

not have reached the 6 weeks or additional data from any of the first 6 subjects who may have been dosed for longer than 6 weeks. This guideline will apply to further cohorts as well. All available safety information from ongoing subjects will be used for safety evaluation in opening the next dose cohort. This includes safety data also from the subjects who may have escalated from a previous cohort. Details on the criteria for dose escalation can be found in the DMC charter.

Any subject from dose cohort X can escalate to the dose level Y only after dose Y has been opened (i.e., after data from 6 subjects is available after 6 weeks of treatment), the subject in dose cohort X has been treated for at least 12 weeks and meets the individual dose escalation criteria described in the study design section. Equally, any subject from dose cohort Y can escalate to the dose level Z only after dose Z has been opened and the subject in dose cohort Y has been treated for at least 12 weeks at dose level Y.

The current PK/PD model will be updated with data from a minimum of 6 subjects dosed for 6 weeks in each cohort and will include any additional data from all ongoing subjects prior to decision for opening a cohort. This updated model will be used to propose the next dose level for the new cohort.

7.5 Blinding

Not applicable in this open-label study.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/clinical research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IWRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

7.7 Treatment compliance

Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records.

Subjects will be issued an electronic patient diary (EPD) to record date and time of self-administration of study drug as well as every bleeding episode with details of the bleeding and applied medications. The EPD will be reviewed at every subsequent visit/regular contact with the subject during the study. Used and unused vials of study medication will be returned to the clinic for accounting beginning at the Week 12 visit through the end of the study.

8. Non-study therapy

8.1 Prior and concomitant therapy (including treatment of bleeds)

No immunomodulatory drugs are allowed as concomitant medication.

Treatment of bleeds

If bleeds requiring additional control occur, subjects will treat these bleeds with their previously assigned treatment (treatment in place before enrollment). An exception will be made for subjects previously treated with emicizumab, whose bleeds will be treated with rFVIIa.

The dose level, dose interval, and number of doses of FVIII, FIX (in subjects without or with low-titer inhibitors), rFVIIa, and aPCC will take into account the subject's pre-study regimen. However, given the potential additive effect of BAY 1093884 and concomitant medication, it is recommended to treat bleeds with the lowest approved doses of the prescribed replacement factor or bypassing agent, and that dose can be repeated if bleeding is not resolved, upon investigator's judgment.

For the same reason, the investigator must carefully consider the intensity and the location of a trauma for which bleeding has not yet occurred before the preventive use of a replacement factor or a bypassing agent during treatment with BAY 1093884. Careful oversight of bleed treatment by the Investigators will ensure the patients' safety

All medications used for the treatment of bleeds during the study will be documented in the subject EPD.

Any other treatments used during bleeding episodes such as painkillers, must be reported by the subject to the Investigator, and must be documented in the corresponding CRF.

8.2 Post-study therapy

Subjects who completed the study may continue treatment with BAY 1093884 throughout the extension part until Marketing Authorization. During this period, safety and efficacy evaluations will be performed every 12 weeks (see Section 7.1.1).

Subjects who discontinued prematurely the study will discontinue treatment with BAY 1093884 and will revert to their pre-study treatment or will receive any other treatment at the physician's discretion.

9. Procedures and variables

9.1 Tabular schedules of evaluations

Table **9–1** gives an overview on the visit schedules of PK and non-PK subjects.

Table **9–1** Visit schedule overview

	Non-PK Subject	PK Subject
Visit 1*	Screening	Screening
Visit 2	Start treatment = Day 0	—
Visit 2.1	—	Start treatment – PK Day 0 (pre and 4h post-dose)
Visit 2.2	—	PK Day 1 (= 24 h post-dose)
Visit 2.3	—	PK Day 4 (= 96 h post-dose)
Visit 3	Week 1	—
Visit 3.1	—	PK Day 7 (= 168 h post-dose)
Visit 4	Week 3	Week 3, incl. PK pre-dose
Visit 5	Week 6	Week 6, incl. PK pre-dose
Phone call	Week 9	Week 9
Visit 6.1	—	Week 11 – PK Day 0 (pre and 4h post-dose)
Visit 6.2	—	PK Day 1 (= 24 h post-dose)
Visit 6.3	—	PK Day 4 (= 96 h post-dose)
Visit 6.4	—	PK Day 7 (= 168 h post-dose) (Week 12 – dose decision)
Visit 6	Week 12 – dose decision	—
Visit 7	Week 24 – dose decision	Week 24 – dose decision
Every 12 weeks until end of study*	Recurring visit – dose decision	Recurring visit – dose decision
If required*	1 week and 6 weeks after dose escalation visit	1 week and 6 weeks after dose escalation visit
Final Visit*	or Early Termination visit	or Early Termination visit
Follow-up Call*	Follow-up call	Follow-up call

PK = pharmacokinetic
* Identical procedures for non-PK subjects and PK subjects.

Detailed tabular presentations of the study visits are provided in Table **9–2** and Table **9–3** (non-PK subjects) and Table **9–4** and Table **9–5** (PK subjects).

9.2 Visit description

9.2.1 Visit description for non-PK subjects

The following flow chart and visit descriptions apply to non-PK subjects. The corresponding visit descriptions for PK subjects are provided in Section 9.2.2.

Note: For many visits, the same general assessments apply for PK subjects compared with non-PK subjects, however, PK subjects must always come to site on the day of the scheduled

injection, without having injected yet for the first 12 weeks. While for non-PK subjects this only applies at Visits 2 and 6. Therefore, the visit windows are often more stringent for PK subjects (see Table **9–4**, and Table **9–5** for details). From "Part B" onwards, visits for PK and non-PK subjects are the same.

Table **9–2** Tabular schedule of assessments (subjects not participating in PK evaluations; Screening and Part A)

Non-PK subjects	**Screening**		**Part A**					
Visit Number	**Visit 1**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Phone call**	**Visit 6**
Visit Name	**Screening**	**Eligibility check**	**Start of treatment**	**Week 1**	**Week 3**	**Week 6**	**Week 9**	**Week 12**
Time	≤6 wks before V2	2-3 wks before V2	≤6 wks after V1	1 wk ± 1 d after V2	3 wks ± 2 d after V2	6 wks ± 2 d after V2	3 wks ± 2 d after V5	12 wks ± 1 d after V2
Procedures								
Informed consent	X							
Eligibility check	X	X **a**	X **a**					
Demographic data	X							
Med., disease and surgical history	X							
Medication history	X							
Physical examination	X		X **m**	X	X	X		X **m**
Vital signs	X		X **b**	X	X	X		X **b**
Blood sampling	X **f,g,h**		X **g,i,j,k,m**	X **g,i,j**	X **g,i,j**	X **g,i,j**		X **g,i,j,m**
Adverse events	X		X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X
EPD device: training and dispense	X							
EPD device: review			X	X	X	X	X	X
EPD device: return								
Remind subject on wash-out from pre-study product before next visit	X							
Subject to come to site taking wash-out from pre-study product into account	X		X					
Body weight	X		X					X
Local 12-lead ECG			X	X	X	X		X
Confirm eligibility in IWRS to trigger first shipment of study drug		X						
HJHS			X					
Administration of study drug			X					X **c**
Dispense study drug for home infusions			X					X
Return used and unused vials of study drug								X
Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subjects to come next visit un-injected							X	X **d**
Subject to come un-injected								X
Evaluate dose escalation criteria								X
Start 4-weekly contact with subjects								X **d**
Schedule additional safety visits 1 week ± 1 day and 6 weeks ± 1 day after dose escalation								X **e**

Abbreviations: d = day, ECG = Electrocardiogram, EPD = Electronic patient diary, HJHS = Hemophilia Joint Health Score, IWRS = Interactive web responding system, PK = Pharmacokinetic, V = visit, wk = week

Table **9–3** Tabular schedule of assessments (subjects not participating in PK evaluations; Part B through end of study)

