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A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe haemophilia A under prophylaxis therapy

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

- **Original protocol**, Version 1.4, dated 20 SEP 2010
- **Amendment 01** (described in Section 13.1)
  forming integrated protocol Version 2.0, dated 31 MAR 2011
- **Amendment 03** (described in Section 13.2)
  forming integrated protocol Version 3.0, dated 03 SEP 2012
- **Amendment 04** (described in Section 13.3)
  forming integrated protocol Version 4.0, dated 08 APR 2014
- **Amendment 06** (described in Section 13.4)
  forming integrated protocol Version 5.0, dated 19 FEB 2016
- **Amendment 07** (described in Section 13.5)
  forming integrated protocol Version 6.0, dated 30 MAY 2017
- **Amendment 08** (described in section 13.6)
  forming integrated protocol version 7.0, dated 31 JAN 2019

Amendments not included in the consecutive numbering of amendments are local amendments which are not part of this integrated global protocol.

Title page

Study title

A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe haemophilia A under prophylaxis therapy

Short title: BAY 81-8973 pediatric safety and efficacy trial

Test drug:	BAY 81-8973 / octocog alfa		
Study purpose:	Safety and efficacy		
Clinical study phase:	III	Date:	**01 FEB 2019**
EudraCT no.:	2010-021781-29	Version no.:	**7.0**
Study no.:	BAY 81-8973 / 13400		

Sponsor:

Non-US territory: Bayer AG, D-51368 Leverkusen, Germany
US territory: Bayer HealthCare Pharmaceuticals Inc.,
100 Bayer Boulevard, P.O. Box 915,
Whippany NJ 07981-0915, US *(as of Amd 7)*

Sponsor's medical expert:

PPD

Bayer
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Tel: PPD

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 integrated clinical study protocol as presented.

Name: PPD
(*as of Amd 6*)

Role: Global Clinical Leader (GCL)
(*as of Amd 7*)

Date: 4th February 2019

Signature: PPD

Signature of the investigator

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

Name:

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

Synopsis

Title	A multicenter Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy
Short title	BAY 81-8973 pediatric safety and efficacy trial
Clinical study phase	III
Study objective(s)	**Primary objective** • To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A **Secondary objectives** • To assess the ***safety and efficacy (as of Amendment 1 [Amd 1])*** of BAY 81-8973 during surgeries • To assess incremental recovery ***of BAY 81-8973 (as of Amd 1)*** • To characterize pharmacokinetics in a subset of ***a minimum of 6*** previously treated patients (PTPs), ***previously untreated patients (PUPs), or Minimally Treated Patients (MTPs)*** (***as of Amd 6***) if parents' consent (participation for pharmacokinetic (PK) sampling is optional). ***(as of Amd 3)***
Test drug(s)	BAY 81-8973
Name of active ingredient	Octocog alfa; full-length, unmodified plasma protein-free, recombinant factor VIII (rFVIII)
Dose(s)	***Part A:*** *PTPs:* 25 -50 International Units (IU)/kilogram (kg) *(rounded to nearest size vial)*; prophylaxis with at least 2 *infusions* per week *and treatment for breakthrough bleeds (as of Amd 1)* ***Part B:*** ***PUPs/MTPs 15-50 IU/kg; prophylaxis with at least 1 infusion per week and treatment for bleeds (as of Amds 1 and 6)***
Route of administration	Intravenous
Duration of treatment	6 months ***and/or*** >50 exposure days (ED). ***(as of Amd 1)*** Optional extension study ***for at least 100 cumulative ED)***
Reference drug(s)	None
Indication	Hemophilia A
Diagnosis and main criteria for inclusion	Severe hemophilia A (< 1% Factor VIII concentration [FVIII:C]), ***Part A: male,*** age 0-12 years, ***≥ 50 ED (as of Amd 1),*** no inhibitor history, no other bleeding disorder ***Part B: male, PUPs, no prior exposure to factor VIII (FVIII) concentrate (as of Amds 1 and 6) or MTPs who do not have more than 3 EDs with any FVIII concentrate and no current evidence of inhibitor antibody (as of Amd 6)***
Study design	Multicenter, open label, single treatment arm, uncontrolled

Methodology	***Part A (as of Amd 1):*** The study consists of 6-months *of treatment in PTPs with BAY 81-8973 for prophylaxis and* treatment *of breakthrough bleeding events to achieve at least* 50 ED. *All subjects will be evaluated for inhibitor development and incremental recovery at Baseline*, Months 1, 2, and 6. *Enrollment in the study will be staggered, with subjects age 6-12 years entering first, followed by subjects <6 years. (as of Amd 3)* ***Part B (as of Amds 1 and 6):*** ***PUPs/MTPs will be treated with BAY 81-8973 for all bleeding events and are required to start prophylaxis. Treatment will continue until at least 50 ED. Screening and baseline visits may be combined for PUPs.*** ***Subjects will be tested for inhibitors every 3-5 ED up to 20 ED and again at 50 ED. Incremental recovery will be measured at Baseline, 20 ED, and 50 ED.*** ***Pharmacokinetics (PK) samples will be collected in a subset of subjects at pre-infusion and then 20-30 minutes, 4 hours (h), and 24 h post infusion.*** ***Participation in the PK portion of the study is voluntary and requires specific consent. (as of Amd 1)*** ***In both Part A and Part B, all infusions and bleeding events will be documented in an electronic patient diary (EPD) throughout the study. (as of Amd 1)*** ***<u>Optional extension study (as of Amd 1):</u>*** ***Subjects in both Part A and B will be offered participation in an optional extension study to continue treatment with BAY 81-8973, to accumulate at least 100 ED. During the extension study, visits to the treatment center will take place every 6 months. (as of Amds 1 and 6)*** The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.
Type of control	None
Number of subjects	***Part A:*** ***Total Number (N) = 50 PTPs*** ***age group 6-12 years: N=25*** ***age group <6 years: N=25*** ***Part B:*** ***N= at least 25 PUPs, plus approximately an additional 25 PUPs/MTPs (as of Amds 3, 6 and 7)*** ***age group <6 years*** ***Total = approximately 100 (includes both Part A and B) (as of Amds 1, 3 and 7)***
Primary variable	Response to treatment in relation to number of bleeding events and response to treatment of bleeds
Plan for statistical analysis	Descriptive statistics

Protocol Amendment Summary of Changes Table

The changes in this table have been implemented as part of global amendment 8.

Section number and name	Description of change	Brief rationale
Title page Section 3 Investigators and other study participants	Medical Expert contact information update	Contact information for Medical expert has been updated
Synopsis Section 5.1.1 Inclusion criteria	Change in the definition of MTP from 3 injections to 3 Exposure days	Clarification that MTPs do not have more than 3 EDs with any FVIII concentrate, as number of injections and exposure days are not necessarily identical.
Section 4 study design	Addition that screening can continue whilst first cohort completes 20 ED	Protocol Amd 7 introduced a staggered enrollment and treatment approach to limit the entry of patients into the study until safety data related to inhibitor development during the first 20 EDs could be assessed in the next 10 subjects treated (first cohort). Safety evaluation of the first 5 patients in this first cohort shows that inhibitor development is within the expected range. The intention of this change in Amd 8 is to allow identification and screening of subjects while the safety evaluation in the first cohort of 10 subjects is completed. Amd 8 also clarifies that patients may receive treatment other than BAY 81-8973 during the screening interval if medically indicated. If there are no safety concerns identified in the first cohort the patients may start treatment with study drug provided they still meet the protocol definition of MTP. Screening therefore can continue to ensure continued enrollment in the study.
Section 4 Study design Section 6.1.1 Regular	Participation in the extension study is continued only until 100 ED are reached.	Kovaltry is now marketed, and therefore the extension study is offered until 100 ED and not until marketing authorization.

Section number and name	Description of change	Brief rationale
prophylaxis Section 6.8 Post-study therapy Section 7.1.1 Tabulated overview Section 7.1.2 Timing of assessments Section 7.1.2.10 Extension – final visit		
Section 6.1.5 Immune tolerance induction	Immune tolerance induction should be continued until the inhibitor is eradicated successfully, or until failure, for approximately 18 months. Treatment beyond 18 months requires approval from the sponsor and the coordinating investigator.	In accordance with the recommendation of the data monitoring committee, in cases where subjects have a clinical response with ITI, if deemed clinically necessary, ITI can be continued beyond 18 months following discussion with the sponsor and coordinating investigator.
Section 8.5 Planned interim analyses	An additional analysis that will be performed when all PUPs/MTPs have completed part B was added.	An additional analysis was added for when all PUPs/MTPs have completed part B.

In addition, editorial and administrative changes have been made throughout the document.

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase (also known as SGPT, *qv*)
Amd 1	***Amendment 1 (as of Amd 1)***
Amd 3	***Amendment 3 (as of Amd 3)***
Amd 4	***Amendment 4 (as of Amd 4)***
Amd 6	***Amendment 6 (as of Amd 6)***
Amd 7	***Amendment 7 (as of Amd 7)***
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase (also known as SGOT, qv)
AUC	Area under the curve
BMI	Body mass index
BU	Bethesda Unit
°C	Degrees centigrade
Ca	Calcium
CBC	Complete blood count
CHMP/BPWP	Committee for Medicinal Products for Human Use/Blood Products Working Party
Cl	Chloride
CL	Clearance
Cmax	Maximum concentration
CO	Bicarbonate
CPMP/BPWG	Committee for Proprietary Medicinal Products/Blood Products Working Group
CRF	Case Report Form (either paper or electronic)
CRO	Clinical research organization
CSP	Clinical Study Protocol
DD	Day
dL	Deciliter
DMC	Data Monitoring Committee ***(as of Amd 1)***
EC	Ethics Committee
ECG	Electrocardiogram
ED	Exposure day(s)
eg	*Exempli gratia*, for example
EMA/PDCO	European Medicines Agency/Paediatric Committee
EMEA	European Agency for the Evaluation of Medicinal Products
ePRO	Electronic patient reported outcome
EP USP	European and US Pharmacopeia
EPD	Electronic ***Patient*** Diary ***(as of Amd 1)***
EU	European Union
FDA	Food and Drug Administration
FVIII	Human coagulation factor VIII
FVIII:C	Factor VIII concentration

FIX	Factor nine
GCL	Global Clinical Leader
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HSP-70	Heat Shock Protein 70
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICU	Intensive care unit
lbs	Pounds
i.e.	*Id est,* that is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITI	Immune Tolerance Induction
ITT	Intent-to-treat
IU	International Units
IV	Intravenous
IVIG	Intravenous Immunoglobulin
IVRS	Interactive voice randomization system
h	Hour
HLA	Human leukocyte antigen
K	Potassium
kg	Kilogram
Kogenate FS	Kogenate Formulated with Sucrose
X-linked	A gene on the X chromosome
LDH	Lactate dehydrogenase
LETE	Less than expected therapeutic effect
MD	Medical Director/Doctor
MedDRA	Medical Dictionary for Regulatory Affairs
min	Minute
mL	Milliliter
MM	Month
mm^3	Cubic millimeter
MRT	Mean Residence Time
MTP	Minimally treated patient, ≤3ED *(as of Amd 6)*
N	Number
Na	Sodium
NC	North Carolina
NSAIDs	Non-steroidal anti-inflammatory drugs
PICU	Pediatric intensive care unit
PID	Patient identification
PK	Pharmacokinetic
PTP	Previously treated patient
PUP	Previously untreated patient
QA	Quality assurance

RAVE	Data base for electronic case report ***form (as of Amd 1)***
rFVIII	Recombinant factor VIII
SAE	Serious Adverse Event
SE	Sweden
SNP	***Single nucleotide polymorphisms (as of Amd 4)***
SPM	Study Procedure Manual
SUSAR	***Serious*** unexpected ***suspected*** adverse reaction ***(as of Amd 1)***
$t_{1/2}$	Half-life
TOSCA	Toolbox for System Configuration and Administration
USA	United States of America
YYYY	Year
WHO	World Health Organization

1. Introduction

Background

Hemophilia A is an X-linked (gene on the X Chromosome) congenital bleeding disorder with a frequency of 1 in 10,000 births caused by a deficiency of functional coagulation factor VIII (FVIII). Individuals with severe hemophilia A (<1% functional FVIII) experience frequent bleedings and recurrent spontaneous bleeds into the soft tissue and joints, leading to joint damage and severe disability with major effects on physical, psychosocial, quality of life, and financial condition of the hemophilia subjects. Many studies have shown that, even at high doses, on-demand therapy is not effective in preventing arthropathy[1, 2] Observations that subjects with moderate hemophilia (FVIII >0.01-0.05 IU/milliliter [mL]) rarely develop chronic arthropathy are the rationale for prophylactic treatment of severe hemophilia[3]. Based on these observations, there is a widely accepted hypothesis that maintaining the factor VIII activity above 1% with prophylactic therapy may prevent bleeding and ultimately arthropathy in subjects with severe hemophilia. This observation was shown by the Swedish[4-6], British[7], and German[8] observational studies, as well as the international orthopedic outcome study[2] and the comparison of different treatment regimens in France, The Netherlands, and Sweden[9]. The advantage of prophylactic therapy was further confirmed by a prospective, randomized controlled study that compared the joint outcome between on-demand and prophylactic regimen in young children. The data confirmed that children on prophylaxis had significant less joint damage than on-demand treated children at the age of 6 years[10].

Recombinant coagulation Factor VIII (rFVIII) is a mainstay in the treatment of subjects with hemophilia A. Bayer HealthCare has produced two rFVIII products, KOGENATE® (introduced in 1993) and its sucrose-formulated successor Kogenate® FS (KOGENATE® Bayer in Europe), which together have an excellent safety and efficacy profile demonstrated in clinical trials and in the normal clinical setting.[11-14] In the 20 years since clinical testing for these products began, more than 8 billion IU have been infused.

Recombinant FVIII is one of the largest and most complicated human therapeutic proteins manufactured. In the last 2 decades, major advances in production techniques have included the development of large-scale continuous perfusion fermentation technology and an assay to evaluate the presence of blood-borne prion pathogens. More recently, Bayer has implemented advances in biological manufacturing that have simplified the process and have achieved a more consistent rFVIII product.

Enhancement of the viability of the expression cell line during fermentation through co-expression of the human heat-shock protein 70 (HSP-70) has permitted the generation of an improved rFVIII manufacturing process for BAY 81-8973[15]. HSP-70 has the dual effect of inhibiting apoptosis, and thereby the release of intracellular proteases that could damage FVIII molecules, and serving as a chaperone molecule that increases the proper folding of the FVIII protein, thereby reducing protein aggregation.