Non-PK subjects	**Start of Part B to End of Study**	**Study Part Independent Visits**		
Visit Number	**Visit 7 and every 12 weeks after Visit 7**	**Additional safety visits**	**Final visit or**	**Follow-up phone call**
Visit Name	**Week 24 onward**	**if dose escalated**	**Early termination visit**	
Time	24 wks ± 7 d after V2 **n** Every 12 wks ± 7 d after V2 **n**	1 wk ± 1 d after previous visit and 6 wks ± 1 d		4 wks ± 2 d after Final/Early Termination visit
Procedures				
Physical examination	X **m**	X	X	
Vital signs	X **b**	X	X	
Local 12-lead ECG	X	X		
Body weight	X			
Blood sampling	X **g,i,j,m**	X **g,i,j**	X **g,i,j**	
Adverse events	X	X	X	X
Concomitant medication	X	X	X	X
EPD device: training and dispense				
EPD device: review	X	X	X	
EPD device: return			X	
HJHS			X	
Administration of study drug	X **c**			
Dispense study drug for home infusions	X			
Return used and unused vials of study drug	X		X	
Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subjects to come next visit un-injected	X **d**	X		
Subject to come un-injected	X			
Evaluate dose escalation criteria	X			
Start 4-weekly contact with subjects	X **d**	X		
Schedule additional safety visits 1 week ± 1 day and 6 weeks ± 1 day after dose escalation	X **e**			

a Confirmation of eligibility including check of laboratory test results

b To be performed before and 30-60 minutes after study drug administration

c If the subject meets the dose-escalation criteria, the subject will receive the next higher dose; to be done under medical supervision

d If subject maintains current dose

e If subject is escalated to higher dose

f Only in subjects who consented to the optional pharmacogenetic research project: Blood sampling for pharmacogenetics (PgX). Once consent is obtained, the sample may be taken at any time point during the study.

g Blood sampling for CBC, platelets, serum chemistry

h Blood sampling for FVIII/FIX level and FVIII/FIX inhibitor level

i Blood sampling for aTFPI-Ab

j Blood sampling for PK, PD and exploratory biomarkers

k Blood sampling for low-density lipoprotein (LDL)

m To be performed prior to study drug administration

n Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have >8 days in between 2 injections of BAY 1093884.

9.2.1.1 Visit 1 – Screening visit

The screening visit should not take place more than 6 weeks prior to Visit 2 (start of treatment). If required, the data to be recorded at this visit may be collected over more than one day.

The following procedures will be performed and data recorded:

- Obtain written informed consent from the subjects/legal representative.
  Note: No screening procedures can be performed unless written informed consent has been obtained.
- Eligibility check. No subject may start treatment with study drug until all inclusion and exclusion criteria are met as listed in Sections 6.1 and 6.2. Confirmation of selection criteria may be based on medical records for some conditions, but laboratory test results must be available for the listed items to confirm eligibility. For FVIII/FIX level and for inhibitor levels, subjects should not have received pre-assigned treatment within the times specified in Section 7.1.1, Table 7–2. In subjects whom screening laboratory does not confirm the severity of hemophilia (due to inadequate washout), the diagnosis must be supported by acceptable documentation.
- Demographic data: Year of birth, age at informed consent, sex, race and ethnicity (as allowed by local regulation), height, weight
- Medical history (see Section 9.3.2)
- Disease history (see Section 9.3.3)
- Medication history (see Section 9.3.4)
- Physical examination (see Section 9.6.3.2)
- Adverse events (see Section 9.6.1)
- Concomitant medications
- Vital signs (see Section 9.6.3.3)
- Blood samples for laboratory tests:
  - Complete blood count (CBC; see Section 9.6.3.1), platelets, serum chemistry (see Section 9.6.3.1)
  - FVIII/FIX level
  - FVIII/FIX inhibitor level.
    Note: If a subject has a documented inhibitor positivity and is tested inhibitor negative at this visit, he is still eligible for enrolment as “subject with inhibitors”, provided he is on treatment with a bypassing agent.
  - Optional pharmacogenetic testing (PgX; see Section 9.3.5). Sample may be obtained at any point during the study once the separate informed consent form has been signed by the subject.
- Training on and dispense of EPD device
- Remind subject on wash-out from his pre-study product before next visit (see Table 7–2 in Section 7.1.1).

9.2.1.2 Eligibility check (2-3 weeks prior to Visit 2)

This is not an on-site visit for the subjects, but a reminder for site staff to evaluate laboratory results from the screening visit and to confirm eligibility in the IWRS for triggering first shipment of study drug to the site.

9.2.1.3 Visit 2 – Start of BAY 1093884 treatment at the respective dose (≤ 6 weeks after Visit 1)

This visit should take place within 6 weeks of Screening visit. The wash-out times for FVIII, FIX products and FEIBA as listed in Section 7.1.1 (Table 7–2) must be observed prior to the first injection of BAY 1093884.

The following procedures will be performed and data recorded:

- Confirmation of eligibility including check of laboratory test results
- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD entries
- Local 12-lead ECG
- Body weight
- Hemophilia joint health score (HJHS; see Section 9.4.4)
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
    - Blood sampling for LDL
- Administration of study drug
- Procedures 30-60 minutes after administration of study drug:
  - Vital signs
- Dispense study drug for home injections for 12 weeks

9.2.1.4 Visit 3 (1 week ± 1 day after Visit 2)

This visit should take place 1 week ± 1 day after Visit 2 (Start of treatment).

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Physical examination (see Section 9.6.3.2)
- Vital signs (see Section 9.6.3.3)
- Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
  - CBC, platelets, serum chemistry
  - aTFPI-Ab
  - PD and exploratory biomarkers
  - PK sample

9.2.1.5 Visit 4 (3 weeks ± 2 days after Visit 2)

This visit should take place 3 weeks ± 2 days after Visit 2 (Start of treatment).

The same procedures as at Visit 3 will be performed and data recorded. Please refer to Section 9.2.1.4. Please note difference in time window compared with Visit 3.

9.2.1.6 Visit 5 (6 weeks ± 2 days after Visit 2)

This visit should take place 6 weeks ± 2 days after Visit 2 (Start of treatment).

The same procedures as at Visit 3 will be performed and data recorded. Please refer to Section 9.2.1.4. Please note difference in time window compared with Visit 3.

9.2.1.7 Phone call (3 weeks ± 2 days after Visit 5)

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subject to come next visit without having injected yet.

9.2.1.8 Visit 6 (12 weeks ± 1 day after Visit 2) assessment of dose escalation

The subject's eligibility for dose escalation will be assessed at this visit. Therefore, subjects need to come to the site prior to the scheduled BAY 1093884 injection.

The following procedures will be performed and data recorded 12 weeks ± 1 day after Visit 2:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Body weight
- Decision if subject will stay on the current dose or if escalation is required (does not apply for subjects in Cohort 3 on Z dose; refer to Section 7.1.1 for dose escalation criteria)
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
- Administration of study drug
  - If the subject meets dose-escalation criteria, and the DMC has approved the next higher dose, the subject will receive the next higher dose under medical supervision.
  - If the subject does not meet dose-escalation criteria, or the DMC has not approved the next higher dose, the subject will receive their current dose, does not necessarily need to be injected under medical supervision.
- Procedures 30-60 minutes after administration of study drug (in case of dose escalation):
  - Vital signs (see Section 9.6.3.3)
- Return of all used and unused study medication since the last visit
- Dispensation of new study medication for next 12 weeks
- In case of dose maintenance:
  - Start documented regular contact with the subject every 4 weeks to discuss adverse events, concomitant medication, EPD review and number of untreated bleeds.
  - Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subject to come next visit without having injected yet.

- In case of dose escalation:
  - Schedule additional safety visits 1 week (± 1 day) and 6 weeks (± 1 day) after dose escalation

9.2.1.9 Visit 7 (24 weeks ± 7 days after Visit 2) assessment of dose escalation

The subject's eligibility for dose escalation will be assessed at this visit. Therefore, subjects need to come to the site prior to the scheduled BAY 1093884 injection.

Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have more than 8 days in between 2 injections of BAY 1093884.

The same procedures as at Visit 6 will be performed and data recorded. Please refer to Section 9.2.1.8. Please note difference in time window compared with Visit 6.

9.2.1.10 Every 12 weeks visit (± 7 days calculated from Visit 2)

The subject's eligibility for dose escalation will be assessed at this visit. Therefore, subjects need to come to the site prior to the scheduled BAY 1093884 injection.

Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have more than 8 days in between 2 injections of BAY 1093884.

The same procedures as at Visit 6 will be performed and data recorded. Please refer to Section 9.2.1.8. Please note difference in time window compared with Visit 6.

9.2.1.11 Additional safety visits after dose escalation (if applicable)

This visit must be performed 1 week (± 1 day) and 6 weeks (± 1 day) after the previous visit, if the dose was escalated during the previous visit.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Physical examination (see Section 9.6.3.2)
- Vital signs (see Section 9.6.3.3)
- Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
  - CBC, platelets, serum chemistry
  - aTFPI-Ab
  - PD and exploratory biomarkers
  - PK sample

- Start documented regular contact with the subject every 4 weeks to discuss adverse events, concomitant medication, EPD review and number of untreated bleeds
- Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subject to come next visit without having injected yet.