Other significant changes to rFVIII manufacturing have been introduced. ***BAY 81-8973 has the same amino acid composition as Kogenate® FS/Bayer. (as of Amendment 1 [Amd 1])*** Compared to its predecessors, BAY 81-8973 has more complete sialic acid capping of N-

terminal glycan groups on the molecular surface, a post-translational modification step that is critical to the activity and stability of some mammalian proteins. Although pathogen contamination of a recombinant protein product is a theoretical possibility, the BAY 81-8973 purification process achieves a greater level of viral clearance than the current process through the addition of a new viral filtration step. Overall, the complexity of the rFVIII manufacturing process has been substantially simplified for BAY 81-8973 compared to its predecessor products. This allows for a faster production time that may also reduce the buildup of aggregation and breakdown products, which may be linked to suboptimal yields of rFVIII products. In addition, any human or animal additives have been eliminated from the fermentation process. The result of the technological innovations implemented for BAY 81-8973 is the production of a full-length unmodified rFVIII product that more consistently reflects the conformation and glycan structure of the native human FVIII protein

Based on PK data from 26 subjects who received a single 50 IU/Kg dose of BAY 81-8973 and Kogenate FS (Kogenate formulated with Sucrose) in a cross over fashion, it has been demonstrated that BAY 81-8973 is non-inferior to Kogenate® FS/Bayer. (as of Amd 1)

Rationale of the study

The study is planned to demonstrate safety and efficacy of BAY 81-8973 for prophylaxis therapy and treatment of breakthrough bleeds in children with severe hemophilia A.

The overall clinical program consist***s*** of 3 safety and efficacy studies, one study in subjects ≥ 12 years of age (adults and adolescents) including two pharmacokinetic evaluations (baseline and month 6), one study in adults and adolescents ≥ 12 years of age comparing on-demand and prophylaxis treatment, and the present study in children from 0-12 years. The first study in adults and adolescents is ongoing ***and has completed enrollment***. ***(as of Amd 1)*** The comparative pharmacokinetic study of BAY 81-8973 and Kogenate FS/Bayer has been completed and non-inferiority to the licensed product Kogenate FS/Bayer was demonstrated. ***The demonstration of safety in at least 20 adolescents and adults who received a minimum of 50 ED was a necessary requirement to open this study to enrollment of children 12 years of age and younger. (as of Amd 1)***

Benefit-risk assessment

The investigational product is an unmodified recombinant human FVIII produced by a well characterized cell line and similar to the predecessor product with an excellent safety and efficacy profile based on 20 years clinical experience.

All subjects will receive a replacement therapy at the highest level of standard of care. For previously untreated patients (PUPs), ***and minimally treated patients (MTPs) (as of Amendment 6 [Amd 6])***, there is a well-known risk for inhibitor development during the first 20 exposure days (ED) with any FVIII product which decreases with increasing exposure.

Further details can be found in the Investigator's Brochure, which contains comprehensive information on the study drug.

2. Study objectives

Primary objective

The primary objective is to evaluate the safety and efficacy of the treatment with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeds in children with ***severe (as of Amd 1)*** hemophilia A.

Secondary objectives

The secondary objectives are

- To assess the ***safety and efficacy (as of Amd 1)*** of BAY 81-8973 during surgeries.
- To assess incremental recovery ***of BAY 81-8973***. ***(as of Amd 1)***
- To assess pharmacokinetic parameters in a subset of children. (***PTPs and PUPs/MTPs -participation in pharmacokinetic [PK] sampling is voluntary and requires consent***). ***(as of Amds 1, 3 and 6)***

3. Investigators and other study participants

Sponsor's Medical Expert

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Coordinating Investigator for the Study

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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.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments/integrated

protocols must be signed and dated by the principal investigator before coming into 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 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.

4. Study design

Design overview

This is a phase-III multicenter, open-label uncontrolled study to demonstrate safety and efficacy of treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds, and surgeries in children with severe hemophilia A. The study will be conducted worldwide.

The study is divided into two parts: Part A will investigate a total of 50 PTPs up to 12 years of age. Part B will include at least 25 PUPs, plus up to additional 25 PUPs/MTPs (as of Amd 6). All subjects will receive prophylactic administration of BAY 81-8973. Subjects in Part A will be treated with 25-50 IU/kg at least 2 times per week, or more frequently as needed for prophylaxis.

Treatment in Part B may begin with start of prophylaxis with 15-50 IU/kg (minimum dose 250 IU) at least one day a week, or with the subject's first bleeding event. The study drug will be used both for treatment of bleeding events and prevention of bleeds and with surgical procedures. Individual subject dose decisions are at the discretion of the investigator. (as of Amds 1 and 3)

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns ***in previous studies with BAY 81-8973***. PTPs age ***6 to 12 years*** will begin enrollment first, followed by PTPs ***<6 years (as of Amd 3).*** Part B, for PUPs***/MTPs*** (***as of Amd 6***) will begin enrollment after 20 children in Part A have had 50 ED. ***As of Amd 7, enrollment in Part B will be staggered. 10 patients will be enrolled, and will commence treatment for 20 ED.*** While safety assessment of the first cohort is ongoing, screening for the next sequence of 10 patients will continue. Treatment of next sequence/10 patients will start if no safety concerns are identified in the previous cohort following completion of 20 EDs. In the event patients would require FVIII treatment, they could still be eligible according to protocol definitions in case no more than 3 EDs of an alternative FVIII product has been administered.

Enrollment will be suspended if the inhibitor rate in the first cohort exceeds 50% following discussion with an independent Data Monitoring Committee (DMC). (as of Amd 7)

The total study duration (including screening period) per subject ***in Part A (as of Amd 1)*** will be approximately 6***-8*** months ***(as of Amd 1)*** during which the subjects will accumulate at least 50 ED. ***For Part B, subjects will continue in the study until achieving 50 ED.***

Consequently the duration will vary depending upon the frequency of prophylactic infusion and number of bleeding events.

All subjects ***in both Parts A and B (as of Amd 1)*** will be offered participation in an open-label extension study for ***an additional*** 6-12 months ***to allow observations for (as of Amd 1)*** at least 100 ED. In countries where BAY 81-8973 is marketed under the proprietary name Kovaltry, the option to transition to marketed drug after completion of part B (50EDs) is possible. ***Enrollment of PUPs/MTPs (as of Amd 6) in Part B and the extension study may continue after Part A and the extension study for PTPs have been completed. (as of Amd 1)***

During the study, all subjects will receive treatment only with BAY 81-8973 ***for prophylaxis and treatment of bleeds. In Part A, the (as of Amd 1)*** dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. In Part B, PUPs***/MTPs*** (***as of Amd 6***) may start at a lower ***dose at (as of Amd 1)*** once per week schedule at the investigator's discretion. ***(as of Amd 1)***

The dosing for breakthrough bleeds will be dependent upon the bleeding location ***and*** severity, and will be consistent with ***local (as of Amd 1)*** standards of care. Bleeding and ***treatment (as of Amd 1)*** information will be collected using an electronic ***patient (as of Amd 1)*** diary (EPD), which will be provided to the parents/caregivers. ***(as of Amd 1)***

Incremental recovery and trough levels of BAY 81-8973 will be assessed in all subjects. Suitable subjects will be given the opportunity to participate in the pharmacokinetic (PK) evaluation (as of Amd 3). Participation is optional, and requires consent. PK parameters (maximum concentration [C_{max}], half-life, area under curve [AUC], Mean Residence Time [MRT] and clearance) may be assessed using a sparse sampling schedule.

In the event that any subject acquires an inhibitor to FVIII, Immune Tolerance Induction (ITI) will be offered. The subject may receive BAY 81-8973 up to 200 IU/kg daily or 100 IU/kg twice a day for 18 months. Treatment will be at the discretion of the treating physician, although the detailed treatment plan should be agreed with the Coordinating Investigator (as of Amd 7). Subject commences on ITI therapy will be followed up within the extension study. Data on treatment, FVIII measurements, and inhibitor levels will be collected. (as of Amds 1 and 6)

Primary variable

Annualized number of total bleeds (sum of spontaneous bleeds and trauma bleeds) within 48 hours (h) after a prophylactic infusion. (as of Amd 1)

Justification of the design

The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99 and taking into account the revised draft version of this guideline CHMP/BPWP/144533/09[16] (Committee for Proprietary Medicinal Products/Blood Products

Working Group; Committee for Medicinal Products for Human Use/Blood Products Working Party).

End of study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject (including subjects in the extension study) for all centers in the respective country has occurred.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

The primary completion date for this study according to the Food and Drug Administration (FDA) Amendment Act is specified in a separate document (not part of this Clinical Study Protocol [CSP]).

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

In order to be included in the study, subjects must ***have (as of Amd 1)*** all of the following criteria upon evaluation at the Screening or Baseline visit:

Part A (as of Amd 1)

1. Male, age ≤ 12 years. ***Enrollment will begin with subjects 6-12 years before it is opened to all age groups. (as of Amd 1, Amd 3)***
2. Severe hemophilia A defined as < 1% FVIII concentration (FVIII:C) based on ***documented prior testing (as of Amd 1) or*** screening laboratory (***Amd 3***)
3. ≧ 50 ED with any FVIII ***concentrate (as of Amd 1, Amd 3)***
4. No current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU)/mL] within 2-3 week***s of*** last ***FVIII (as of Amd 1)*** administration. ***PTPs (as of Amd 1)*** may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing ***at the Screening visit***. ***(as of Amd 1)***
5. No history of FVIII inhibitor formation. Documentation of negative result in medical records required. [Subjects with a maximum historical titer of 1.0 BU on no more than 1 occasion with the classical Bethesda assay but at least 3 successive negative (<0.6 BU) results thereafter are eligible.]
6. Willingness and ability of subjects and/or parents to complete training in the use of the electronic patient diary (EPD) and to document ***infusions (as of Amd 1)*** during the study.
7. Written informed consent by parent/legal representative. Assent should be sought from subjects if appropriate

- **Part B (PUPs*/MTPs*):** *Enrollment **s*** may start after *safety is evaluated in 20* children *in Part A with* 50 ED ***(as of Amds 1 and 6)***.

1. Male, <6 ***years (as of Amd 3)***

2. Severe hemophilia A defined as < 1% FVIII:C based on ***prior documented testing or confirmed on (as of Amd 1, Amd 3) screening*** laboratory

3a. PUPs: No previous exposure to any FVIII ***product (as of Amd 1)***

3b. MTPs: Have no more than 3 EDs with any FVIII product and who have no current evidence of inhibitor antibody measured centrally using the Nijmegen-modified Bethesda assay [<0.2 Bethesda units (BU)/mL] at screening, with confirmation using local laboratory testing at baseline (<0.6 Bethesda unit [BU/mL]) (as of Amd 7). MTPs may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing at the Screening and Baseline visits. (as of Amd 6 and Amd 7)

3c. MTPs: No history of FVIII inhibitor formation. (as of Amd 6)

4. PUPs may be included if they will receive their first FVIII dose ***with BAY 81-8973 for treatment of first bleeds and agree to start*** prophylaxis ***as part of their care. (as of Amd 1). MTPs may be included if they agree to start prophylaxis as part of their care (as of Amd 6)***

5. Willingness and ability of parents to complete training in the use of the EPD and to document all treatment during the study. (as of Amd 1)

6. Written informed consent by parent/legal representative. (as of Amd 1).

5.1.2 Exclusion criteria

Subjects who meet any of the following criteria at Screening or Baseline visits will be excluded from participating in the study:

Parts A and B

1. Any individual with another bleeding ***disorder (as of Amd 1)*** that is different from Hemophilia A (eg, von Willebrand disease, Hemophilia B)
2. Any individual with thrombocytopenia (platelet count < 100 000/mm^3)
3. ***Creatinine > 2x upper limit of normal or Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) > 5x upper limit of normal (as of Amd 1)***
4. Any individual without ***a*** negative inhibitor testing ***at screening*** (except for PUPs) ***(as of Amd 3)***
5. Any individual who is receiving ***chemotherapy, immune modulatory drugs (Intravenous immunoglobulin [IVIG], cyclosporine, chronic use of oral or i.v. corticosteroids), has received another investigational FVIII product*** within the last month, or received another experimental drug within ***the last*** 3 months. (***as of Amd 1, Amd 3***)
6. Any individual who requires any pre-medication to tolerate FVIII ***treatment (as of Amd 1)*** (eg, antihistamines)

7. Any individual who is unwilling to comply with study visits or other protocol requirements, for example (eg. prophylaxis treatment) or is not suitable for participation in this study for any reason, according to the Investigator***'s judgment***. ***(as of Amd 1)***
8. Known hypersensitivity to active substance, mouse, or hamster protein.
9. Previous participation in this study

Part B only ***(PUPs/MTPs [as of Amd 6])***:

10. First treatment with BAY 81-8973 ***for high risk bleeding situations (eg, surgery, intracranial bleed), or requiring intensive or prolonged treatment***. ***(as of Amd 1)***
11. ***Unable to tolerate volume of blood draws required for study participation (See Section 14.4). (as of Amd 1)***

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

Subjects *must* be withdrawn from the study for ***any of the (as of Amd 1)*** following reasons:

- At their own request or at the request of their ***parent/***legal representative ***(as of Amd 1)***
- At any time during the study and without giving reasons a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- A positive inhibitor result at Screening or Baseline ***visits (as of Amd 1). Evidence of inhibitor formation in MTPs prior to starting treatment with study drug (defined as ≥0.2 BU/mL by central laboratory testing at screening, and/or ≥0.6 BU/mL by local laboratory testing at baseline) (as of Amd 7).***

(Some text deleted as of Amd 1)

- At the request of the sponsor
- If, in the judgment of the investigator or the sponsor, the subject is not compliant with the protocol.

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

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

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

Details for the premature termination of the study as a whole (or components thereof, eg, centers) are provided in Section 10.

5.2.2 Replacement

Subjects who are withdrawn after start of treatment will not be replaced. Subjects who are withdrawn due to ***failure to meet screening criteria, or who have (as of Amd 1)*** a positive inhibitor result at screening/baseline will be replaced.

5.3 Subject identification

Subjects will be identified by a unique patient identification (PID) number with 9 digits. The first 5 digits will identify the country and study site, the last 4 digits are assigned to the subject of the specific site in increasing order.

6. Treatments

6.1 Treatments to be administered

6.1.1 Regular prophylaxis

Test drug: BAY 81-8973

Dosage: 25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, ***15-50 International Unit (IU)/kg;*** ≥ 1 ***time*** per week in PUPs***/MTPs***. ***(as of Amds 1 and 6). Recommendations for starting prophylaxis in PUPs/MTPs are described below. (as of Amd 7)***

(Smallest size vial is 250 IU, which may be used for initial treatment of PUPs/MTPs of any weight) (as of Amds 1 and 6)

Route of administration: Manual intravenous (IV) ***infusion*** over 1 – ***15 minutes (as of Amd 4)*** according to total volume ***(as of Amd 1)***

Note: PTPs will continue their previous treatment up to 48 h before the first dose of BAY 81-8973 (as of Amd 3).