9.2.1.12 Final visit or early termination visit

Planning of this visit depends on the time when the decision on the next step of the development program for BAY 1093884 will have been made (i.e., the visit time is independent of the previous visit date). This visit will also be performed in subjects who prematurely terminate the study.

The following procedures will be performed and data recorded:

- Recording of concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Physical examination (see Section 9.6.3.2)
- Vital signs (see Section 9.6.3.3)
- HJHS (see Section 9.4.4)
- Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
  - CBC, platelets, serum chemistry
  - aTFPI-Ab
  - PD and exploratory biomarkers
  - PK sample
- Return of all used and unused study medication
- Return EPD device
- Plan Follow-up phone call 4 weeks (± 2 days) later

9.2.1.13 Follow-up phone call (4 weeks ± 2 days after "final or early termination visit")

A phone call to the subject must be made to report adverse events and concomitant medication since final or early termination visit. This includes occurrence and treatment of bleeds, because the EPD device can no longer be used.

9.2.2 Visit description for PK–subjects

The following flow chart and visit descriptions apply to subjects who consented to PK-subanalyses.

For details on pharmacokinetic/pharmacodynamics evaluations, please refer to Section 9.5.

Note: For many visits, the same general assessments apply for PK subjects compared with non-PK subjects. However, PK subjects must always come to site on the day of the scheduled injection without having injected yet for the first 12 weeks. While for non-PK subjects this only applies for Visits 2 and 6. Therefore, the visit windows for some visits are more stringent for PK subjects (see Table **9–4** and Table **9–5** for details). From "Part B" onwards, the visits for PK and non-PK subjects are the same.

Table **9–4** Tabular schedule of assessments (subjects participating in PK evaluations; Screening and Part A)

PK subjects	**Screening**		**Part A**						
Visit Number	**Visit 1**		**Visit 2.1**	**Visit 2.2**	**Visit 2.3**	**Visit 3.1**	**Visit 4**	**Visit 5**	**Phone call**
Visit Name	**Screening**	**Eligibility check**	**Start of treatment & PK day 0**	**PK day 1**	**PK day 4**	**Week 1 & PK day 7**	**Week 3**	**Week 6**	**Week 9**
Time	≤6 wks before V2	2-3 wks before V2	≤6 wks after V1	24 h after dosing at V2.1	96 h after dosing at V2.1	1 wk (168 h) after dosing at V2.1	3 wks ± 1 d after V2.1	6 wks ± 1 d after V2.1	3 wks ± 2 d after V5
Procedures									
Obtain informed consent	X								
Eligibility check	X	X **a**	X **a**						
Demographic data	X								
Med., disease and surgical history	X								
Medication history	X								
Physical examination	X		X **m**			X **n**	X	X	
Vital signs	X		X **b**	X	X	X **n**	X	X	
Blood sampling	X **f,g,h**		X **g,i,k,m,n**	X **k**	X **k**	X **g,i,k,n**	X **g,i,l,n**	X **g,i,l,n**	
Adverse events	X		X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X
EPD device: training and dispense	X								
EPD device: review			X	X	X	X	X	X	X
Remind subject of wash-out from pre-study product before next visit	X								
Subject to come to site considering wash-out from pre-study product	X		X						
Body weight	X		X						
12-lead ECG			X	X	X	X	X	X	
Confirm eligibility in IWRS to trigger first shipment of study drug		X							
HJHS			X						
Administration of study drug			X						
Dispense study drug for home infusions			X						
Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subjects to come next visit un-injected.					X	X	X	X	X
Subject to come un-injected						X	X	X	

Abbreviations: d = day, ECG = Electrocardiogram, EPD = Electronic patient diary, HJHS = Hemophilia Joint Health Score, IWRS = Interactive web responding system, PK = Pharmacokinetic, wk = week, V = visit

Table **9–5** Tabular schedule of assessments (subjects participating in PK evaluations; Part B through end of study)

PK subjects (continued)	**Part A (continued)**				**Start of Part B to End of Study**	**Study Part Independent Visits**		
Visit Number	**Visit 6.1**	**Visit 6.2**	**Visit 6.3**	**Visit 6.4**	**Visit 7 and every 12 weeks after Visit 7**	**Additional safety visits**	**Final visit or**	**Follow-Up Phone call**
Visit Name	**PK day 0**	**PK day 1**	**PK day 4**	**Week 12 & PK day 7**	**Week 24 onwards**	**if dose escalated**	**Early Termination visit**	
Time	11 wks ± 1 d after V2.1	24 h after dosing at V6.1	96 h after dosing at V6.1	12 wks ± 1 d after V2.1. 1 wk /168 h after dosing at V6.1	24 wks ± 7 d after V 2.1 ° Every 12 wks ± 7 d after V2 °	1 wk ± 1 d and 6 wks ± 1 d after previous visit		4 wks ± 2 d after Final/Early termination visit
Procedures								
Physical examination	X **n**			X **n**	X **n**	X	X	
Vital signs	X **n**	X	X	X **b**	X **b**	X	X	
Body weight				X	X			
12-lead ECG	X	X	X	X	X	X		
Blood sampling	X **g,i,k,n**	X **k**	X **k**	X **g,i,k,n**	X **g,i,j,n**	X **g,i,j**	X **g,i,j**	
Adverse events	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
EPD device: training and dispense								
EPD device: review	X	X	X	X	X	X	X	
EPD device: return							X	
HJHS							X	
Administration of study drug	X			X **c**	X **c**			
Dispense study drug for home infusions				X	X			
Return used and unused vials of study drug				X	X		X	
Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subjects to come next visit un-injected			X	X **d**	X **d**	X		
Subject to come un-injected	X			X	X			
Decision on dose escalation versus maintain current dose				X	X			
Start 4-weekly contact with subjects				X **d**	X **d**	X		
Schedule additional safety visits 1 week ± 1 d and 6 weeks ± 1 d after dose escalation				X **e**	X **e**			

a Confirmation of eligibility including check of laboratory test results

b To be performed before and 30-60 minutes after study drug administration

c If the subject meets the dose-escalation criteria, the subject will receive the next higher dose; to be done under medical supervision

d If subject maintains current dose

e If subject is escalated to higher dose

f Only in subjects who consented to the optional pharmacogenetic research project: Blood sampling for pharmacogenetics (PgX). Once consent is obtained, the sample may be taken at any time point during the study.

g Blood sampling for CBC, platelets, serum chemistry

h Blood sampling for FVIII/FIX level and FVIII/FIX inhibitor level

i Blood sampling for aTFPI-Ab

j Blood sampling for PK, PD and exploratory biomarkers

k Blood sampling for PK, PD and exploratory biomarkers as per PK schedule: pre-dose, and 4 h, 24 h, 96 h, 168 h post-dose

l Blood sampling for PK, PD and exploratory biomarkers prior to injection of study drug

m Blood sampling for LDL

n To be performed prior to study drug administration

o Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have more than 8 days in between 2 injections of BAY 1093884.

9.2.2.1 Visit 1 – Screening visit

Please refer to "Visit 1 – Screening visit" for non–PK subjects (Section 9.2.1.1). The same assessments apply.

9.2.2.2 Eligibility check (2-3 weeks prior to Visit 2)

Please refer to "Eligibility check" for non–PK subjects (Section 9.2.1.2). The same assessments apply.

9.2.2.3 Visit 2.1 – Start of BAY 1093884 treatment at the respective dose (≤ 6 weeks after Visit 1) and 1st PK day 0

This visit should take place within 6 weeks of Screening visit. The wash-out times for FVIII, FIX products and FEIBA as listed in Section 7.1.1 (Table 7–2) must be observed prior to the first injection of BAY 1093884.

The following procedures will be performed and data recorded:

- Confirmation of eligibility including check of laboratory test results
- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD entries
- Local 12-lead ECG
- Body weight
- HJHS (see Section 9.4.4)
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - CBC, platelets, serum chemistry
    - aTFPI-Ab
    - PD and exploratory biomarkers
    - PK sample: pre-dose
    - Blood sampling for LDL
- Administration of study drug
- Procedures 30-60 minutes after administration of study drug:
  - Vital signs
- Procedures 4 h after administration of study drug:

  - Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 4 h post-dose

- Dispense study drug for home injections for 12 weeks

9.2.2.4 Visit 2.2 – 1st PK Day 1 (24 h)

This visit should take place 24 h after the recorded injection time at Visit 2.1.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Vital signs (see Section 9.6.3.3)
- Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 24 h post-dose

9.2.2.5 Visit 2.3 – 1st PK Day 4 (96 h)

This visit should take place 96 h after the recorded injection time at Visit 2.1.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Vital signs (see Section 9.6.3.3)
- Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 96 h post-dose
- Reminder to the subject to come next visit without having injected yet.

9.2.2.6 Visit 3.1 – 1st PK Day 7 (168 h)

This visit should take place 168 h after the recorded injection time at Visit 2.1.

Subjects need to come to the site prior to the scheduled BAY 1093884 injection to take the 168 h PK/PD sample before the next regular scheduled injection.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)

- Review of EPD data
- Local 12-lead ECG
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
- Plan next visit on day of scheduled injection of BAY 1093884. Reminder to the subject to come next visit without having injected yet.
- Administration of study drug either at the site or at home. Infusion data to be documented in the EPD.

9.2.2.7 Visit 4 (3 weeks ± 1 day after Visit 2)

Note: PK subjects need to come to the site prior to the scheduled BAY 1093884 injection.

This visit should take place 3 weeks ± 1 day after Visit 2.1 (Start of treatment).

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
- Plan next visit on day of scheduled injection of BAY 1093884. Reminder to the subject to come next visit without having injected yet.

- Administration of study drug either at the site or at home. Infusion data to be documented in the EPD.

9.2.2.8 Visit 5 (6 weeks ± 1 day after Visit 2)

Note: PK subjects need to come to the site prior to the scheduled BAY 1093884 injection.

This visit should take place 6 weeks ± 1 day after Visit 2 (Start of treatment).

Please refer to Section 9.2.2.7 for procedures. The same procedures apply:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
- Plan next visit on day of scheduled injection of BAY 1093884. Reminder to the subject to come to the visit at Week 11 without having injected yet.
- Administration of study drug either at the site or at home. Infusion data to be documented in the EPD.

9.2.2.9 Phone call (3 weeks ± 2 days after Visit 5)

Please refer to "Phone call 3 weeks after V5" for non–PK subjects (Section 9.2.1.7). The same assessments apply.

9.2.2.10 Visit 6.1 (11 weeks ± 1 day after Visit 2) 2nd PK Day 0

Note: PK subjects need to come to the site prior to the scheduled BAY 1093884 injection.

The following procedures will be performed and data recorded 11 weeks ± 1 day after Visit 2:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data

- Local 12-lead ECG
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - CBC, platelets, serum chemistry
    - aTFPI-Ab
    - PD parameters and exploratory biomarkers
    - PK sample: pre-dose
- Administration of study drug
- Procedures 30-60 minutes after administration of study drug:
  - Vital signs
- Procedures 4 h after administration of study drug:
  - Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 4 h post dose

9.2.2.11 Visit 6.2 – 2nd PK Day 1 (24 h)

This visit should take place 24 h after the recorded injection time at Visit 6.1.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Vital signs (see Section 9.6.3.3)
- Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 24 h post-dose

9.2.2.12 Visit 6.3 – 2nd PK Day 4 (96 h)

This visit should take place 96 h after the recorded injection time at Visit 6.1.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data

- Local 12-lead ECG
- Vital signs (see Section 9.6.3.3)
- Blood sampling for PK/PD (incl. exploratory biomarkers; see Section 9.5): 96 h post-dose
- Reminder for the subjects to come uninjected to the next visit, because next visit is PK Day 7

9.2.2.13 Visit 6.4 – 2nd PK Day 7 (168 h) and assessment of dose escalation

This visit should take place 168 h after the recorded injection time at Visit 6.1.

Subjects need to come to the site prior to the scheduled BAY 1093884 injection to take the 168 h PK/PD sample before the next regular scheduled injection. The subject's eligibility for dose escalation will be assessed at this visit.

The following procedures will be performed and data recorded:

- Concomitant medications
- Adverse events (see Section 9.6.1)
- Review of EPD data
- Local 12-lead ECG
- Body weight
- Procedures before administration of study drug
  - Physical examination (see Section 9.6.3.2)
  - Vital signs (see Section 9.6.3.3)
  - Blood samples for laboratory tests (see Sections 9.6.3.1 and 9.5.2):
    - Complete blood count (CBC), platelets, serum chemistry
    - Antibody against aTFPI (aTFPI-Ab)
    - Blood sampling for PD and exploratory biomarkers
    - PK sampling
- The decision as to whether the subject will stay on the current dose or if escalation is required (does not apply for subjects in Cohort 3 on Z dose; refer to Section 7.1.1 for dose escalation criteria)
- Administration of study drug
  - If the subject meets dose-escalation criteria, and the DMC has approved the next higher dose, the subject will receive the next higher dose under medical supervision.
  - If the subject does not meet dose-escalation criteria or the DMC has not approved the next higher dose, the subject will receive their current dose; this does not necessarily need to be injected under medical supervision.

- Procedures 30-60 minutes after administration of study drug (if the dose was escalated)
  - Vital signs (see Section 9.6.3.3)
- Return of all used and unused study medication from the last visit
- Dispensation of new study medication for next 12 weeks
- In case of dose maintenance:
  - Start documented regular 4-weekly (phone) contact with the subject to discuss adverse events, concomitant medication, EPD review and number of untreated bleeds.
  - Plan next visit on day of scheduled injection with BAY 1093884. Reminder to subject to come next visit without having injected yet.
- In case of dose escalation:
  - Schedule additional safety visits 1 week (± 1 day) and 6 weeks (± 1 day) after dose escalation.

9.2.2.14 Visit 7 (24 weeks ± 7 days after Visit 2) assessment of dose escalation

The subject's eligibility for dose escalation will be assessed at this visit. Therefore, subjects need to come to the site prior to the scheduled BAY 1093884 injection.

Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have more than 8 days in between 2 injections of BAY 1093884.

The same procedures as at Visit 6 for non-PK subjects will be performed and data recorded. Please refer to Section 9.2.1.9. Please note difference in time window compared with Visit 6.

9.2.2.15 Every 12 week visit (± 7 days calculated from Visit 2)

The subject's eligibility for dose escalation will be assessed at this visit. Therefore, subjects need to come to the site prior to the scheduled BAY 1093884 injection.

Visit windows of ±7 days (calculated from Visit 2) are allowed, but the next scheduled BAY 1093884 injection must be kept in mind to ensure subjects will not have more than 8 days in between 2 injections of BAY 1093884.

The same procedures as at Visit 6 for non-PK subjects will be performed and data recorded. Please refer to Section 9.2.1.10. Please note difference in time window compared with Visit 6.

9.2.2.16 Additional safety visits after dose escalation (if applicable)

Please refer to "Additional safety visits after dose escalation" for non–PK subjects (Section 9.2.1.11). The same assessments apply.

9.2.2.17 Final visit or Early Termination visit

Please refer to the "Final visit" for non-PK subjects (see Section 9.2.1.12). The same procedures apply.

9.2.2.18 Follow-up phone call (4 weeks ± 2 days after "final or early termination visit")

Please refer to the "Follow-up phone call" for non-PK subjects (see Section 9.2.1.13). The same procedures apply.

9.3 Population characteristics

9.3.1 Demographic

The following demographic characteristics will be collected:

- Year of birth
- Age at Informed Consent
- Sex
- Race (as allowed by local regulation)
- Ethnicity (as allowed by local regulation)
- Height
- Weight

9.3.2 Medical history

Medical history findings (i.e., previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Disease history

The following baseline characteristics will be collected 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(s), dose and frequency of administration)
- Number of exposure days

- Type of FVIII of FIX gene mutation (from history)
- Family history
- FVIII or FIX level and type of assay
- Family and personal history of past inhibitor formation
- Current inhibitor level
- Current ITI status
- Current treatment product and regimen
- Number and type of bleeds in the past 6 months
- Presence and location of target joints

9.3.4 Medication history

Medication history to be collected and recorded at Screening and will 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.

The details for all medications recorded in the eCRF should include:

- Medication trade name and dose
- Reason for medication
- Start date and end date or if ongoing

Additional information regarding dates of vaccinations will be collected with emphasis on most recent vaccinations (prior 12 months).

9.3.5 Pharmacogenetic testing - optional

All subjects will be invited to participate in a voluntary research project involving genetic analyses of a blood sample.

The purpose of the genetic analysis is the evaluation of polymorphism of TFPI, but also of other genes involved in blood coagulation in different hemophilia subjects with different genetic background.