Duration: ***Part A:*** 6 months ***and*** at least 50 ED

Part B: 50 ED

Extension study: at least 100 cumulative ED in subjects participating in the optional extension study

(Enrollment of PUPs/MTPs may continue after PTPs have completed participation in Part A and the extension study) (as of Amds 1 and 6)

Effective prophylaxis requires replacement therapy in order to maintain FVIII ***activity*** in ***the blood*** above 1%. Based on the kinetics***, optimal prophylactic treatment requires infusion at least*** 3 ***times a*** week. ***As*** FVIII clearance is higher in children than in adults, the ***optimal infusion*** schedule for children ***may require treatment as frequently as*** every other day. Frequent injections may be difficult for small children and their ***caregivers. Consequently,*** the benefit ***for each individual child*** must be evaluated against ***this*** burden, ***particularly in very young children for whom venous access may be difficult***. ***(as of Amd 1)***

Recent studies have demonstrated that the timing of the first exposures ***to FVIII*** may be critical for the tolerance of the drug. The CANAL study showed that ***early intensive treatment such as that required for surgery or*** severe bleeds increased the risk for inhibitor development, whereas ***regular*** prophylaxis ***was associated with a lower*** risk [(17)]. This observation was ***subsequently supported by studies demonstrating lower inhibitor rates in boys treated with low dose early prophylaxis in*** treatment centers in Germany [(18)]. ***(as of Amd 1)***

Taking into account these observations, the following is recommended ***for PUPs/MTPs participating in Part B (as of Amds 1 and 6):***

Treatment recommendations (as of Amd 7)

- ***Treatment can be initiated with an on-demand regimen. Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion. (as of Amd 1 and 6)***
- ***Alternatively, prophylaxis can be started directly*** with a once-a-week schedule low dose of 250 IU (15-25 IU/kg)***; the starting dose may be tailored to the subject's weight or demonstrated bleeding tendency. (as of Amd 1 and 6)***
- Increase frequency ***of infusion or dose as needed for breakthrough bleeding, increased*** physical activity, ***or weight gain. (as of Amd 1)***
- ***Avoid starting prophylaxis during febrile illness or other identified inflammatory events. (as of Amd 1)***
- ***Avoid surgery or need for high dose intensive treatment lasting more than 4 days during the first 20 ED. (as of Amd 1)***
- ***Do not give FVIII as prophylaxis for vaccinations. (as of Amd 1)***

After treatment with BAY 81-8973 begins (as of Amd 1), inhibitor testing every 3-5 ED ***is required (as of Amd 1)*** until 20 ED are accumulated or in case of non-response to treatment ***(Section 14.5) (as of Amd 1)***

6.1.2 Breakthrough bleeds and surgeries

BAY 81-8973 will be used for the treatment of breakthrough bleeds. The dosage will be at the discretion of the investigator. ***For PUPs/MTPs in Part B, see Section 6.1.1. (as of Amds 1 and 6)***

For any surgery that may occur during the course of the study, BAY 81-8973 should be used. During surgery *(both major and minor)* dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide varying instructions based upon the type of surgical procedure to be undertaken. ***For PUPs /MTPs in Part B (as of Amds 1 and 6),*** surgery is not allowed as first treatment ***and should be avoided, when possible, during the first 20 ED. (as of Amd 1)***

If the study site routinely takes pharmacokinetic (PK) measurements prior to surgical procedures, these results may be used to fulfill the optional PK, provided that consent is given in advance, the subject undergoes a 48 hour washout, sampling is obtained at the designated time points, and samples are sent to the central laboratory for evaluation. (as of Amds 1 and 3)

In case of severe or potentially life threatening bleeding events, or the need for unplanned or emergency surgery, the subject should be managed following local standard of care, using readily available factor products. (as of Amd 1)

6.1.3 Missed infusions due to difficult venous access or family travel

During the trial, it is expected that all reasonable attempts will be made to ensure that subjects will comply with and adhere to their designated prophylaxis infusion schedule with few interruptions. However, there may be situations when problems related to difficult venous access, or travel to locations where appropriate support for infusions is not available, may necessitate a brief hiatus in the treatment schedule. Parents should inform the investigator of all such situations, and the reason documented in the medical record. Prolonged or repeated breaks in the prophylaxis schedule should be avoided, and could result in the subject being removed from the study. (as of Amd 1)

6.1.4 Optional pharmacokinetic measurements

Test drug: BAY 81-8973

Dosage: 50 IU/kg as a single IV ***infusion***, at least 48 h after any previous ***treatment with*** FVIII. ***(as of Amd 1)***

Suitable subjects will be given the opportunity to participate in the PK sub-study, either during the main study, or during the extension period (as of Amd 3).

6.1.5 Immune tolerance induction

If a subject develops an inhibitor, ITI should be considered. ***Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with***

a decreased recovery (as of Amd 3). Subject commences on ITI therapy will be followed up within the extension study. All treatments, FVIII measurements, and inhibitor levels will be documented. (as of Amds 1 and 6).

Test drug: BAY 81-8973

Dosage: ***Up to*** 200 IU/kg per day as initial dose, either once a day ***or*** 100 IU/kg ***twice a day*** at the investigator's discretion until the inhibitor is eradicated successfully, or until failure, for approximately 18 months. Treatment beyond 18 months requires approval from the sponsor and the coordinating investigator. ***The detailed treatment plan should be agreed with the Coordinating Investigator. (as of Amd 1) Details on ITI therapy should be documented. Technical guidance on how to document this information will be provided in the study manual. (as of Amd 4)***

The following criteria are applied for success:

1. no detectable inhibitor based on Nijmegen assay (< 0.6 BU)
2. normal recovery (> 66% of predicted)
3. normal half-life (≥ 6 h)

Failure is defined as no response (< 20% decrease in the inhibitor level) within a 6 months period in the absence of any infection. ***(some text deleted as of Amd 1)***

6.2 Identity of Investigational Medicinal Product

6.2.1 Manufacture

The study drug, BAY 81-8973 is a rFVIII product (formulated in sucrose) containing full length unmodified rFVIII protein.

The BAY 81-8973 manufacturing process has been significantly improved from the current Kogenate® FS/Bayer manufacturing process. Key BAY 81-8973 manufacturing improvements include: removal of all human and animal derived raw materials from the cell culture fermentation and purification process, introduction of a new higher producing cell bank, new isolation technology, an optimized and simplified purification process, and the addition of a robust viral nanofiltration step.

The rFVIII molecule itself is comparable to the current Kogenate® FS/Bayer molecule, with some overall differences, such as reduced high molecular weight proteins. The molecule is highly glycosylated, with increased levels of highly branched glycans and more consistently high sialylation of terminal galactose residues. For further details see Investigator Brochure. ***(some text deleted as of Amd 1)***

The rFVIII is stabilized in a final formulation using sodium chloride, calcium chloride, histidine, glycine, sucrose, and polysorbate-80. The product contains no preservatives.

6.2.2 Supply and Packaging

BAY 81-8973 will be supplied lyophilized in glass vials. Study vials may contain 250 IU, 500 IU or 1000 IU of FVIII activity. The nominal potency of the drug, *as determined by chromogenic assay,* will be indicated on the labels of each vial unit pack. The medication is manufactured at Bayer HealthCare in Berkeley, California, United States. The vials of BAY 81-8973 will be packaged together with a pre-filled syringe of the appropriate amount of sterile water for injection, European and US Pharmacopeia (EP) (USP), for reconstitution. For BAY 81-8973, the volume of the solvent is 2.5 mL for all vial sizes. The BAY 81-8973 vials will also be supplied with the following medical devices to facilitate the ***treatment (as of Amd 1)***: infusion set with filter and needle protection, plunger rod, and 10 mL sterile syringe.

For preparing reconstitution, BAY 81-8973 will be provided in either of two presentations:

1. ***Vial with BIO-SET reconstitution cap: See Section 14.1.1 for Instructions for Use. Before infusion, the product should be filtered using the infusion set provided or another approved filtration device (as of Amds 3 and 6).***
2. ***Vial and vial adapter: (see section 14.1.2 for Instructions for Use). (as of Amd 6).***

6.2.3 Labeling

Each vial will be labeled with the nominal amount of FVIII activity in International Units (IU) based on chromogenic assay determination according to EU Pharmacopeia. One IU, as defined by the World Health Organization (WHO) Standard for Blood Coagulation Factor VIII, human, is approximately equal to the level of FVIII activity found in 1.0 mL of fresh pooled human plasma.

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 ware 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 study file.

6.2.4 Storage

BAY 81-8973 must be stored under refrigeration (2°C to 8°C). Freezing should be avoided. Reconstituted concentrate must be infused immediately after reconstitution.

Parents/caregivers will be provided with detailed instructions for proper storage of the study medication.

6.2.5 Instructions for Administration

Before reconstitution of rFVIII, allow the water for injection to reach room temperature, then reconstitute the study drug and administer immediately. Once reconstituted, the preparation

should not be refrigerated or frozen. Detailed information about reconstitution can be found in Appendix 14.1.

The rate of administration can be adapted to the response of the individual subject. Experience with Kogenate® FS/Bayer indicates that a dose may be administered over a period of 1 to 15 minutes. For PK and recovery studies, the entire dose should be administered over a 5-minute period depending on the total volume. ***(some text deleted as of Amd 1)***

Parents/caregivers will receive training and detailed information regarding the administration of ***the*** study medication. ***(as of Amd 1)***

6.3 Treatment assignment

All subjects will be assigned to one single treatment arm.

6.4 Dosage and administration

The dose selections for this study are based on the recommended dosage for Kogenate® FS/Bayer.[6] The study medication, BAY 81-8973, has been shown to have similar biological activity to Kogenate® FS/Bayer, which is currently approved in more than 50 countries for the treatment of hemophilia A.

In Part A of this study (as of Amd 1), subjects will receive prophylaxis treatment with BAY 81-8973 at least 2 times weekly with a dose of 25-50 IU/kg at the choice of the investigator and according to local standards and previous treatment. The dose ***should be*** rounded to ***the appropriate vial size. In Part B, prophylaxis may be started with a low dose, once a week treatment schedule. The recommended dose is 15-50 IU/kg, (minimum 250 IU) (as of Amd 6). For all subjects, the (as of Amd 1)*** frequency as well as the dose may be adapted to the individual needs up to daily if needed to accommodate for the subject's activities ***or sports participation. (as of Amd 1)***

Any bleeding ***events*** occurring in subjects receiving prophylactic care will be treated according to the ***local*** standard of care and severity of the bleed. ***(as of Amd 1)***

Subjects will be injected by parents/caregivers at home***, at a*** facility near ***the*** subject's home, ***homecare nurse (as of Amd 1),*** or by the investigator/delegate during the study visits. Children may also ***self-infuse, if under the supervision of a responsible adult to ensure adherence to the prescribed treatment regimen. (as of Amd 1)***

For the optional PK study, each subject will receive ***an exact*** dose of 50 IU/kg of BAY 81-8973. The dose will be prepared by a pharmacist or nurse at the study ***site***. This dose ***is*** expected to increase the plasma level of FVIII to approximately 80-100% FVIII activity. ***(as of Amd 1)***

During surgery (both major and minor) dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14.1). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide instructions based upon the type of surgical procedure to be undertaken. ***(some text deleted as of Amd 1)***

6.5 Blinding

Not applicable. This is an open-label study.

6.6 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 study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug in writing ***(some text deleted as of Amd 1)*** and 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.

Written instructions on medication destruction will be made available to affected parties as applicable.

6.7 Treatment compliance

Parents/caregivers will be provided with an EPD for the whole study (for details see Section 7.3.2.2). These logs will be used to collecting the ***treatment (as of Amd 1)*** data and bleeding episodes. ***The subject/parent/caregiver will interact with the Investigator or delegate weekly to verify and complete the EPD entries, and monthly during the extension study***. ***(as of Amd 1)***

Data on the EPD ***will be transmitted after each treatment is entered. The (as of Amd 1)*** EPD will be ***used*** to assess the ***subject's*** compliance with the prophylaxis treatment schedule and with the recording of ***treatments and*** bleeding events, and ***assist in study (as of Amd 1)*** medication inventory. ***See Section 6.1.3 for discussion of missed treatments. (as of Amd 1)***

Participation in the study may be terminated at the sponsor's discretion if a subject fails to comply with ***the above*** protocol requirements. ***(as of Amd 1)***

Empty vials of study medication must be returned to the study center at each ***study*** visit. At the end of the study, all used and unused study ***drug vials will be counted and collected by the sponsor's representative (as of Amd 1)*** for final drug accountability.

6.8 Post-study therapy

At the end of the study, all participants who ***have*** completed ***Part A or B (as of Amd 1)*** will be offered participation in an extension study. ***Participation in the extension study will allow (as of Amd 1)*** continuation of treatment for at least 100 ED. ***The extension (as of Amd 1)*** study requires continued documentation of ***infusions, bleeding events, monthly interaction with the treatment center, and visits every 6 months for inhibitor testing and recovery measurements***. ***(as of Amds 1 and 6)***

After completion of the extension study, or if the subjects or their parents/caregivers are not willing to participate in the extension study, ***treatment with study drug will end. Subsequent (as of Amd 1)*** treatment will be mutually agreed upon by the parents/caregivers and the investigator.

6.9 Prior and concomitant therapy

BAY 81-8973 will be used as the sole FVIII source. Pre-medications ***to tolerate treatment with BAY 81-8973 are not allowed. Use of topical anesthetics prior to venipuncture is permitted. (as of Amd 1). Note: PTPs will continue their previous treatment up to 48 h before the first dose of BAY 81-8973 (as of Amd 3).***

All medications and blood products required by the subject during the study will be listed in the CRF. No other experimental drugs may be taken during the subject's participation in this study.

No immunosuppressive/immunomodulatory drugs may be taken during the subject's participation in the study. If such therapy is deemed necessary for the subject's welfare, or due to pre-existing illness, the situation should be discussed with the Sponsor before enrollment. Medications which cause a bleeding diathesis (for example, Aspirin® or acetylsalicylic acid) are contraindicated in any individual with hemophilia and should be avoided, except as specifically prescribed by a treating physician. Use of non-steroidal anti-inflammatory drugs, COX-2 inhibitors, or brief courses of corticosteroids to treat pain or acute synovitis, or inhaled or topical steroid medications (as for the treatment of asthma or eczema) are allowed. (as of Amd 1)

All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements) ***will*** be recorded ***in the CRF (as of Amd 1)*** at screening and throughout the treatment and follow-up periods.