Approval for pharmacogenetic sampling must be obtained. A separate informed consent form (ICF) will be provided. Subjects will be asked to participate in the optional pharmacogenetics. If subjects elect to participate, a blood sample will be collected. Once consent is obtained, the sample may be taken at any time point during the study. Samples will be prepared and labeled according to laboratory specifications. Details of the sample collection and shipment procedures will be explained in the laboratory manual.

A subject does not need to agree to participate in the pharmacogenetic research project to be enrolled in the study.

9.4 Efficacy

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9.4.1 Electronic patient diary (EPD)

Treatment logs are commonly used for hemophilia subjects for documentation of their home treatment. Home treatment and bleeding information are the key variables evaluated in this study. Study specific treatment logs will be provided in national language. The preferred system for this study will be EPD devices since they are interactive, allow for real time data transmission, record-stamp date and time of fulfillment, and facilitate the clarification of data with the site and during the data cleaning process. Subjects or their caregivers will be provided with EPDs for the whole study. At Screening visit, subjects and caregivers will be trained in the use of the device. These logs will be used to collect the treatment data and bleeds by the caregivers or subjects, and the data will be verified for accuracy and completion by the investigator or delegate during regularly scheduled interactions with the subject or caregiver. Thus, the EPD will be considered the source for these data.

For each self-administered injection of study drug, information must be recorded on the EPD as follows:

Each injection of BAY 1093884

- Date and time [*24 hour clock*]
- Individual vial number (bar code scan from vial label)
- Number of vials used
- Volume in mL that was injected

Injections of study drug as part of protocol-mandated visits and procedures will be recorded on the respective CRF pages.

All bleeding episodes (regardless if treated or not, or treated at home or under medical supervision) as well as the potential treatment with pre-study hemophilia drugs will be recorded in the EPD:

Bleeding episode (onset)

- Date and time [*24 hour clock*] of onset
- Type of bleed [*spontaneous, non-spontaneous/non-traumatic, traumatic*]
- Location [*joint, muscle, skin or mucosa, internal, other; body map*]
- Intensity [*mild, moderate, severe;* according to subject's own judgment]
- Treated [*yes/no*];
  if "yes": Date and time [*24 hour clock*]
  Product class used
  Number of injections, doses

9.4.2 Dose of pre-study hemophilia medication administered and number of injections needed to stop a bleeding event

The subjects will document dose of pre-study hemophilia medication used and the number of injections needed to stop a bleeding event. Subjects assess the cessation of their own bleeding episode based on their long-term experience of coping with bleeds since childhood. The investigator and clinical staff will review the subject EPD to check for the dose used and the number of injections applied (including the date, time, and the severity of all bleeding events).

9.4.3 Assessment of adequacy of hemostasis during minor surgical interventions

Pre-study medication used for minor surgery will be recorded on the CRF. The doses administered and the frequency of any treatment will be collected.

The investigator, surgeon, or interventionalist will be asked to compare estimated blood loss from experience with non-hemophilic subjects undergoing comparable procedures, and assess intraoperative efficacy at the end of the procedure (Table 9–6). Post-surgical efficacy will be assessed at least 24 h after the end of the procedure by the investigator or surgical staff at drain removal, if required, and by the investigator or hematologist at discharge.

Table 9–6 Criteria for the assessment of efficacy in minor surgery (5)

Excellent	Intra-operative and post-operative blood loss similar (within 10%) to the non-hemophilic patient. • No doses of FVIII/FIX/bypassing agents needed AND • Blood component transfusions required are similar to non-hemophilic patient
Good	Intra-operative and/or post-operative blood loss slightly increased over expectation for the non-hemophilic patient (between 10-25% of expected), but the difference is judged by the involved surgeon/anesthetist to be clinically insignificant. • No doses of FVIII/FIX/bypassing agents needed AND • Blood component transfusions required are similar to the non-hemophilic patient
Fair	Intra-operative and/or post-operative blood loss increased over expectation (25-50%) for the non-hemophilic patient and additional treatment is needed. • FVIII/FIX/bypassing agents needed OR • Increased blood component (within 2 fold) of the anticipated transfusion requirement
Poor/none	Significant intra-operative and/or post-operative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia • Unexpected hypotension or unexpected transfer to ICU due to bleeding OR • Substantially increased blood component (> 2 fold) of the anticipated transfusion requirement

Data on blood loss will be collected, as estimated at the time of surgery, change or drop in hemoglobin/hematocrit, the need for additional or other hemostatic medications, and the type and number of blood products transfused. Hemostatic-related surgical complications will also be obtained including data on specific diagnostic evaluations needed (example: Imaging to follow size of a hematoma).

9.4.4 Hemophilia joint health score (HJHS)

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The HJHS score will be evaluated at the start of treatment and the final visits.

The HJHS measures joint health in the domain of body structure and function (i.e., impairment) of the joints most commonly affected by bleeding in hemophilia: Elbows (left/right), knees (left/right), ankles (left/right).

Items to be assessed per joint: Swelling, duration (swelling), muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and strength.

The possible range per joint is 0-20 score points, where 0 denotes the best possible and 20 the worst joint status. Thus, the sum for all 6 joints is 120 score points at maximum. In addition, general gait is to be assessed: 0-4 score points.

The HJHS total score is the sum of the 6 joint scores plus the score for general gait and ranges from 0 to 124 score points.

9.5 Pharmacokinetics/pharmacodynamics

9.5.1 Pharmacokinetics

9.5.1.1 Drug measurements

Blood samples for PK analyses of BAY 1093884 (anti-TFPI mAb) in plasma will be collected at the time points given in the study flow chart (see Table **9–1**).

Plasma concentrations of BAY 1093884 will be measured using a validated ligand binding assay method. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration, QC, and study samples will be reported in the bioanalytical report, which will be included in the clinical study report for this study.

Samples should be collected as close as possible to the nominal sample collection time. The actual sampling time should be documented on the eCRF pages and actual sampling time will be used when calculating the pharmacokinetic parameters. Deviations from planned PK blood sampling times are not considered as protocol violations. In the case of missing records of the actual sampling times, planned sampling times may be used for PK evaluation.

Information on the collection, processing, storage and shipment of biomarker samples will be provided in a separate document.

In case a subject bleeds during the period of dense sampling for PK, subject must treat the bleed and continue PK sampling with no modifications to the PK sampling schedule.

9.5.1.2 Pharmacokinetic evaluation

Non-compartmental analysis

PK parameters will be calculated using the model-independent compartment-free method according to the current Bayer guidelines using the PK software WinNonlin, version 5.3 or higher. Based on the concentration time data, the following PK parameters will be calculated:

BAY 1093884 in plasma

Main PK parameters: $AUC(0\text{-}t_{last})$, $AUC(0\text{-}t_{last})/D$, C_{max}, C_{max}/D

Additional parameters: Optionally AUC, AUC/D, $t_{1/2}$, V_{ss}, CL, MRT, V_z, $\%AUC(t_{last\text{-}\infty})$, points terminal may be estimated. Normalization of AUC to dose and/or body weight may be performed.

For multiple dose administration, the following parameters may also be estimated in addition to the parameters listed as main PK parameters:

After the first dose: $AUC_{0\text{-}7d}$, $AUC_{0\text{-}7d}/D$, C_{max}, C_{max}/D

After the last dose: $AUC_{\tau,md}$, $AUC_{\tau,md}/D$, $C_{max,md}$ and $C_{max,md}/D$, and accumulation ratios (R_AC_{max}, R_AAUC)

Additional PK parameters may also be estimated.

In addition, data obtained from this study may be subject to PK modeling and simulation.

Details of the model development and evaluation will be described in a separate Evaluation Plan and the results reported in a separate Evaluation Report.

9.5.2 Pharmacodynamics and biomarkers

Pharmacodynamic parameters will include:

- PT, aPTT, D-dimer, fibrinogen, FV level (clotting assay), antithrombin activity, protein C activity, thrombin generation assay (TGA/CAT PPP), TFPI activity (chromogenic), total (i.e., LDL-devoid and LDL-bound) TFPI concentration in plasma, FVIIa, dPT (dilute PT), prothrombin fragment 1 and prothrombin fragment 2 (F1+2), thrombin-antithrombin complex (TAT)

Optional pharmacodynamic parameters (locally, if specific instrument is available):

- Thrombelastometry/thrombelastography (ROTEM/TEG)
- Thrombin generation assay (TGA/CAT PRP)

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Procedures for processing, shipping and analysis of samples will be described in a separate manual.