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

Table 7–1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1** *(+/- 1 week) (as of Amd 1)*	**Visit 4 Month 2** *(+/- 1 week) (as of Amd 1)*	**Final visit Month 6** *(Minimum 50 ED [as of Amd 1])*	**Extension Visit every 6 months** [e]	**Extension Final Visit** [e]
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events	*X*	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X		
FVIII baseline level and inhibitor (one stage) (*Amd 3*)	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	*X*	X	X	X [f] (*Amd 6*)	X (*Amd 6*)
Pharmacokinetics (optional)		← ----------			X [b]	---------- →	
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Electronic patient diary (EPD) documentation		← ---------- continuously ---------- →					
Healthcare *Resources* Utilization *Questionnaire (as of Amd 1)*	*X (as of Amd 1)*	← ---------- monthly ---------- →					
Interaction between subject/parent and investigator		← weekly →				← monthly →	
Concomitant medication	X	← ---------- continuously ---------- →					

a. Complete Blood Count (CBC), Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII *(as of Amd 1)*
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension
e. For the regular Extension Visit every 6 months, a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained. *(as of Amd 4)*
f. At the first extension visit 6 months after the start of the extension and at any time in case of inhibitor development (*as of Amd 6*)

Table 7–2b: Schedule of evaluations (Part B – PUPs/MTPs)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening [k]	**Visit 2 Baseline**	***Combined Screening and Baseline (PUPs only)*** *(as of Amd 6)*	**Visit 3 ED ~5** *(as of Amd 6)*	**Visit 4 ED ~10** *(as of Amd 6)*	**Visit 5 ED ~15** *(as of Amd 6)*	**Visit 6 ED ~20** *(as of Amd 6)*	**Interim Visit** ***30-40 ED*** *(as of Amd 1)*	**Final Visit or 50 ED** [f]	**Extension Visit every 6 months** [f]	**Extension Final Visit** [f]
Informed consent	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	*X* (*Amd 7*)	*X* (*Amd 7*)
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)	X [h] (*Amd 6*)	X[h] (*Amd 7*)	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X [j]	X
Epitope mapping (inhibitor positive patients) (Amd 4)				←	←	←	←	*X* [e]	→	→	→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X	X [j] (*Amd 6*)	X (*Amd 6*)
Pharmacokinetics (optional) (Amd 3)		←	←	←	←	←	*X* [d]	→	→	→	→
Biomarker investigation (recommended) (Amd 4 and Amd 7)		←	←	←	←	←	*X* [g]	→	→	→	→
Infusion of study drug *(Amd 1)*		←	←	←	←	←	continuously in accordance with the prophylaxis regimen	→	→	→	→
Electronic patient diary (EPD) documentation		←	←	←	←	←	continuously	→	→	→	→
Healthcare Resources Utilization Questionnaire(Amd 1)	*X (Amd 1)*	←	←	←	←	←	monthly	→	→	→	→
Interaction between subject/parent and investigator		←	←	←	weekly	→	→	→	←	monthly	→
Concomitant medication	X	←	←	←	←	←	continuously	→	→	→	→

For footnotes please see next page

a CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c Measured at least 48 h after last dose of FVIII
d Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
e Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies *(as of Amd 4)*
f The Final Visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved
g The recommended biomarker investigation (pharmacogenetics) requires a separate signed informed consent (as of Amd 7). The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amd 4)
h Inhibitor to be evaluated at screening (central laboratory testing), and at baseline (central and local laboratory testing), in MTPs only (ie, unnecessary to evaluate in PUPs) (as of Amd 6, include retention sample for inhibitor assessment by ELISA for MTPs). Study drug administration should start upon availability of result from local laboratory testing. (as of Amd 6 and Amd 7)
j At the first extension visit 6 months after the start of the extension, and at any time in case of inhibitor development (as of Amd 6)
k In case of MTPs, the screening visit should only take place after a washout period of at least 48 hours following any previous treatment with any FVIII replacement product (as of Amd 6).

7.1.2 Timing of assessments

The main study consists of a Screening period ***followed by at least*** 50 ED per subject. ***The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs/MTPs (as of Amd 6) or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits. (as of Amd 1)***

In Part A, PTPs, a minimum of 50 ED will be accumulated during a 6 month treatment period. Visits are scheduled at Month 1, Month 2 and Month 6. (as of Amd 1)

In Part B, the treatment period will be extended until 50 ED have been accumulated. The duration of Part B will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events. Blood sampling for inhibitor testing is required every 3-5 ED up to 20 ED, and again at 50 ED. As most subjects will begin prophylaxis 1x week, study visits during the first 20 ED are expected to occur monthly. However, it is understood that bleeding events resulting in added doses, delayed start of prophylaxis after first bleeds, or missed infusions due to difficult i.v. access may result in some variation in the number of ED a subject has obtained at each visit or the exact interval between visits. Likewise, those subjects who receive more frequent infusions may require study visits more often than once a month. (as of Amd 1)

After completing Part A or B, all (as of Amd 1) subjects will be offered ***continued*** treatment in an extension study until a total number of at least 100 ED per subject ***are*** accumulated. ***Participation will require (as of Amd 1)*** additional visits every 6 months.

7.1.2.1 Visit 1 – Screening

At the screening visit, the following procedures and assessments will be performed:

- Obtain written informed consent from the parents/legal representative. ***Assent should be (as of Amd 1)*** obtained from subjects, depending on their age and intellectual status ***or according to local practice***. ***(as of Amd 1)***
  Note: No Screening procedures may be performed unless written informed consent (and assent, if applicable) has been obtained. (see Section 11.2)
- ***Assignment (as of Amd 1)*** of a unique PID number (see Section 5.3)
- Eligibility check
  No subject may ***receive treatment with study drug (as of Amd 1)*** unless all ***inclusion and exclusion*** criteria ***are met (as of Amd 1)*** as given in Section 5.1. Confirmation of selection criteria may be based on medical records, but laboratory test results must confirm eligibility. The severity of ***hemophilia may be*** based on ***documented*** FVIII level at diagnosis. ***(as of Amd 1)***
- Recording of ***demographic data***, medical and surgical history, ***and any adverse events (AEs) occurring after signing of informed consent. (as of Amd 3)***
- Recording of prior and concomitant medication ***and Healthcare Resources Utilization Questionnaire. (Appendix 14.3)***. ***(as of Amd 1)***

- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. ***Blood pressure may be deferred if appropriate cuff size or equipment is not available***. ***(as of Amd 1)***
- Physical examination including measurement of body height***/length*** and weight
- Blood samples for laboratory tests:
    - Complete blood count (CBC)
    - ***Serum chemistry (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin. (See Section 14.4 for children <10 kg) (as of Amd 1)***
- ***FVIII:C level for PUPs and MTPs, inhibitor testing (not required for PUPs but required for MTPs incl. a retention sample for ELISA) (as of Amds 1 and 6)***
- ***Training on*** and ***dispensing (as of Amd 1)*** of the EPD. ***Note: the EPD may be given to the subjects to take home at any time between Screening and Baseline, but no entries are to be made before the first injection at Baseline (as of Amd 3).***

In case of MTPs, the screening visit should only take place after a washout period of at least 48 h following any previous treatment with any FVIII replacement product (as of Amd 6).

7.1.2.2 Visit 2 – Baseline

This visit will serve as the Baseline visit. It will include the first administration of study drug.

For subjects in Part A (PTPs) (as of Amd 1), the Baseline visit should take place within 8 weeks after Screening visit and at least 48 h after last FVIII administration.

For PUPs, the Baseline ***visit (as of Amd 1)*** may be combined with the Screening visit if all selection criteria can be confirmed based on medical records. ***The first dose of BAY 81-8973 may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment (see Section 6.1.1). (as of Amd 1 and Amd 7)***

This visit should start with the following assessments:

Confirmation of eligibility including check of laboratory test results.
Note: Eligible subjects (except PUPs) must be inhibitor negative at Baseline. ***MTPs must be inhibitor negative as evaluated via central laboratory testing at Screening visit (as of Amd 6). A confirmatory inhibitor test must be taken at Baseline visit. Results from local laboratory testing must be negative (<0.6 BU/mL) prior to administration of study drug. (as of Amd 7)***

The following activities will be performed ***(as of Amd 7)***:

- ***Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment). (as of Amd 1)***
- Measurement of body height***/length (as of Amd 1)*** and weight

- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before ***infusion. (Blood pressure may be deferred if appropriate cuff size or equipment is not available)***. ***(as of Amd 1)***
- Update of concomitant medication and ***Healthcare Resources Utilization Questionnaire (as of Amd 1)***. (Appendix 14.3)
- HSP-70 antibodies ***(in children > 7kg) (as of Amd 1)***
- ***Infusion*** of the first dose of study drug ***or dispensation of study drug for on-demand treatment in Part B (as of Amd 6).***

Note: ***For subjects in Part B (PUPs/MTPs), first exposure to study drug may be either for treatment of an uncomplicated bleed or for start of prophylaxis***. Inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated. ***See discussion on treatment of PUPs/MTPs in Section 6.1.1. (as of Amds 1 and 6)***

- Vital signs (Heart rate, temperature, blood pressure) after ***infusion***. ***(as of Amd 1)***
- Blood sample for the determination of recovery to be taken at 20-30 min after end of ***infusion***. ***(as of Amd 1) (Only for subjects who start prophylaxis at Baseline, for others, recovery should be done when prophylaxis is started [as of Amd 6].)***
- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with European Medicines Agency (EMA) guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amds 4 and 6). Additional informed consent is required. (as of Amd 7)***
- Documentation of AEs
- Check of ***understanding of EPD use. Repeat training on the device if required***. ***(as of Amd 1)***
- Instruction on the prophylaxis regimen to be administered to the subject

Begin regular weekly contact between parents and the ***site*** to check the EPD documentation until next clinic visit. ***Contacts should be documented in the medical record. (as of Amd 1)***

7.1.2.3 Visit 3 – *Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B (as of Amd 1)*

The following procedures and assessments will be performed:

- Check of EPD ***entries*** and bleeding history. ***Collect information on*** AEs, ***update of concomitant medication and completion of Healthcare Resources Utilization Questionnaire. (Appendix 14.3). (as of Amd 1 and Amd 3)***
- Measurement of body height***/length (as of Amd 1)*** and weight
- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available). (as of Amd 1)***
- ***Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment). (as of Amd 1)***
- ***Infusion*** of study drug ***(Part A only) (as of Amd 1)***
- Vital signs after ***infusion, if given (as of Amd 1)***
- Blood sample for the determination of recovery to be taken at 20-30 min after end of ***infusion (Part A only) (as of Amd 1)***
- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B subjects also at 20-30 min after end of infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Regular weekly contacts between parents and the ***site*** to check the EPD documentation until next clinic visit.

7.1.2.4 Visit 4 – *Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B (as of Amd 1)*

The following procedures and assessments will be performed:

- Measurement of body height***/length (as of Amd 1)*** and weight
- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available). (as of Amd 1)***

- Documentation of interval history including AEs and concomitant medication and ***Healthcare Resources Utilization Questionnaire (as of Amd 1)*** (Appendix 14.3).
- Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII ***treatment***) ***(as of Amd 1)***
- ***Infusion*** of study drug ***(Part A only) (as of Amd 1)***
- Vital signs after ***infusion, if given***. ***(as of Amd 1)***
- Blood sample for the determination of recovery to be taken at 20-30 min after end of ***infusion. (Part A only) (as of Amd 1)***
- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B subjects also at 20-30 min after end of infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***
- Check of EPD ***entries (as of Amd 1)*** of interval treatment and bleeding history.

Regular weekly contacts between parents and the ***site (as of Amd 1)*** to check the EPD documentation until next clinic visit.

7.1.2.5 Visit 5 – *Part B only; ED ~15 (14 ED +/- 1) (as of Amd 1)*

The following procedures and assessments will be performed:

- ***Measurement of body height/length and weight***
- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).***
- ***Documentation of interval history including AEs and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.2).***
- ***Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment).***
- ***Check of EPD entries of interval treatment and bleeding history.***

- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B subjects also at 20-30 min after end of infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Regular weekly contact between parents and the site to check the EPD entries until next clinic visit. (as of Amd 1)

7.1.2.6 Visit *6 – Part B only; ED 20 (20 ED +/- 1) (as of Amd 1)*

The following procedures and assessments will be performed:

- Measurement of body height***/length*** and weight ***(as of Amd 1)***
- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available). (as of Amd 1)***
- Documentation of interval history including AEs and concomitant medication and ***Healthcare Resources Utilization Questionnaire (as of Amd 1)*** (Appendix 14.3).
- Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII ***infusion***). ***(as of Amd 1)***
- ***Infusion (as of Amd 1)*** of study drug.
- ***Vital signs after infusion. (as of Amd 1)***
- Blood sample for the determination of recovery to be taken at 20-30 min after end ***of infusion***. ***(as of Amd 1)***
- Check of EPD ***entries (as of Amd 1)*** of interval treatment and bleeding history.
- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B subjects also at 20-30 min after end of infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less

than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Regular weekly contacts between parents and the ***site (as of Amd 1)*** to check the EPD documentation until next clinic visit.

7.1.2.7 Interim visit – *Only for Part B (30-40 ED) (as of Amd 1)*

Visit only required for PUPs and MTPs who have less than 40 ED, 6 months after the Baseline visit. The intent is to have at least one scheduled visit between completion of 20 ED and the expected date of accumulating 50 ED. The primary purpose of the visit is to assess the well-being of the subject, ensure continued compliance with the treatment, and make any needed adjustments in dosage or infusion frequency based upon weight or bleeding events.

The following procedures and assessments will be performed:

- ***Measurement of body height/length and weight***
- ***Documentation of interval history including AEs and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.2).***
- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).***
- ***Check of EPD entries of interval treatment and bleeding history.***

Regular weekly contacts between parents and the site to check the EPD documentation until next clinic visit. (as of Amd 1)

7.1.2.8 *Final* Visit (end of the main study and start of the optional extension study)

For subjects in Part A (as of Amd 1), this visit will take place 6 months after baseline and at least 50 ED were accumulated, or in case of early termination.

For PUPs and MTPs in Part B, this visit will take place after 50 ED with study medication are accumulated, or in the case of early termination (as of Amd 6). It is expected 50 ED will be achieved for most subjects between 6 and12 months after start of prophylactic treatment. (as of Amd 1)

The following procedures and assessments will be performed:

- Physical examination including measurement of body height***/length (as of Amd 1)*** and weight

- ***Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available). (as of Amd 1)***
- Documentation of interval history including AEs and concomitant medication and ***Healthcare Resources Utilization Questionnaire (Appendix 14.3). (as of Amd 1)***
- ***Blood samples for laboratory tests:***
  - ***Complete blood count [CBC]***
  - ***Serum chemistry (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin. (See Section 14.4 for children <10 kg) (as of Amd 1)***
- Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII ***treatment). (as of Amd 1)***
- HSP-70 antibodies ***(in children > 7 kg). (as of Amd 1)***
- ***Infusion*** of study drug. ***(as of Amd 1)***
- ***Vital signs after infusion. (as of Amd 1)***
- Blood sample for the determination of recovery to be taken at 20-30 min after end of ***infusion. (as of Amd 1)***
- ***Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B subjects also at 20-30 min after end of infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***
- Check of EPD ***entries*** of interval treatment and bleeding history.

For subjects not participating in the optional extension study:

- Return of EPD
- Return of used and unused study ***vials (as of Amd 1)*** for final drug accountability

- **Follow-up phone call (1-2 weeks after end of treatment)**
  Call parents/caregiver via telephone and review any new AEs and changes in concomitant medication since the last study visit.

For subjects participating in the optional extension study:

- Informed consent signed by parents/legal representative must be available.
- Continuation of prophylaxis treatment
- ***Begin*** regular ***monthly*** contacts between parents and the ***site*** to check the EPD documentation until next clinic visit. ***(as of Amd 1)***

7.1.2.9 *Extension study visits – 6 months after completion of Part A or B; then* every 6 months *(as of Amd 1)*

The following procedures and assessments will be performed:

- Measurement of body height***/length,*** weight, ***and vital signs (as of Amd 1 and Amd 7)***.
- ***Documentation of interval history including AEs and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3). (as of Amd 1)***
- Check of EPD ***entries of (as of Amd 1)*** interval treatment and bleeding history
- Blood sample for inhibitor testing ***and determination of FVIII:C trough level (≥48 h after last FVIII treatment) (as of Amds 1).***
- ***Blood sample for recovery measurement to be collected only at the first extension visit at 6 months. Blood sample to be taken at 20-30 min after end of infusion (as of Amd 6).***
- ***Optional PK: Additional blood samples at 20-30 min, 4 h and 24 h post infusion (can also be performed at a later visit; obtained only once during study.)***
  Note to investigators: In compliance with EMA guidance and for subject safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 1, Amd 3)
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***
- ***Regular monthly contacts between parents and the site to check the EPD documentation, update information on AEs and concomitant medication, completion of Healthcare Resources Utilization Questionnaire before next clinic visit. (as of Amd 1, Amd 3)***

7.1.2.10 *Extension* final visit

This visit will take place at the end of the extension period, or in the event of early termination. (as of Amd 3)

The extension study will be ***continued (as of Amd 1) for at least 100 cumulative ED***.

The final study visit must be performed at the time of switch to commercial drug.

The following procedures and assessments will be performed:

- ***Measurement (as of Amd 1)*** of body height, weight, ***and vital signs (as of Amd 7)***
- Documentation of interval history including AEs and concomitant medication ***and Healthcare Resources Utilization Questionnaire (Appendix 14.3). (as of Amd 1)***
- ***Blood sample for inhibitor testing and determination of FVIII:C trough level (≥48 h after last FVIII infusion) (as of Amd 1)***
- Check of EPD ***entries (as of Amd 1)*** of interval treatment and bleeding history
- Return of EPD
- Return of used and unused study ***vials (as of Amd 1)*** for final drug accountability
- ***Recovery measurement, blood sample to be taken at 20-30 min after end of infusion. (as of Amd 6)***
- ***(Some text deleted as of Amd 1)***
- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Follow-Up Phone Call (1-2 weeks after end of treatment)

Call parents/caregiver via telephone and review any new AEs since the last study visit.

7.2 Population characteristics

7.2.1 Demographic

Demographic characteristics to be recorded at Screening will include age and race. In addition, a complete physical examination including pulse, blood pressure, body temperature, height, weight, and a review of body systems will be performed and the results documented. ***If known, any gene mutation should be noted (as of Amd 3).***

7.2.2 Medical history

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

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) AEs can be found in Section 7.5.1.1.

7.2.3 Disease history

Disease history to be recorded at Screening will include date of diagnosis, start of therapy, number of ED, family history, past inhibitor testing, current treatment regimen, FVIII level and type of assay, number of bleeds in the last 12 months, and presence of target joints.

7.3 Efficacy

7.3.1 Efficacy variables

The primary variable is the annualized number of ***total*** bleeds (***sum of spontaneous bleeds and traumatic bleeds) during prophylaxis that occurs*** within 48 h ***of the last prophylaxis infusion. Both joint and non-joint bleeding will be assessed. (as of Amd 1***) Additional efficacy parameters include:

- Subject/parents' assessment of the response ***to*** treatment of bleeding events, which is assessed as excellent, good, moderate or ***poor***. ***(as of Amd 1)***
- Annualized number of ***total*** bleeds ***(sum of spontaneous and trauma bleeds) (as of Amd 1)*** during prophylaxis treatment
- Assessment of ***adequacy of hemostasis (as of Amd 1)*** during surgical interventions
- Number of infusions for the treatment of a bleed
- Consumption of FVIII

The main surrogate efficacy parameter is the ***recovery of FVIII after infusion. (as of Amd 1)***

If an infusion is given to control a bleed at the same location within 72 hours of the previous dose for a bleed at that site, it is to be considered a follow-up infusion and not treatment of a new bleed, unless both bleeds are skin/mucosa bleeds (as of Amd 3).

The complete list of variables to be analyzed for this study will be provided in the Statistical Analysis Plan.

7.3.2 Efficacy procedures

7.3.2.1 Incremental recovery *of Factor VIII (as of Amd 1)*

Samples for FVIII trough levels will be collected in the ***clinic*** before the next planned ***prophylactic infusion*** as scheduled. Recoveries should be performed in conjunction with planned prophylaxis ***infusions, using the subject's usual dose (exception, during optional PK). Infusions given at study visits will not be recorded in the EPD, but in the site patient records, which will be the source document and will be used to enter this information in the CRF. (as of Amd 1)***

Levels ***of BAY 81-8973*** will be determined in a central laboratory with the chromogenic ***method***. ***(as of Amd 1)***

FVIII trough levels will be determined in the blood samples collected before the ***scheduled*** BAY 81-8973 ***infusions*** at Baseline, Month 1, Month 2, and Month 6 (or final visit) ***in Part A; or at Baseline, ED 20, and final visit (ED 50) in Part B.*** The measurement should be performed ***at least*** 48 h ***after last infusion of BAY 81-8973. (as of Amd 1)***

Incremental recovery at 20-30 min after end of ***infusions (as of Amd 1)*** will be determined at Baseline, Month 1, 2, Month 6 (or final visit)***, 1st extension visit and final extension visit (as of Amd 6).*** Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after ***infusion (as of Amd 1)*** have to be documented in the CRF.

A determination of recovery should also be performed with the confirmatory inhibitor test (as of Amd 7).

7.3.2.2 *Treatment* logs / bleeding verification

Treatment (as of Amd 1) logs are commonly used for hemophilia subjects for documentation of their home treatment. Home treatment and bleeding frequency are key variables evaluated in this study. Study specific 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 also the data cleaning process.

Subjects/parents/caregivers will be provided with EPDs for the whole study. At Screening and Baseline visits, subjects and parents/caregivers will be trained in the use of the device. These logs will be used to collect the ***treatment (as of Amd 1)*** data and bleeding episodes by the parents/caregivers or subjects, and interact on a ***regularly scheduled (as of Amd 1)*** basis with the investigator or delegate to verify and complete the ***data on (as of Amd 1)*** the EPD. Thus, the EPD will be considered the source for these data.

For each ***use*** of study medication including the ***infusions*** administered during a planned visit for evaluation of recovery, information must be recorded on the ***Treatment (as of Amd 1)*** Logs as follows:

1. Date and time
2. Lot numbers / number of vials administered

3. Reason for ***treatment (as of Amd 1)*** (prophylaxis, spontaneous bleed first treatment, trauma bleed first treatment, follow-up treatment, surgery, other). ***(If an infusion is given in response to a fall or identified trauma, such as may occur when a child has an uncomplicated blow to the head and there is no clinical sign or evidence of bleeding, the event should be recorded as prophylaxis.) (as of Amd 1)***

If treatment is for a bleeding episode: site of bleeding, severity (severe, moderate, mild), and response to treatment (excellent, good, moderate***, poor, too early to tell) are to be recorded. If 'too early to tell' is entered, the subject will be queried for a response the next time they use the device. For guidance to the subject or their caregivers, the following definitions for response to treatment are suggested. Individual subject responses may vary (as of Amd 1):***

- ***Excellent: Abrupt pain relief and /or improvement in signs of bleeding with no additional infusion administered (as of Amd 1)***
- ***Good: Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution (as of Amd 1)***
- ***Moderate: Probable or slight improvement in signs of bleeding, with at least one additional infusion for complete resolution (as of Amd 1)***
- ***Poor: No improvement at all between infusions or condition worsens. (as of Amd 1)***

7.4 Pharmacokinetics (optional – consent required) (as of Amd 1)

Participation in the PK evaluations is optional. The minimal number of subjects in the optional PK is 6. If consent***/assent is obtained, PK will be assessed using the (as of Amd 1)*** sampling time points ***specified in this protocol (as of Amd 1)***. The pharmacokinetics of the study drug in plasma ***can*** be determined ***at any time, and should be scheduled to coincide with a scheduled visit to measure incremental recovery, if possible (as of Amd 1)***. There must be a washout of previous FVIII of at least 48 h before the first ***infusion (as of Amd 1)*** of study drug and the subject must have no signs or symptoms of an acute bleeding episode. ***All samples will be processed in the central laboratory. (as of Amd 1)***

Subjects will be administered a dose of 50 IU/kg. Blood samples will be obtained pre-***infusion (as of Amd 1)*** and at 20-30 min, ***4 h, and 24 h (as of Amd 1)*** after the end of ***infusion (as of Amd 1)*** of study medication. FVIII levels will be determined by the chromogenic assay. Details of the blood sampling and processing procedures for all laboratory measurements will be provided in ***the Laboratory Manual, developed by the central laboratory (as of Amd 3),*** that accompanies this protocol. ***A dose preparation worksheet will be provided in the Pharmacy manual (as of Amd 1).***

Note to investigators: In compliance with EMA guidance and for patient safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.3). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study. (as of Amd 3)

Based on the plasma concentration time data the following pharmacokinetic parameters will be calculated: Maximum concentration (C_{max}), recovery, AUC, half-life ($t_{1/2}$), MRT and clearance (CL).

7.5 Safety

7.5.1 Adverse events

7.5.1.1 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.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal, eg, physical examination findings, symptoms, diseases, laboratory values.

- 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 (eg, seasonal allergy without acute complaints, abnormal laboratory finding at screening).
- 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 (eg, allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

Note: Any bleeding event occurring during the study will not be documented as ***an*** AE, because this ***event (as of Amd 1)*** is captured in the assessment of efficacy. However, if the bleed requires hospitalization, it must be reported as a Serious Adverse Event (SAE) (see Section 7.5.1.4).

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 in subject 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 hours
   - The admission is pre-planned
     (i.e. elective or scheduled surgery arranged prior to the start of the study)
   - The admission is not associated with an AE
     (eg, 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 medically important serious event as judged by the investigator.

Note: Any inhibitor development is considered an SAE.

7.5.1.2 Classifications for adverse event assessment

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

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories, taking into account the possible range of the intensity of the event:

- Mild
- Moderate
- Severe

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF.

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 clear alternative explanation, eg, mechanical bleeding at surgical site.

or

2. Non-plausibility, eg, 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 there is a reasonable suspicion that the AE is associated with the use of the study treatment.

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 subjects response after re-challenge should be considered in the 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 may be suspected to cause the event in question.

- 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.

7.5.1.2.4 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 reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 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

7.5.1.3 Assessments and documentation of adverse events

Subjects must be carefully monitored for AEs. All AEs occurring after signed informed consent was obtained must be fully recorded in the subject's CRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality occurring after screening considered clinically relevant, eg, causing the subject to

withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken, and outcome.

7.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.5.1.1.

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.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

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

Notification of the Independent Ethic Committees (IECs) / Institutional Review Boards (IRBs)

Notification of the IECs / IRBs about all relevant events (eg, 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 (eg, SAEs, 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 (eg, SUSARs) according to all applicable regulations.

7.5.1.5 Expected adverse events

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

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current 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.

7.5.2 Pregnancies

Not applicable in this pediatric male subject population.

7.5.3 Further safety

7.5.3.1 Vital signs

Systolic and diastolic blood pressure, heart rate, and body temperature will be measured at ***all visits. Blood pressure may be deferred in infants if appropriate size cuff or equipment is not available. (as of Amd 1)***

7.5.3.2 Physical examination

A complete physical examination including the measurement of body height, weight and temperature will be performed at the Screening visit and at the Month 6 (or final visit). ***Body length will be measured instead of height, as age appropriate. (as of Amd 1)***

At the ***other*** visits***, and during the (as of Amd 1)*** optional extension study (every 6 months until switch to commercial drug), only the subject's body height, temperature and weight will be measured.

7.5.3.3 Standard safety laboratory

The following blood (as of Amd 1) samples will be collected at Screening and Month 6 (or final visit):

- CBC with differential: erythrocytes, hemoglobin, hematocrit, platelets, leukocytes, neutrophils, eosinophils, basophils, monocytes, and lymphocytes
- ***Serum chemistry (electrolytes (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin) (as of Amd 1)***

The following blood samples will be collected at Baseline and Month 6 (or final visit) (as of Amd 1):

- HSP-70 antibody ***(except in subjects <7kg) (as of Amd 1)***

7.5.3.4 Inhibitor testing

Premise for inclusion ***requires confirmed diagnosis of severe hemophilia A (<1% FVIII) and documentation of a (as of Amd 1)*** negative test result of inhibitor at Baseline.

Blood samples for FVIII inhibitor testing will be taken at Screening ***(PTPs and MTPs only)***, Baseline, ***at regularly scheduled intervals throughout the study, and at the (as of Amds 1 and 6)*** final visit. The premise for inclusion of PTPs ***and MTPs*** in this study is the availability of a negative inhibitor ***result (as of Amds 1 and 6)*** as measured in the blood sample at Screening ***and Baseline (as of Amd 7).*** A further sample will be taken at baseline before the first ***infusion (as of Amd 1)***. If the inhibitor testing result changes from negative at screening

to positive at baseline, before the first ***infusion (as of Amd 1)*** of study medication, the subject must be withdrawn from the trial.

In Part B, the ***requirement for a*** FVIII inhibitor testing before study ***entry (as of Amd 1)*** is not applicable for PUPs ***but is applicable for MTPs (as of Amd 6). The absence of inhibitors will be assessed using central laboratory testing at Screening (<0.2 BU/mL), with confirmation using local laboratory testing at Baseline (<0.6 BU/mL) (as of Amd 7). After treatment is started (as of Amd 1),*** PUPs***/MTPs*** must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated ***(as of Amd 6), and at the final visit (50 ED) (as of Amd 7). Afterwards, blood samples for inhibitor testing and determination of FVIII:C trough level (>48 h after last FVIII treatment) are to be taken:***

- ***every 6 months in the extension study until finalization of the study, and at the final visit (as of Amds 1 and 6).***

The laboratory analyses will be performed at central laboratories.