9.6 Safety

Safety variables:

- Incidences of drug-related AEs, SAEs, adverse events of special interest (AESIs), injection site reactions (ISRs) and clinically relevant[a] abnormal laboratory values.
- Incidences of binding and neutralizing antibodies against BAY 1093884

Safety measures will include:

- AEs/SAEs/AESIs and ISRs by

[a] "Clinically relevant" implies the presence of a clinical sign or symptom that requires medical action.

  - Relationship to study drug
  - Severity
- AEs leading to discontinuation of study drug
- Anti-TFPI antibodies (immunogenicity)
- Clinical laboratory data including:
  - CBC with differential count and platelets
  - Serum chemistry
- Vital signs
- Evaluation of concomitant medication
- Physical examination

9.6.1 Adverse events

Please note:

Any bleeding event occurring during the study will not be documented as an AE, because this event is captured in the assessment of efficacy. However, if the bleed requires hospitalization or fulfills another seriousness criterion, it must be reported as an SAE (see Section 9.6.1.3.1).

Please note:

Any thromboembolic or thrombotic microangiopathic event is an AESI and will be considered to be an SAE (see Section 9.6.1.4). Any thromboembolic or thrombotic microangiopathic event will be sufficient to require a review of safety by the DMC (see Section 13.1.2). Dosing will be suspended in the affected subject(s) until consultation with the DMC (see Section 9.6.1.7).

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal (e.g., physical examination findings, symptoms, diseases, laboratory, ECG).

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE, if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 h
   - The admission is pre-planned
     (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g., social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

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)

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation (e.g., mechanical bleeding at surgical site)

or

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

An assessment of “yes” indicates that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessment and documentation of adverse events

The investigator has to record all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase on the respective CRF pages. After the end of the follow-up phase, there is no requirement to actively collect AEs, including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs), the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.3.1 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 h of the investigator's awareness) all SAEs and AESIs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs/IRBs

Notification of the IECs/IRBs about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, suspected unexpected serious adverse reactions [SUSARs]) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g., SUSARs) according to all applicable regulations.

9.6.1.3.2 Expected adverse events

For this study, the applicable reference document is the current version of the investigator's brochure (IB).

If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.4 Adverse events of special safety interest

Thromboembolic and thrombotic microangiopathic (TMA) events

Subjects will be closely monitored for any signs of thromboembolic and TMA events (e.g., myocardial infarction, ischemic cerebrovascular accident, arterial thrombosis, deep vein thrombosis, pulmonary embolism) after study drug administration and during the follow-up visits. If signs and symptoms of any thromboembolic event or signs of TMA are present during the study, the site physician will assess these symptoms/signs, order and review diagnostic procedures (ECG, ultrasound, computed tomography, magnetic resonance imaging, Doppler sonography, and blood tests, which include CBC, coagulation parameters, including D-dimer, platelets, and fibrinogen, TFPI, ATIII, and protein C etc.), as appropriate, to confirm or refute the diagnosis. If symptoms are suggestive of deep vein thrombosis, pulmonary embolism, or TMA, the guidelines for diagnosis and intervention will be followed.

Subjects will be provided with a subject alert card which includes a checklist of symptoms and the advice to seek medical attention in case of occurrence of any symptoms (see separate document).

Thromboembolic and TMA events are defined in this study as SAEs and must be documented accordingly on the corresponding AE pages of the eCRF and reported within 24 h of the investigator's awareness as SAEs.

Hypersensitivity reactions

Hypersensitivity in this study is defined as AESI and must be documented on the corresponding adverse events of special safety interest pages of the eCRF and reported within 24 h of the investigator's awareness. Non-serious hypersensitivity events should not automatically be upgraded by the reporting investigator to serious.

If allergic or anaphylactic reactions occur, the injection will be stopped immediately and symptomatic treatment and therapy for hypersensitivity should be instituted, as appropriate. Subjects will be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension, and nausea during or after the injection can constitute an early warning for hypersensitivity and anaphylactic reactions. In such cases, the subject should immediately notify the investigator or the site staff of these symptoms. In the event of shock, the current medical standards for shock treatment should be observed.

The first injection of every dose level will be administered under medical supervision. Subjects will be monitored at the site for about 1 h after study drug injection.

9.6.1.5 Reporting of medical device failures[b]

The investigator must immediately report all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.6.1.6 Dose-limiting toxicities

Dose-limiting toxicities (DLTs) are defined as any of the following events that are clearly unrelated to underlying disease and occurring at any dose level.

- Presence of any symptoms or signs of TE or TMA
- Platelets <100 giga/L or fibrinogen <100 mg/dL at any visit
- Any grade ≥3 according to CTCAE criteria version 5.0 (CTCAE criteria do not apply for toxicities related to underlying disease like aPTT)
- Grade ≥2 toxicities according to CTCAE criteria in case of symptoms of disseminated intravascular coagulation (DIC) or hemolysis

9.6.1.7 Adverse events requiring an *ad hoc* DMC meeting

Occurrence of any of the following events will require that an *ad hoc* meeting of the DMC take place.

1. Events resulting in suspension of treatment in the affected subject(s).
    a. Occurrence of a single drug-related Serious Adverse Event (SAR), or two severe or clinically significant drug-related AEs
    b. Subject experiencing a DLT as defined in Section 9.6.1.6
2. Events resulting in suspension of enrollment
    a. Two subjects experiencing the same DLT as listed in Section 9.6.1.6
    b. Death of a subject that is considered related to BAY 1093884 by the investigator

[b] Only applicable for study sites located in Japan.

9.6.2 Pregnancies

Not applicable in this male study population.

For a pregnancy in the partner of a male study subject, all efforts will be made to obtain information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as for an SAE.

9.6.3 Further safety

9.6.3.1 Clinical laboratory assessments

Blood samples for clinically laboratory will be drawn at the time points specified Table **9–2** and Table **9–3**for non-PK subjects, and Table **9–4** and Table **9–5** for PK subjects.

All laboratory analyses will be performed at central laboratories. Investigators will be provided with a laboratory manual containing instructions on how to collect and process samples, and will be provided with a copy of results for their subjects.

Remaining biological material may be used later for further safety analysis, if required.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g., clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

Standard safety laboratory

The following blood samples will be collected for laboratory analyses:

- CBC with differential: Hemoglobin, hematocrit, platelets, leukocytes, neutrophils, eosinophils, basophils, monocytes, and lymphocytes
- Serum chemistry: Sodium [Na], potassium [K], bicarbonate [CO_2], chloride [Cl], blood urea nitrogen [BUN], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin, lactate dehydrogenase [LDH]
- Fibrinogen

FVIII/FIX inhibitors

Antibody to FVIII/FIX (inhibitor) testing will be done according to the Nijmegen modified Bethesda assay. A positive inhibitor test is defined with a threshold of ≥0.6 BU/mL at the central laboratory.

BAY 1093884 inhibitory antibodies (aTFPI-Ab)

If there is loss of efficacy (e.g., unexpected break-through bleeds):

- Blood for central laboratory: Antibodies against BAY 1093884.

Hypersensitivity reactions

If a hypersensitivity reaction is clinically suspected, the subject is to be managed according to local standard of care. The investigator should immediately notify the sponsor. The following information and blood tests should be obtained within 7 days of the reported event. Confirmatory studies may be required.

- Time and dose of last BAY 1093884 injection
- Number of BAY 1093884 injections
- Infused/injected product for the treatment of bleeds (if applicable)
- Blood for central laboratory: CBC, antibodies against BAY 1093884, and immunoglobulins.

If the above samples cannot be obtained, collection of local samples stored at the site may be requested for testing in the central laboratory. In the event of a confirmed hypersensitivity event, the subject should be removed from the trial, and subsequent treatment options should be discussed.

Thromboembolic and thrombotic microangiopathic events

Blood for central laboratory: CBC, coagulation parameters, including D-dimer, platelets, and fibrinogen, TFPI, ATIII, and protein C, LDH

9.6.3.2 Physical examination

The physical examination (by means of inspection, palpation, and auscultation) will be performed by a physician at the study site, and must at least cover the organs of the cardiovascular, respiratory, and abdominal systems. Orientating tests of neurological function will be included.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.6.3.3 Vital signs

Systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature will be recorded (after resting for at least 5 minutes) before and within 30-60 minutes after the end of injection of the study medication that are given under medical supervision.

9.6.3.4 Electrocardiogram

ECGs will be conducted to assess safety at Visits 2 through 7, Every 12 Weeks Visit, and at any Additional Safety Visits.

9.7 Other procedures and variables

Contraception

It has been shown that there is no target-related specific transport mechanism for BAY 1093884 into semen or from semen into the conceptus. Following administration to a male subject, BAY 1093884 would not be bioavailable via seminal delivery to the developing conceptus of an untreated partner. Therefore, no method of contraception is needed.