Investigators will be provided with a detailed laboratory manual and a copy of the individual results. Inhibitor testing will be done according to the Nijmegen modified Bethesda inhibitor assay ***at the central laboratory (as of Amd 1)***. A positive inhibitor testing is defined with a threshold of ≥ 0.6 BU in the central laboratory. Any positive test must be confirmed by a second ***plasma (as of Amd 1)*** sample ***and a determination of recovery should be performed. (as of Amd 6)***

For any subject confirmed positive for inhibitors, epitope mapping will be performed (see Section 7.6.1 for details). (as of Amd 4)

Remaining rest of the plasma samples collected at specified study visits could be used for immunology or additional coagulation analysis, or for clarification of any clinical or laboratory adverse event and in no case for genetic analyses. (as of Amd 6)

7.6 Other procedures and variables

7.6.1 Epitope mapping *(as of Amd 4)*

In the event a subject tested positive for inhibitor, additional blood, up to a maximum allowable as described in Table 14-4a, should be taken to confirm the result (retesting). If the result upon retesting is also positive, epitope mapping will be performed with the additional blood sample that was taken. Details of sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

7.6.2 Biomarker investigation (pharmacogenetics) (recommended – consent required) *(as of Amd 4 and Amd 7)*

The purpose of this genetic analysis is to identify markers for risk of inhibitor development in subjects treated with BAY 81-8973. The markers to be analyzed are type of FVIII gene mutation if not available, single nucleotide polymorphisms (SNPs) in immunoregulators (eg, IL 10), HLA genotype, and FVIII polymorphisms. This biomarker analysis is exploratory and will be analyzed for PUPs and MTPs only. (as of Amds 4 and 6)

A separate informed consent for pharmacogenetic sampling is required and participation is recommended. (as of Amd 4 and Amd 7)

If a subject elects to participate, a blood sample can be collected at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw. Samples will be prepared and labeled according to laboratory specifications. Details of the sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

A subject does not need to agree to participate in the pharmacogenetic sub-study to be enrolled in the main study. (as of Amd 4). However, as this analysis provides important information about inhibitor development, participation is the sub study is recommended. (as of Amd 7)

7.7 Appropriateness of procedures / measurements

All procedures / measurements are established and validated in this therapeutic area. The assessments closely follow the recommendations specified in CPMP/BPWG/1561/99.

8. Statistical methods and determination of sample size

8.1 General considerations

Statistical analyses will be performed using SAS release 9.1 or higher (SAS Institute Inc., Cary, North Carolina [NC], United States of America [USA]). The version used will be specified in the Statistical Analysis Plan. (As of Amd 1)

8.2 Analysis sets

Efficacy and safety data will be collected from all subjects who received study medication. The intent-to-treat (ITT) population will include all subjects randomized into the study who received study drug. The per-protocol population will exclude subjects who are deemed invalid in the Validity Review Report. Subjects from Part A and Part B will be summarized separately. (as of Amd 1)

8.3 Variables

Baseline

Demographic characteristics, including age, weight, height and race as well as previous exposure to FVIII will be presented for all treated subjects, in the form of summary statistics. Other baseline characteristics, including laboratory findings and vital signs, will be handled similarly.

Extent of Exposure

Extent of exposure to the study drug, including ***treatment (as of Amd 1)*** characteristics, will be documented in subject diaries and summarized for each subject receiving any amount of drug.

Safety

Safety data will be summarized for all subjects in the safety population. Laboratory findings, AEs, concomitant medications, and medical history data will be provided in subject listings.

Laboratory values and vital signs will be summarized. Individual listings of AEs [including AEs as reported, start, duration, severity, relation to study drug] will be provided. The incidence of treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Affairs (MedDRA). ***(some text deleted as of Amd 1)***

Inhibitor development, as measured by Nijmegen assay, will be summarized by time point and presented in subject listings. ***The purpose of the listing is to delineate the clinical factors which may be positively associated with development of the inhibitor. (as of Amd 1)***

The frequency of subjects who develop positive inhibitor titers (Bethesda $\geq$ 0.6 BU) and ***confirmed by repeat measurement (as of Amd 1)*** will be presented by time point. ***If the inhibitor value drops below 0.6 BU on repeat measure without intervention, the inhibitor will be determined as being transient. We will classify inhibitor patients as being either low titer or high titer based upon persistence of an inhibitor >5 BU. (as of Amd 1)*** The rate of inhibitor development associated with BAY 81-8973 will be determined. Subjects with no inhibitors are required to have at least 50 ED to be counted in the denominator.

Efficacy

Efficacy data will be summarized for all subjects in the ***intent-to-treat (as of Amd 1) (***ITT***)*** population. The primary efficacy variable will be the annualized number of *total* ***bleeds (sum of spontaneous bleeds and traumatic bleeds) (as of Amd 1)*** within 48 h after a prophylaxis ***infusion (as of Amd 1)***. Other variables summarized will be the physician's***/subject's/***parents' ***(as of Amd 1)*** assessment of the response to treatment of bleeds (excellent***, good, moderate, poor***) ***(as of Amd 1)*** and during surgeries. The number of treatments required to control bleeds, the ***proportion (as of Amd 1)*** of prophylaxis infusions with less than expected therapeutic effect (LETE) (defined as a prophylaxis infusion followed by a bleed within 48 h), annualized number of ***total bleeds (sum of spontaneous bleeds and trauma bleeds) (as of Amd 1)*** during prophylaxis, FVIII usage and recovery will be summarized. ***A detailed Statistical Analysis Plan with be provided (as of Amd 1).***

Pharmacokinetics / pharmacodynamics (Optional)

For investigation of drug exposure and potential relationships to drug effects, selected subjects will participate in pharmacokinetic (PK) sampling. Any subject's participation in PK sampling is voluntary and consent***/assent is required (as of Amd 1)***.

Based on the known PK of FVIII in hemophilia subjects it is expected that a ***reduced (as of Amd 1)*** sampling strategy will be sufficient to calculate relevant pharmacokinetic parameters.

Blood samples for population PK analyses will be collected according to a sampling schedule. Blood sampling for the determination of FVIII:C in plasma will be taken at baseline ***before*** the ***infusion (pre-infusion)*** at 20-30 minutes, ***4 h, and 24 h*** after end of ***infusion. Attempt should be made to collect the sample as close as possible to the times indicated above. If there is a delay in collecting a sample, the sample should still be collected so that there are at least 3 samples post infusion. In all cases the exact time of start and end of infusion and the time of actual sample collection should be noted in the CRF. (as of Amd 1)***

A minimal number of 6 subjects is required. The following parameters will be calculated: C_{max}, AUC, recovery, clearance, MRT and t ½ using non-compartmental methods.

8.4 Statistical and analytical plans

The data will be summarized using the software package SAS release 9.1 or higher (SAS Institute Inc., Cary, North Carolina [NC], United States of America [USA]). All data will be listed and summary tables will be provided. The number of data available and missing data, mean, standard deviation, and other summary statistics will be calculated for continuous data. Frequency tables will be generated for categorical data. No formal statistical tests will be performed.

8.5 Planned interim analyses

The main study has a duration of 6 months. The 6-month data ***for PTPs (as of Amd 1)*** will be analyzed for regulatory purposes as an interim analysis. ***An interim analysis will be performed for 25 PUPs after they will have completed in Part B (as of amd 6). An additional analysis will be performed when all PUPs/MTPs have completed part B. If required for regulatory purposes, Part B data will be described in an interim analysis if at least 5 PUPs have been recruited(as of Amd 3). The overall study will be closed after all subjects in Parts A and B (as of Amd 1)*** have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

When safety has been assessed in 10-20 PTPs who have received at least 50 ED, enrollment will begin in Part B. All subjects will have the option of continuing in the extension trial. The trial data will be reviewed periodically by an independent DMC. The DMC will review certain safety and efficacy data sets as defined in the charter, as well as the planned interim analysis, and provide written reports to the sponsor. The decision to open enrollment to each age group will be made following recommendation of the DMC. (as of Amd 1).

8.6 Determination of sample size

Sample size has been determined according to the ***requirements set forth by (as of Amd 1)*** guideline CPMP/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), ***and taking into account the revised draft version, CHMP/BPWP/144533/09. Age groups are in accordance with the International Conference on Harmonization (ICH)/CPMP guideline E11 (Clinical Investigation of Medicinal Products in the Pediatric Population[19]) and sample sizes have been confirmed on consultation with the European Medicines Agency Paediatric Committee [EMA/PDCO] on submission of the Pediatric Investigation Plan. (as of Amd 1)***

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study c***onsists of two parts. Part A (as of Amd 1)*** will include ***a total of 50 PTPs (as of Amd 1)***; 25 subjects age ***6*** – 12 years ***(as of Amd 3)*** and 25 subjects age <6 ***years. Part B will enroll at least 25, plus approximately an additional 25 PUPs/MTPs*** age <6 ***years. (as of Amd 3 and Amd 7)*** The total sample size will be ***approximately 100*** subjects. (***as of Amds 3, 6 and 7***)

9. Data handling and quality assurance

9.1 Data recording

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. ***A source document is defined as the first place data are recorded; the CRF is not a source document. The site must ensure the existence of source documents. (as of Amd 1)*** A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

The patient reported data may be entered directly into the EPD, for all other data source documentation must be available.

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. ***(some text deleted as of Amd 1)***

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

- Data are authentic, accurate and complete
- 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) agree to allow the monitor direct access to all relevant documents.

9.2 Data processing

The data collection tool for this study will be a validated electronic system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (eg, Toolbox for System Configuration and Administration [TOSCA]; SAS). Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (eg, EPD, Interactive voice randomization system [IVRS], laboratory, electrocardiogram [ECG], electronic patient reported outcome [ePRO], adjudication committees).

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

9.3 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 Independent Ethics Committee (IEC)(s)/Institutional Review Board (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.

9.4 Archiving

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

Subject (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 (eg, relocation or transfer of ownership).

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

The investigator's contract will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [eg, 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 (eg, SAEs***)***
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on eg, toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (eg, recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the study 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:

- Closure should occur only after consultation between involved parties.
- All affected institutions (eg, 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 given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post-study follow-up, must be ***treated (as of Amd 1)*** of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 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 under 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 also forwarded to the Sponsor. The responsible unit (eg, Ethic Committee [EC]/IRB, head of the study center/medical institution) must supply to the

Sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the EC/IRB is organized and operates 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 study 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 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject/parent information sheet and informed consent form provided by the sponsor or the study center. A sample subject/parent 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 / parent / legal representative or proxy consenter (if the subject is under legal protection), prior to his/her 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 have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) 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 subject'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 minors, consent shall be given by the ***parents/***legal ***representative. (as of Amd 1)*** The ***assent (as of Amd 1)*** of a minor shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

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/parents' 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/her 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.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

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

11.4 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.

11.5 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 (eg, 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.

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13. Protocol amendments

13.1 Amendment 1

Description of Amendment

Amendment 1 implements revisions and clarifications secondary to the recommendations of regulatory agencies and in response to specific questions and comments received from pediatric specialists and investigators. These include provision of an improved explanation of the staggered enrollment by subject age, a more exact definition of the number of subjects to be enrolled into the study, clarification of the timing of start of prophylaxis in PUPs, and reduction of the number of blood draws and blood volumes required for study participation in all age groups. The PK sampling scheme in Part A has been revised to reduce the burden on subjects and allows participation of all PTPs as PK measures may be required after start of study to make decisions regarding individualized dosing regimens. The duration of study participation and timing of study visits and blood draws in Part B are further clarified since the time to accumulate 50 ED in PUPs may vary. Important additions were made regarding the risk of inhibitor development, including instructions on possible methods to avoid their development, how to respond if an inhibitor occurs, clarification that such subjects will be offered an immune-tolerance regimen with BAY 81-8973using the study drug, and added detail on how inhibitors will be defined and evaluated.

Updated information was added reflecting current clinical studies using BAY 81-8973. The chromogenic assay used to measure the potency of the investigational drug is mentioned, since this information may be important to investigators when picking the appropriate dosages for subjects. Inclusion and exclusion criteria and measurements of vital signs were clarified to be more consistent with pediatric practice. Finally, editorial changes, correction of typographical errors, and minor revisions of language were made to ensure clarity and consistency throughout the document. As the terms injection and infusion were previously used interchangeably, infusion is now used preferentially.

13.1.1 Overview of changes

Change 1: Specification of the exact number of subjects to be enrolled and clarification of the time points in which each age group will be allowed to enter the study.

A total of 75 subjects will participate in study 13400, with 25 subjects enrolled in each age group. A clarification that the sample size was defined by the requirements of European Agency for the Evaluation of Medicinal Product (EMEA) guidance and direct feedback by regulatory agencies has been added.

It is now more clearly defined that the study consists of 2 parts, Part A for PTPs, and Part B for PUPs. Part A opens only after 20 adolescents and adults in another study have been treated with at least 50 ED. Part A will first enroll PTPs age >6-12 years, followed by PTPs age 0-6 years. Part B for PUPs will not begin enrollment until after 20 subjects in Part A have received at least 50 ED. As an external DMC has been formed to provide independent

assessment of the safety prior to opening the study to each age group, the existence of this committee and their role has been added to the protocol.

Sections affected include:

- Synopsis – Duration of treatment
- Synopsis – Methodology
- Synopsis – Number of Subjects
- Section 4, Study design
- Section 7.1.1, Tabulated overview
- Section 7.1.2, Timing of assessments
- Section 8.5, Planned interim analyses
- Section 8.6, Determination of sample size

Change 2: Several changes have been introduced with the primary intent to reduce the burden on children incurred by recurrent blood draws or withdrawal of volumes which may be unsafe.

The original protocol included the requirement for a plasma sample to be retained for repeat measurements of coagulation studies. This sample was mistakenly referred to as a serum sample in several places in the protocol and its specific use was not well defined. Reappraisal of procedures in the central laboratory and sample volumes resulted in the determination that storage of a plasma sample is not needed. Consequently the retention sample has been removed. An inconsistency was also identified in which a sample for HSP-70 antibody was required in the schedule of visits, but not in the text. This has been clarified by removing the requirement for the sample to be drawn from the chart. Another inconsistency specifying the required serum chemistry analytes to be measured was identified and corrected, as this could result in larger blood draw volumes than intended.

Review of procedures in Part B for the PUPs identified potential confusion regarding blood draws required for mandatory inhibitor screening during the first 20 ED, as this could possibly occur on a day that is not a scheduled study visit. To reduce the likelihood that more blood samples are obtained than needed, these procedures were clarified. The blood volumes for required studies were reassessed and it was determined that the total might exceed safe levels in the smallest subjects. The protocol has been revised to provide specific information on the blood volumes to be collected at each study visit and provides methods to modify the samples to be drawn in infants who weigh less than 10 kg. In this population, HSP-70 antibody measurements will be not be obtained, and the local pediatric specialty laboratory may be used for serum chemistries and blood counts if needed. To reduce the potential for blood loss from study procedures greater than 1% in any single day, or 3% over a 30-day interval, the requirement to obtain recovery samples at Months 3, 4, and 5 (ED 5-15) was removed. Inability to tolerate the blood volumes required for study participation has been added as an exclusion criterion.

Sections affected include:

- Section 7.1.1, Tabulated overview
- Section 7.1.2, Timing of assessments
- Section 7.1.2.1, Visit 1 – Screening
- Section 7.1.2.2, Visit 2 – Baseline
- Section 7.1.2.3, Visit 3 – Month 1
- Section 7.1.2.4, Visit 4 – Month 2
- Section 7.1.2.5, Visit 5, Part B only; ED ~15 (14 ED +/- 1)
- Section 7.1.2.6, Visit – Month 2, only for PUPs
- Section 7.1.2.8, Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9, Visit 7 – Month 12 and every 6 months
- Section 7.1.2.10, Final visit
- Section 7.5.3.3, Standard safety laboratory
- Section 7.5.3.4, Inhibitor testing
- Section 14.4, Blood draws in subjects weighing less than 10 kg
- Section 14.5, Laboratory evaluation for suspected inhibitor

Change 3: Regulatory agencies requested division of the study procedures required for PTPs and PUPs. The protocol is now revised to more clearly demonstrate that the trial is separated in two sections, Part A for PTPs, and Part B for PUPs. Procedures and timing of visits for subjects in Part A is unchanged with the exception of a clarification that the maximum interval between the Screening and Baseline visit is 8 weeks and that total study participation may be from 6-8 months due to this interval. A +/- 1 week window has been added to allow flexibility with scheduled monthly visits.