9.8 Appropriateness of procedures/measurements

The majority of the safety parameters, as well as the methods to measure them, are recognized clinical assays, and are reliable, accurate and relevant. The safety evaluation for BAY 1093884 will be based on clinical and laboratory assessments including coagulation and immunological tests as well as on reported AEs.

10. Statistical methods and determination of sample size

10.1 General considerations

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. 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.

Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan (SAP).

10.2 Analysis sets

The statistical analysis sets are defined as follows:

Safety set (SAF)	All subjects with at least one intake of study drug. Safety analyses will use treatments actually received (in case where this differs from assignment to treatment).
Per protocol set (PPS)	All SAF subjects who completed Part A and Part B of the study with no major protocol deviations.
PK set	All subjects with evaluable PK profiles will be included.

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.

Demographics and other baseline characteristics will be analyzed based on the SAF and PPS.

The primary analysis population for the safety analysis will be the SAF. The efficacy analyses will be based on the PPS and sensitivity analyses will be based on the SAF as appropriate.

10.3 Variables and planned statistical analyses

The **primary endpoint is safety** as defined by the frequency of drug-related AEs, SAEs, AESIs and clinically relevant[c] abnormal laboratory values.

Another safety endpoint will be the frequency of binding and neutralizing antibodies against BAY 1093884.

The measures used for the assessment of the safety of BAY 1093884 are listed in Section 9.6.

CCI **efficacy variables** are listed in Section 9.4. Other efficacy variables may be defined in the statistical analysis plan (SAP).

Pharmacokinetic parameters are listed in Section 9.5.1.

Pharmacodynamic parameters are listed in Section 9.5.2.

Subgroups

Subgroups will be defined by type of hemophilia (A or B), presence of inhibitors, previous prophylaxis or OD treatment, age group, race and region. Further subgroups will be defined, if appropriate.

10.3.1 Baseline

Demographic characteristics, including age, weight, height and ethnicity will be presented for all subjects exposed to BAY 1093884 in the form of summary statistics. The presentation will also be given for subgroups. Other baseline characteristics, including laboratory findings and vital signs, will be handled similarly.

10.3.2 Extent of exposure

Extent of exposure to the study and reference drug (rescue medication, pre-study medication), including injection characteristics, will be summarized for all subjects receiving any amount of drug.

10.3.3 Analysis of efficacy

CCI no multiplicity adjustment will be done for the evaluation of the different dose levels.

[c] "Clinically relevant" implies the presence of a clinical sign or symptom that requires medical action.

All endpoints will be summarized by descriptive statistics. For selected efficacy variables 90% confidence intervals will be given.

The efficacy analyses will be based on both Part A and Part B. The proportion of responders 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. Further efficacy analyses will include all bleeding data available at the time when Cohort 3 will have completed Part B of the study.

Further details will be clarified in the SAP.

Missing data

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 bleeds, but not for the corresponding subgroup of bleeds.

Each subject's bleeding period start and stop 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. Otherwise, imputation rules will be specified in the statistical analysis plan or the analysis datasets specification document.

A detailed missing data-handling plan will be provided in the statistical analysis plan.

10.3.4 Analysis of PK/PD parameters

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 where appropriate.

10.3.5 Analysis of safety

The safety profile will be analyzed using the SAF population and safety data collected during Part A. Vital signs, AEs, and laboratory data will be analyzed by descriptive statistics, such as summary statistics and frequency tables. All AEs will be tabulated according to the affected system organ class and preferred term, as coded by the medical dictionary for regulatory affairs (MedDRA).

Further safety analyses will include all safety data available at the time when Cohort 3 will have completed Part A and Part B of the study. For each subject, safety variables will be

analyzed by study part and the respective visits and by dose actually received, both by dose cohort and by study medication actually received during the respective interval. This includes safety analyses by dose last received.

The evaluation of safety data and the version of MedDRA used for coding will be detailed in the SAP.

10.4 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

CCI [redacted]

10.5 Planned interim analyses

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.

For safety, AEs will be assessed for all subjects per dose level. In case of comparable clinical safety, the routine lab findings will be evaluated. In case of comparable clinical and laboratory safety, thrombosis and hemostasis markers will determine safety evaluation.

For efficacy, the number of subjects without spontaneous bleeds requiring treatment in addition to BAY 1093884 will be assessed; all other efficacy variables will be assessed for the dose levels observed.

11. Data handling and quality assurance

11.1 Data recording

The data collection tools for this study will be an eCRF; a validated electronic data capture system called RAVE, and an EPD (see Section 9.4.1) will be used. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (CIE/LSH; SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of

software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. EPD data will be considered source documentation.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (subject number; year of birth/age; sex; if applicable, race/ethnicity)
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
  - The SAE itself
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g., IWRS, laboratory, ECG).

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

11.4 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).

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the

performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g., relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

At the end of the study, sites will receive their EPD data electronically for archiving.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification for destruction is given by the sponsor.
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.3.1.

13. Ethical and legal aspects

13.1 Investigators and other study personnel

13.1.1 Investigators

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before taking effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.1.2 External bodies

In this study, there will be a Steering Committee (SC) and a Data Monitoring Committee (DMC).

Steering Committee (SC)

The SC will consist of external key experts in the field of hemophilia. It will advise on all scientific aspects on the study.

A separate SC Charter will describe roles and responsibilities as well as the cooperation with the sponsor in detail.

Data Monitoring Committee (DMC)

The primary role of the DMC is the regular review of the safety data and provision of recommendations for dose escalation to the next dose level.

The DMC will consist of a chair and members who have recognized expertise in clinical trials and in the field of hemophilia as well as biostatistics. They are not members of the SC or involved as investigators or otherwise in the trial.

A separate DMC Charter will describe roles and responsibilities of the committee in detail.

The DMC will review key safety data throughout the study, including the extension part, and may issue recommendations on:

Dose opening

Based on safety evaluation of the first 6 subjects after the first 6 weeks of treatment at each dose cohort, DMC will recommend escalation to the next dose level. This also includes the evaluation of the 6 subjects on the Z dose and the subsequent advice on proceeding with the extension part.

Dose escalation

Subjects are allowed to escalate to the next dose only after DMC has opened that dose. Subjects from dose X can only escalate to dose Y and cannot escalate directly to dose Z, even if the z dose has already been opened by the DMC.

Adverse events review

If any of the events listed in Section 9.6.1.7 occurs, an *ad hoc* DMC meeting will be held.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the

Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and forwarded to the sponsor. Upon request, the responsible unit (e.g., IEC/IRB, head of the study center/medical institution) must supply the sponsor with a list of the IEC/IRB members involved in the vote, and a statement confirming that the IEC/IRB is organized and operating according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/ sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject/legal representative or proxy consenter (if the subject is under legal protection), prior to his entry into the study (i.e., before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject/legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit descriptions in Section 9.2 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject material obtained before withdrawal may be used to generate subject-specific data after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he enter the study. Additionally, the investigator will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

For the optional pharmacogenetics testing, a separate informed consent will additionally be obtained according to the procedures described above.

1. If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legal representative(s) or proxy consenter, if present, should be requested. The subject should be informed about the study as soon as possible and his consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent form. The investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his participation in the study by signing the revised informed consent form. Any revised written

informed consent form and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects/insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject’s identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

14. Reference list

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15. Protocol amendments

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

15.1 Amendment 4

Integrated protocol Version 2.0, dated 26 JUN 2018

15.1.1 Overview of changes to the study

Table of main changes

Section # & Name	Description of Change	Brief Rationale
3 Introduction	Text describing the product updated to include most recent data from the ongoing First in Man Phase 1 study	Update of data available for BAY 1093884
2 Synopsis 5 Study design 7.4.1 Selection of doses in the study	Dose escalation criteria and safety rules between cohorts added in addition to those already described within cohorts/subjects	Present a more detailed version of the study design
2 Synopsis 5 Study design 7.1.1 Prophylaxis treatment with BAY 1093884 7.4.1 Selection of doses in the study 7.4.1.1 PK/PD criteria for dose recommendations 9.6.1.7 Adverse events requiring an *ad hoc* DMC meeting 13.1.2 External bodies	Text added providing further detail on the role and responsibilities of the DMC	Clearly describe the safety oversight and decision process of the DMC
5 Study design	Text added describing the rationale for fixed doses	Provide justification for change from weight-based doses to fixed doses
5 Study design	Communication plan added	Description of methods for communicating safety data and dose escalation decisions to investigator sites
6.3.2 Replacement	Text added stating that subjects may be replaced only if they have not withdrawn from the study for drug-related safety concerns	Clarification of description of when subjects may be replaced.