The review of study procedures for Part B highlighted that unifying the schedule of visits for PTPs (who are treated 2x/week or more frequently) and PUPs (who may be treated 1x/week) was potentially confusing for investigators and could result in unnecessary study visits and blood draws. As the intent of the study is to gather observations of at least 50 ED, it is unlikely that PUPs receiving a once-a-week prophylactic regimen could complete the study within the 6 month treatment interval specified in the original protocol. The schedule of visits has thus been modified to account for the different dosing frequency, number of study visits, scheduled laboratory evaluations, and timeline of the two patient groups. Required blood draws are now correlated to the number of ED and no longer to a strict calendar schedule, and have been reduced as discussed above. It is clarified that the total duration of study participation in Part B is the amount of time required to achieve 50 ED.

Sections affected include:

- Synopsis – Doses
- Synopsis – Duration of treatment
- Synopsis – Diagnosis and main criteria for inclusion
- Synopsis – Methodology
- Section 4, Study design

- Section 5.1.1, Inclusion criteria
- Section 5.1.2, Exclusion criteria
- Section 6.1.1, Regular prophylaxis
- Section 7.1.1, Tabulated overview
- Section 7.1.2, Timing of assessments
- Section 7.1.2.1, Visit 1 – Screening
- Section 7.1.2.2, Visit 2 – Baseline
- Section 7.1.2.3, Visit 3 – Month 1
- Section 7.1.2.4, Visit 4 – Month 2
- Section 7.1.2.5, Visit 5, Part B only; ED ~15 (14 ED +/- 1)
- Section 7.1.2.6, Visit – Month 2, only for PUPs
- Section 7.1.2.7, Interim visit – Only for Part B (3-40 ED)
- Section 7.1.2.8, Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9, Visit 7 – Month 12 and every 6 months
- Section 7.1.2.10, Final visit
- Section 8.5, Planned interim analyses
- Section 8.6, Determination of sample size

Change 4: Regulatory agencies requested that the PUP trial be open to all age groups, including newborns. As the original protocol could be interpreted as requiring prophylaxis to start immediately or before the first bleeding event, and because prophylaxis is almost never started in early infancy, there is concern that the protocol risks those patients who may not be able to start prophylaxis for a variety of reasons. The amendment now allows for a limited number of ED prior to start of prophylaxis, an approach more consistent with current pediatric practice. As prophylaxis may begin across a wide range of patient ages, the dose of study medication for PUPs has been changed to 15 -50 IU/kg to account for the frequent use of the 250 IU vial size as a starting dose, irrespective of subject weight.

Sections affected include:

- Synopsis – Doses
- Section 6.1.1, Regular prophylaxis
- Section 6.4, Dosage and administration
- Section 7.1.2.2, Visit 2 – Baseline

Change 5: The voluntary PK sub-study has been modified to reduce the burden on the subjects and their families. The results of the PK assessment in Part A of Study 12954 demonstrate that BAY 81-8973 behaves similarly to Kogenate® FS/Bayer. As the PK of the currently marketed product is very well characterized in children, this data provide the opportunity to reduce the number of blood samples required for the PK sub-study. The 48-hour time point is no longer required. The modified time points are pre-injection, then

post-injection at 20-30 minutes, 4 hours, and 24 hours. This results in 2 additional blood draws for subjects in the PK study.

Feedback from pediatric specialists highlighted that PK measurements may be useful to them in making individualized dosing decisions for their patients, and that such evaluations may be indicated only after a subject has started a new treatment. Since PK evaluations may be required as part of routine care in subjects of all ages, the amendment opens up voluntary participation in the PK sub-study to all age groups in Part A. It is not added to the PUP study due to the need to minimize blood draw volumes. As increased flexibility of scheduling may improve acceptance by families, the protocol is also modified to allow the PK sub-study to be performed at any study visit rather than just at the Baseline visit.

The timing of procedures, wash-out, documentation, and dosage to be used for performance of the PK are further defined, as these were not clear in the original protocol.

Sections affected include:

- Synopsis – Study objectives
- Synopsis – Methodology
- Section 2, Study objectives
- Section 4, Study design
- Section 6.1.2, Breakthrough bleeds and surgeries
- Section 6.1.4, Optional pharmacokinetic measurements
- Section 6.4, Dosage and administration
- Section 7.1.1, Tabulated overview
- Section 7.1.2, Timing of assessments
- Section 7.1.2.2, Visit 2 – Baseline
- Section 7.1.2.3, Visit 3 – Month 1
- Section 7.1.2.4, Visit 4 – Month 2
- Section 7.1.2.8, Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
- Section 7.4, Pharmacokinetics
- Section 8.3, Variables

Change 6: Clarification is provided in the protocol regarding the risk of inhibitors, and information and instructions added regarding procedures that may reduce the risk, or that need to be followed if an inhibitor is detected or clinically suspected. The definition of an inhibitor and how the data will be evaluated is more fully developed in the statistical section. As ‘insufficient response’ to treatment could be due to an inhibitor, this has been deleted as a criterion for withdrawal from the study. Supplementary information has been added to clarify the laboratory procedures to be followed, and a clause specifying that subjects who develop an inhibitor while on study may receive BAY 81-8973 up to 200 IU/kg daily for 18 months has been added. Treatment will be at the direction of the treating physician. Data on treatment, FVIII measurements, and inhibitor levels will continue to be collected.

Recent publications suggest the risk of inhibitors may increase when the first factor exposures occur during periods of inflammatory risk or are high dose and prolonged. This data was summarized in the original protocol, but is now more developed to provide specific recommendations to reduce the risk to the subject.

As 'insufficient response' to treatment could be due to an inhibitor, this has been deleted as a criterion for withdrawal from the study.

Sections affected include:

- Section 4, Study design
- Section 5.2.1, Withdrawal
- Section 6.1.1, Regular prophylaxis
- Section 6.1.5, Immune tolerance induction (ITI)
- Section 7.5.3.4, Inhibitor testing
- Section 14.5, Laboratory evaluation for suspected inhibitor

Change 7: A paragraph providing instructions on handling missed infusions has been added in recognition of the difficulties associated with repeated venous access in small children. The paragraph clarifies that there are specific situations where missed infusions are considered acceptable, and the need for appropriate documentation.

Sections affected include:

- Section 6.1.3, Missed infusions due to difficult venous or family travel

Change 8: The use and administration of the Healthcare Resources Utilization Questionnaire has now been clarified, as specific instructions on its use were missing from the original protocol. It is now clarified that the questionnaire will be administered by the investigator or delegate monthly throughout the study period, and that this may occur at any scheduled visit or subject contact with the study site. The questionnaire has received minor modifications to simplify administration and to clarify the data to be collected.

Sections affected include:

- Section 7.1.1, Tabulated overview
- Section 7.1.2.1, Visit 1 – Screening
- Section 7.1.2.2, Visit 2 – Baseline
- Section 7.1.2.3, Visit 3 – Month 1
- Section 7.1.2.4, Visit 4 – Month 2
- Section 7.1.2.5, Visit 5, Part B only; ED ~15 (14 ED +/- 1)
- Section 7.1.2.6, Visit – Month 2, only for PUPs
- Section 7.1.2.7, Interim visit – Only for Part B (3-40 ED)
- Section 7.1.2.8, Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9, Visit 7 – Month 12 and every 6 months

- Section 7.1.2.10, Final visit
- Section 14.3, Healthcare Resources Utilization Questionnaire

Change 9: Clarification of the use of the electronic patient diary (EPD) throughout the study. The EPD being used in this study was developed independently from the protocol. As a consequence, the terminology used to collect patient reported outcomes on the device was in some cases different from that in the protocol. Additionally, the instructions for transmitting data from the EPD to the study site reflected old devices that are no longer in use. To avoid confusion, the terminology in the protocol has been changed to be consistent with that on the electronic devices being used in the study and the procedures for transmitting data updated.

Due to feedback from investigators and subjects that they were unclear on how to report response of bleeds to treatment on the scale provided (excellent, good, moderately well, poor), suggested definitions are provided.

Additionally it is clarified that treatments given at the study visits should be documented in the CRF and not in the EPD.

Sections affected include:

- Section 6.7, Treatment compliance
- Section 7.3.1, Efficacy variables
- Section 7.3.2.1, Incremental recovery
- Section 7.3.2.2, Injection logs / bleeding verification

Change 10: Clarification of study objections and outcome variable.

The secondary objectives of the study have been reworded to provide better understanding of the goals of the study, but remain unchanged in content. Specifically, the objective which previously stated, “To assess the tolerability profile of BAY 81-8973 during prophylaxis and treatment of breakthrough bleeds and safety and efficacy during surgeries” was redundant with the primary objective. It has been changed to state that the secondary objective is specific to the safety and efficacy of the investigational product during surgery. The objective of assessing incremental recovery has been reworded to specify that the recovery of the investigational product is measured. The third objective is unchanged, but now contains language to emphasize that participation is voluntary.

In the text, the primary variable, the annualized number of total bleeds within 48 hours after a prophylactic infusion is further defined as being the sum of spontaneous bleeds and trauma bleeds combined.

Sections affected include:

- Synopsis – Study objectives
- Section 2, Study objectives
- Section 4, Study design
- Section 7.3.1, Efficacy variables

- Section 8.3, Variables

Change 11: Adaptation/clarification of inclusion criteria. As minor differences in inclusion criteria exist between Parts A and B of the study, the criteria specific to each patient population have been separated. For Part A, it is clarified that enrollment into the study will begin with subjects >6 years, before being opened to younger patients, that documented prior testing for an inhibitor is required, and that subjects must have received at least 50 ED with another FVIII product. For PUPs, the age group has been expanded in response to regulatory agency feedback that documentation of diagnosis is required, but prior testing for an inhibitor is not required. A clause has also been added indicating that the parents of PUPs must agree to begin prophylaxis as part of their care.

Sections affected include:

- Section 5.1.1, Inclusion criteria

Change 12: Adaptation/clarification of exclusion criteria. Exclusion criteria were clarified for better understanding. The exclusion criteria of a serum creatinine value > 2 mg/deciliter (dL) was modified to > 2x the upper limit of normal since pediatric normal ranges may vary by age group. Hepatic dysfunction, defined as AST/ALT > 5x upper limit of normal was added as such patients may have an acquired bleeding diathesis that may impact the primary study variable. The exclusion criteria were also adapted to better define the medications that should not have been taken prior to start of the study. For Part B, a new exclusion criterion was added for inability to tolerate the blood volumes required for study participation.

Sections affected include:

- Section 5.1.2, Exclusion criteria

Change 13: The exclusion criteria specify that immunosuppressive and immunomodulatory medications may not be taken during the study, however many children may use topical or inhaled corticosteroids for common pediatric disorders such as eczema or asthma that would not be considered contraindications to participation in the study. Additionally, although the recommendation is given that medications that cause a bleeding diathesis, such as aspirin should not be used in individuals with hemophilia, other groups of non-steroidal anti-inflammatory drugs (NSAIDs) are sometimes used for the treatment of joint pain or inflammation. In response to requests for clarification from several ethics committees and investigators, a clause has been added to provide further explanation.

Sections affected include:

- Section 6.9, Prior and concomitant therapy

Change 14: Requirements for the physical examination have been modified to be more consistent with pediatric practice. As measurement of length may be more accurate than height in infants and small toddlers, this parameter has been added. Blood pressure measurements in children may be inaccurate if appropriate cuff sizes are not used. As many sites may not have the correct pediatric size blood pressure cuffs, this measurement may be deferred in preference to documentation of an inaccurate measurement.

Sections affected include:

- Section 7.1.2.1, Visit 1 – Screening
- Section 7.1.2.2, Visit 2 – Baseline
- Section 7.1.2.3, Visit 3 – Month 1
- Section 7.1.2.4, Visit 4 – Month 2
- Section 7.1.2.5, Visit 5, Part B only; ED ~15 (14 ED +/- 1)
- Section 7.1.2.6, Visit – Month 2, only for PUPs
- Section 7.1.2.7, Interim visit – Only for Part B (3-40 ED)
- Section 7.1.2.8, Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9, Visit 7 – Month 12 and every 6 months
- Section 7.1.2.10, Final visit
- Section 7.5.3.1, Vital signs
- Section 7.5.3.2, Physical examination

Change 15: Changes in the study administrative structure have been made, specifically, the Sponsor's Study Medical Expert has been replaced.

Sections affected include:

- Title page
- Signature of the sponsor's medically responsible person
- Section 3, Investigators and other study participants

Change 16: Updated information was added reflecting current clinical studies using BAY 81-8973. The chromogenic assay used to measure the potency of the investigational drug is mentioned, since this information may be important to investigators when picking the appropriate dosages for subjects.

Sections affected include:

- Introduction

Change 17: Minor editorial clarifications and typographical/grammatical errors were corrected throughout the protocol.

Sections affected include:

- Abbreviations.
- Section 5.2.2, Replacement
- Section 6.2.1, Manufacture
- Section 6.2.2, Supply and packaging
- Section 6.2.5, Instructions for administration
- Section 6.6, Drug logistics and accountability
- Section 6.8, Post-study therapy
- Section 7.5.1.1, definitions
- Section 8.1, General considerations
- Section 8.2, Analysis sets
- Section 8.6, Determination of sample size
- Section 9.1, Data recording
- Section 10, Premature termination of study
- Section 11.2, subject information and consent
- Section 12, References
- Section 14.1, Introduction for use of study medication

13.1.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text". Corrections of typing errors or omissions are not highlighted in this amendment.

13.1.2.1 Change 1

Synopsis – Duration of treatment
Original protocol

6 months, >50 exposure days (ED).
Optional extension study until marketing authorization

Amended to

6 months <u>and/or</u> >50 exposure days (ED).
Optional extension study until marketing authorization

Synopsis - Methodology
Original protocol

The ~~main~~ study consists of a 6-month treatment ~~period with >~~50 ED. After Screening and Baseline visits, all subjects will be evaluated for inhibitor development at Months 1, 2, and 6. ~~PUPs will be tested every 3-5 ED up to ED 20 and will have an additional visit at Month 3. During the optional extension study, 6-monthly clinic visits with inhibitor testings are scheduled.~~

The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.

Amended to

Part A:

The study consists of 6-months of treatment in PTPs with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeding events to achieve at least 50 ED. After Screening and Baseline visits, all subjects will be evaluated for inhibitor development and incremental recovery at Months 1, 2, and 6. Enrollment in the study will be staggered, with subjects age >6-12 years entering first, followed by subjects 0-6 years.