Section # & Name	Description of Change	Brief Rationale
7.1.2 Treatment of bleeds 8.1 Prior and concomitant therapy (including treatment of bleeds)	Guidance added for use of bypassing agents to treat bleeds during treatment with BAY 1093884	Intensity and location of trauma for which bleeding has not yet occurred must be considered by investigator prior to initiating preventative treatment with a replacement factor or bypassing agent.
7.1.3 Treatment of PK/PD assessments 8.2 Post-study therapy 9.1 Tabular schedules of evaluations 9.2.1.10 Every 12 weeks visit (± 7 days calculated from Visit 2) 9.2.2.15 Every 12 weeks visit (± 7 days calculated from Visit 2)	Every 24-week visit changed to frequency of every 12 weeks	Additional safety monitoring of subjects
7.2 Identity of study treatment	Dose strength changed from “100 mg/mL” to “either 100 mg/mL or 150 mg/mL”	Introduction of 150 mg/mL dose strength
7.4.1.1 PK/PD criteria for dose recommendations	Additional detail provided on the amount and type of safety, PK and PD data collected	Further describe the amount of safety, PK and PD data collected in order to open next dose cohort
9.2.1 Visit description for non-PK subjects 9.2.2 Visit description for PK subjects	Local ECG added at Visits 3 – 7 and every 12 week visits	Additional safety monitoring
9.2.1.3 Visit 2 – Start of BAY 1093884 treatment at the respective dose (≤6 weeks after Visit 1) 9.2.2.3 Visit 2.1 – Start of BAY 1093884 treatment at the respective dose (≤ 6 weeks after Visit 1) and 1st PK day 0	LDL added to blood samples collected at Visit 2	Additional safety laboratory collection
9.6.1.2.2 Intensity	AE intensity should be graded according to NCI CTCAE version 5.0	Updated guidance for the assessment of AEs
9.6.1.5 Reporting of medical device failures	Section added describing reporting of non-approved medical device failures	Guidance specific to Japan sites for reporting of non-approved medical device failures

Section # & Name	Description of Change	Brief Rationale
9.6.1.6 Dose-limiting toxicities	Section added to define DLTs for the study	Additional safety guidance on the reporting of DLTs
9.6.3.1 Clinical laboratory assessments	Lactate dehydrogenase and fibrinogen added to standard safety laboratory analyses	Additional safety laboratory blood samples
9.6.3.1 Clinical laboratory assessments	Immunoglobulins will be collected for hypersensitivity reactions	Addition of immunoglobulins to blood tests collected for hypersensitivity reactions
9.6.3.1 Clinical laboratory assessments	LDH added to central laboratory tests for thromboembolic and thrombotic microangiopathic events	Additional safety laboratory collection
9.6.3.4 Electrocardiogram	Section added to note that ECGs will be performed at PK visits	Description of ECG safety assessment schedule
2 Synopsis 10.3 Variables and planned statistical analyses	Injection site reactions removed as separate endpoint, as these will be collected as part of regular AE reporting	Remove redundant endpoint of injection site reaction
12 Premature termination of the study	Note pertaining to DMC review of thromboembolic or thrombotic microangiopathic events removed, as this is now described in new section 9.6.1.7	Remove redundant DMC review text regarding thromboembolic or thrombotic microangiopathic events

Table of corrections and clarifications

Section # & Name	Description of Change
6.1 Inclusion criteria	Inclusion criteria 1 and 2 combined into one criterion, as subjects cannot satisfy both criteria. Content of criteria not changed.
2 Synopsis 6.2 Exclusion criteria	Exclusion criterion 12 text updated to clarify that patients receiving treatment with an investigational drug 3 months prior to the screening visit are excluded.
6.3.1 Withdrawal 10.5 Planned interim analysis	Definition of completer updated to specify that at least one Part B segment must be completed by the subject.
7.1.1 Prophylaxis treatment with BAY 1093884	Frequency of administration updated from “once weekly” to “every 7 days ± 1 day” for consistency with description of visit schedule.
8.1 Prior and concomitant therapy (including treatment of bleeds)	Wording simplified to state that no immunomodulatory drugs are allowed during the study.

Section # & Name	Description of Change
Table 9-2B Table 9-3B	Part B and subsequent visits combined into one column, as procedures are identical at these visits
Table 9-2A Table 9-2B 9.2.1.1 Visit 1 – Screening visit Table 9-3A Table 9-3B 9.3.5 Pharmacogenetic testing – optional	Clarification that pharmacogenetic sample may be collected at any time point during the study once separate consent is obtained, not just Visit 1
9.4 Efficacy	CCI efficacy variable of primary interest clarified to note that the number of subjects in each 12-week Part B period, as opposed to Part B overall, will be observed
10.1 General considerations 10.3.3 Analysis of efficacy	Description of Part B clarified to note that there are multiple 12-week periods after Part A
10.3.3 Analysis of efficacy	Sentence added: "It should be noted that this kind of analysis must be interpreted carefully, as the restriction is based on post-baseline events."

Typographical, grammatical, and other minor edits are not identified.

15.1.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

15.2 Amendment 5

Integrated protocol Version 3.0, dated 12 FEB 2019

15.2.1 Overview of changes to the study

Table of main changes

Section # and name	Description of change	Brief rationale
Table 9-1 Visit schedule overview Table 9-2 Tabular schedule of assessments (subjects not participating in PK evaluations; Screening and Part A) Table 9-3 Tabular schedule of assessments (subjects not participating in PK evaluations; Part B through end of study)	The visit schedule was updated to include an additional safety visit 6 weeks (± 1 day) after dose escalation.	This change will allow for additional safety monitoring of study subjects after escalation to a higher dose.

Section 9.2.1.8 Visit 6 (12 weeks ± 1 day after Visit 2) assessment of dose escalation Section 9.2.1.11 Additional safety visits after dose escalation (if applicable) Table 9-5 Tabular schedule of assessments (subjects participating in PK evaluations; Part B through end of study) Section 9.2.2.13 Visit 6.4 – 2nd PK Day 7 (168 h) and assessment of dose escalation Section 9.2.2.16 Additional safety visits after dose escalation (if applicable)		
Section 2 Synopsis Section 6.1 Inclusion criteria	Inclusion criterion 1 was modified to specify that subjects with inhibitors against FVIII or FIX also have undetectable FVIII or FIX levels.	DMC recommendation
Section 2 Synopsis Section 6.2 Exclusion criteria	Exclusion criterion 10 was modified to more accurately describe advanced liver disease.	DMC recommendation

Table of corrections and clarifications

Section # & Name	Description of Change
3 Introduction	The portion of the section presenting information on the product was updated to refer the reader to the "current version of the IB" instead of version 3.
7.2 Identity of study treatment	Vial size was corrected from 2 mL to 10 mL. The contents of the 150 mg/mL vial were corrected from 1.6 mL to 1.8 mL of BAY 1093884.
9.2.1.11 Additional safety visits after dose escalation (if applicable)	The ECG erroneously omitted in amendment 4 was added to the description of the additional safety visit.
9.2.2.9 Phone call (3 weeks ± 2 days after Visit 5)	The time window of the phone call at Week 9 was corrected from ±1 day to ±2 days.
9.6.3.1 Clinical laboratory assessments	The unit of measure for FVIII/FIX testing was corrected from BU to BU/mL.

Typographical, grammatical, and other minor edits are not identified.

15.2.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

16. Appendices

16.1 Hemophilia Joint Health Score

Subject ID #:_____ **Name of Physiotherapist:**_____

Assessment # : _____ **Date:** _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals _____

+

Global Gait Score _____

(☐ NE included in Gait items)

NE = Non-Evaluable

HJHS Total Score **=** _____

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Extension loss
(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11°- 20°
3 = > 20°

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____

_____

_____

_____

The HJHS is designed for use by physiotherapists. In order to maintain the precision and validity of the tool (score), the developers of the tool strongly recommend that the tool be used by physiotherapists/healthcare professionals who have hemophilia-related expertise/experience and have been trained in the use of clinical measures, musculoskeletal assessment and specifically administration of the HJHS.

It is essential for the physiotherapist to possess the required expertise and skills necessary to use anthropometric measures such as muscle testing and range of motion /goniometry, as well as posture & gait assessment prior to performing the evaluation (HJHS).