Part B:

PUPs will be treated with BAY 81-8973 for all bleeding events and are required to start prophylaxis. Treatment will continue until at least 50 ED. Screening and baseline visits may be combined for this population. Subjects will be tested for inhibitors every 3-5 ED up to ED 20 and again at ED 50. Incremental recovery will be measured at Baseline, ED 20, and ED 50.

In both Part A and Part B, all infusions and bleeding events will be documented in an electronic patient diary (EPD) throughout the study.

Optional extension study:

Subjects in both Part A and B will be offered participation in an optional extension study to continue treatment with BAY 81-8973 to accumulate at least 100 ED or time of market authorization. During the extension study, visits to the treatment center will take place every 6-months for inhibitor screening.

The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.

Synopsis – Number of Subjects
Original protocol

~~35-50 plus PUPs~~

Amended to

Part A:

Total N= 50 PTP;
age group >6-12 years: N=25
age group 0-6 years: N=25
Part B:
N= 25

Total = 75 (includes both Part A and B)

Section 4, Study Design
Original protocol

This is a phase-III multicenter, open-label uncontrolled study to demonstrate safety and efficacy of treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds and surgeries in children with severe hemophilia A. The study will be conducted worldwide.

~~Thirty-five to fifty PTPs (part A) and PUPs (Part B) (20-25 subjects < 6 years, 15-25 subjects 6-12 years; minimum of 35 PTPs) will be included and receive prophylaxis administration of BAY 81-8973.~~

~~The study (part A)~~ will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without any safety concerns. ~~PUPs (Part B) can be included after 10 children have achieved~~ 50 ED. ~~The incremental recovery will be investigated. Participation in pharmacokinetic evaluations is optional and may be obtained in a subset of 6 to 13 subjects in the age group of 6-12 years, if parents consent to it.~~

The total study duration (including screening period) per subject will be approximately 6-~~7~~ months during which the subjects will accumulate at least 50 ED. ~~Thereafter,~~ subjects will be offered the participation in an open-label extension study for a~~t least~~ 6-12 months to ~~accumulate~~ at least 100 ED or until marketing authorization is obtained.

During the study, all subjects will receive treatment only with BAY 81-8973. The dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. ~~Treatment of~~ PUPs may start at a lower ~~dosing frequency with~~ a once per week schedule at the investigator's discretion.

Amended to

This is a phase-III multicenter, open-label uncontrolled study to demonstrate safety and efficacy of treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds, and surgeries in children with severe hemophilia A. The study will be conducted worldwide.

The study is divided into two parts: Part A will investigate a total of 50 PTPs up to 12 years of age. Part B will include 25 PUPs. All subjects will receive prophylactic administration of BAY 81-8973. Subjects in Part A will be treated with 25-50 IU/kg at least 2x a week, or more frequently as needed for prophylaxis. Treatment in Part B may begin with start of prophylaxis with 15-50 IU/kg (minimum dose 250 IU) at least one day a week, or with the subject's first bleeding event. The study drug will be used both for treatment of bleeding events and prevention of bleeds with surgical procedures. Individual subject dose decisions are at the discretion of the investigator.

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns in another study. PTPs ages 7 to 12 years will begin enrollment first, followed by PTPs 6 years and younger. Part B, for PUPs, will begin enrollment after 20 children in Part A have received 50 ED.

The total study duration (including screening period) per subject in Part A will be approximately 6-8 months during which the subjects will accumulate at least 50 ED. For Part B, subjects will continue in the study until achieving 50 ED. Consequently the duration will vary depending upon the frequency of prophylactic infusion and number of bleeding events. All subjects in both Parts A and B will be offered participation in an open-label extension study for an additional 6-12 months to allow observations for at least 100 ED or until marketing authorization is obtained. Enrollment of PUPs in Part B and the extension study may continue after Part A and the extension study for PTPs have been completed.

During the study, all subjects will receive treatment only with BAY 81-8973 for prophylaxis and treatment of bleeds. In Part A, the dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. In Part B, PUPs may start at a lower dose at a once per week schedule at the investigator's discretion.

Section 7.1.1, Tabulated overview

Original protocol

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Interaction between subject/parent and investigator[d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim [d] Visit**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before infusion and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after infusion)		X	X				X		X		
Infusion of study drug	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Amended to

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1 (+/- 1 week)**	**Visit 4 Month 2 (+/- 1 week)**	**Final visit Month 6 (Minimum 50 ED)**	**Extension Visit every 6 months**	**Extension Final visit**
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20 -30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	*Combined Screening and Baseline*	Visit 3 Month 1 or ED ~5	Visit 4 Month 2 or ED ~10	Visit 5 Month 3 or ED ~15	Visit 6, Month 4 or ED ~20	Interim [d] Visit 30-40 ED	Final visit or ED 50	Extension Visit every 6 months	Extension Final visit
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before infusion and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after infusion)		X	X				X		X		
Infusion of study drug	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Healthcare Resources Utilization Questionnaire	X	← monthly →									
Interaction between subject/parent and investigator	← weekly →								← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Section 7.1.2, Timing of assessments
Original protocol

The main study consists of a screening period ~~of up to 8 weeks and a 6-month treatment period and a minimum of~~ 50 ED per subject ~~will be accumulated. After the Screening and Baseline visits which may be combined to one visit for PUPs, further 3 visits are scheduled at Month 1, Month 2 and Month 6. PUPs will have monthly visits for the first 3 months and blood sampling every 3-5 ED for inhibitor testing~~

~~Thereafter,~~ subjects will be offered ~~to continue~~ treatment in an extension study until a total number of at least 100 ED per subject ~~will be~~ accumulated or until marketing authorisation of the drug~~, with~~ additional visits every 6 months.

Amended to

The main study consists of a Screening period followed by at least 50 ED per subject. The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits.

In Part A, PTPs, a minimum of 50 ED will be accumulated during a 6 month treatment period. Visits are scheduled at Month 1, Month 2 and Month 6.

In Part B, the treatment period will be extended until 50 ED have been accumulated. The duration of Part B will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events. Blood sampling for inhibitor testing is required every 3-5 exposure days up to 20 ED, and again at 50 ED. As most subjects will begin prophylaxis 1x week, study visits during the first 20 ED are expected to occur monthly. However, it is understood that bleeding events resulting in added doses, delayed start of prophylaxis after first bleeds, or missed infusions due to difficult i.v. access may result in some variation in the number of ED a patient has obtained at each visit or the exact interval between visits. Likewise, those patients who receive more frequent infusions, may require study visits more often than once a month.

After completing Part A or B, all subjects will be offered continued treatment in an extension study until a total number of at least 100 ED per subject are accumulated or until marketing authorisation of the drug. Participation will require additional visits every 6 months.

Section 8.5, Planned interim analyses
Original protocol

The main study has a duration of 6 months ~~and~~ the 6-months data will be analyzed for regulatory purposes as an interim analysis. ~~Subjects will continue~~ in the extension trial. The overall study will be closed after all subjects have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

Amended to

The main study has a duration of 6 months. The 6-month data for PTPs will be analyzed for regulatory purposes as an interim analysis. When safety has been assessed in 10-20 PTPs who

have received at least 50 ED, enrollment will begin in Part B. All subjects will have the option of continuing in the extension trial. The overall study will be closed after all subjects in Parts A and B have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

Section 8.6, Determination of sample size
Original protocol

According to the guideline CPMP/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), ~~at least 20 children under the age of 6 years (infants and toddlers) regardless of prior treatment should be included in the investigation. The next age group according to the age classification of International Conference on Harmonization (ICH)/CPMP guideline E11 (Clinical Investigation of Medicinal Products in the Pediatric Population)[19] refers to children up to the age of 11 years.~~ Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973.

Amended to

Sample size has been determined according to the requirements set forth by guideline CPMP/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), and taking into account the revised draft version, CHMP/BPWP/144533/09. Age groups are in accordance with the International Conference on Harmonization (ICH)/CPMP guideline E11 (Clinical Investigation of Medicinal Products in the Pediatric Population)[19] and sample sizes have been confirmed on consultation with the EMA/PDCO on submission of the Pediatric Investigation Plan.

13.1.2.2 Change 2

Section 7.1.1, Tabulated overview

Original protocol

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1	Visit 4 Month 2	Final visit Month 6	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level before injection and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after ~~injection~~)		X		X	X		
~~Plasma retention sample~~							
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Injection of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare utilization					monthly		
Interaction between subject/parent and investigator		← weekly →					
Concomitant medication	X	← continuously →					

a. Complete Blood Count (CBC), Chemistries

b. Blood samples at the following time points: before, 20-30 min, 4 h, 24 h post-injection following a washout of 48 h after last dose of FVIII
Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim Visit**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before injection and inhibitor				X	X	X	X		X	X	X
Recovery (20-30 min after injection)		X	X				X		X		
~~Plasma retention sample~~											
Injection of study drug	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Plasma retention sample											
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > kg at baseline visit
. Interim visit only if less than 40 ED have been achieved by Month 6.

Amended to

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1	Visit 4 Month 2	Final visit Month 6	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level before-injection and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after injection)		X		X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Injection of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare utilization					monthly		
Interaction between subject/parent and investigator		← weekly →					
Concomitant medication	X	← continuously →					

a. Complete Blood Count (CBC), Chemistries
b. Blood samples at the following time points: before, 20-30 min, 4 h, 24 h post-injection following a washout of 48 h after last dose of FVIII
Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6 Month 4 or ED ~20**	**Interim Visit**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before injection and inhibitor				X	X	X	X		X	X	X
Recovery (20-30 min after injection)		X	X				X		X		
Injection of study drug		← continuously in accordance with the prophylaxis regimen →									
Patient diary (EPD) documentation	X	← continuously →									
Plasma retention sample											
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > kg at baseline visit
. Interim visit only if less than 40 ED have been achieved by Month 6.

Section 7.1.2, Timing of assessments
Original protocol

The main study consists of a screening period ~~of up to 8 weeks and a 6-month treatment period and a minimum of~~ 50 ED per subject ~~will be accumulated. After the Screening and Baseline visits which may be combined to one visit for PUPs, further 3 visits are scheduled at Month 1, Month 2 and Month 6. PUPs will have monthly visits for the first 3 months and blood sampling every 3-5 ED for inhibitor testing~~

~~Thereafter,~~ subjects will be offered ~~to continue~~ treatment in an extension study until a total number of at least 100 ED per subject ~~will be~~ accumulated or until marketing authorisation of the drug~~, with~~ additional visits every 6 months.

Amended to

The main study consists of a Screening period followed by at least 50 ED per subject. The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits.

In Part A, PTPs, a minimum of 50 ED will be accumulated during a 6 month treatment period. Visits are scheduled at Month 1, Month 2 and Month 6.

In Part B, the treatment period will be extended until 50 ED have been accumulated. The duration of Part B will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events. Blood sampling for inhibitor testing is required every 3-5 exposure days up to 20 ED, and again at 50 ED. As most subjects will begin prophylaxis 1x week, study visits during the first 20 ED are expected to occur monthly. However, it is understood that bleeding events resulting in added doses, delayed start of prophylaxis after first bleeds, or missed infusions due to difficult i.v. access may result in some variation in the number of ED a patient has obtained at each visit or the exact interval between visits. Likewise, those patients who receive more frequent infusions, may require study visits more often than once a month.

After completing Part A or B, all subjects will be offered continued treatment in an extension study until a total number of at least 100 ED per subject are accumulated or until marketing authorisation of the drug. Participation will require additional visits every 6 months.

Section 7.1.2.1, Visit 1 – Screening
Original protocol

At the screening visit, the following procedures and assessments will be performed:

…

- Blood samples for laboratory tests complete blood count CBC Chemistry ~~(Electrolytes, creatinine, ALT, aspartate aminotransferase [AST], total bilirubin), FVIII:C level, frozen serum sample, inhibitor test)~~
- ~~,~~ FVIII:C level, ~~frozen serum sample,~~ inhibitor test

Amended to

At the screening visit, the following procedures and assessments will be performed:

…

- Blood samples for laboratory tests:
  - Complete blood count [CBC]
  - Serum chemistry (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin. (See Section 14.4 for children <10 kg)
- FVIII:C level, inhibitor test (not required for PUPs)

Section 7.1.2.2, Visit 2 - Baseline
Original protocol

~~Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII injection) and~~ HSP-70 antibodies ~~Injection of the first dose of study drug~~
~~Note: If inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated~~

Amended to

- HSP-70 antibodies (in children > 7kg)
- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment).

Section 7.1.2.3, Visit 3 – Month 1
Original protocol

7.1.2.3 Visit 3 – Month 1

- ~~Blood sample for inhibitor test~~
  ~~Note: If prophylaxis treatment is started in PUPs, inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated~~
- Blood sample ~~for the~~ determination of FVIII trough levels (≥ 48 h after last FVIII ~~injection)~~

Amended to

7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B

- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment).

Section 7.1.2.1, Visit 4 – Month 2
Original protocol

7.1.2.4 Visit 4 – Month 2

- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII ~~injection) and HSP-70 antibodies~~

Amended to

7.1.2.4 Visit 4 – Month 2 <u>for Part A; ED ~10 (9 ED +/- 1) for Part B</u>

- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII <u>treatment</u>)

Section 7.1.2.5, Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (added)

<u>7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1)</u>

- <u>Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment).</u>

Section 7.1.2.6 Visit – Month 3, only for PUPs
Original protocol

7.1.2.6 Visit – ~~Month 3, only for PUPs~~

- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII ~~injection~~)

Amended to

7.1.2.6 Visit <u>6 – Part B only; ED 20 (20 ED +/- 1)</u>

- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII <u>infusion</u>).

Section 7.1.2.8 Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
Original protocol

7.1.2.8 Visit - ~~Month 6 or final visit~~ (end of the main study and start of the optional extension study)

- ~~Blood samples for laboratory tests (CBC, Chemistry (Electrolytes, creatinine, ALT, AST, total bilirubin), frozen serum sample)~~
- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII ~~injection~~) ~~and~~ HSP-70 antibodies ~~Injection~~ of study drug

Amended to

7.1.2.8 Final Visit - (end of the main study and start of the optional extension study)

- Blood samples for laboratory tests:
  - Complete blood count [CBC]
  - Serum chemistry (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin. (See Section 14.4 for children <10 kg)
- Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment).
- HSP-70 antibodies (in children > 7 kg).

Section 7.1.2.9 Visit 7 – Month 12 and every 6 months
Original protocol

7.1.2.9 ~~Visit 7 – Month 12 and every 6 months~~

- Blood sample for inhibitor testing

Amended to

7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)

- Blood sample for inhibitor testing and determination of FVIII:C trough level (>48 H after last FVIII treatment).

Section 7.1.2.10 Final visit
Original protocol

- Blood sample for inhibitor test~~ing~~

Amended to

- Blood sample for inhibitor test and determination of FVIII:C trough level (>48 H after last FVIII infusion).

Section 7.5.3.3 Standard safety laboratory
Original protocol

~~Blood~~ samples will be collected at Screening and Month 6 (or final visit)

~~Standard safety laboratory determinations will include the following parameters:~~

- CBC with differential: erythrocytes, hemoglobin, hematocrit, platelets, leukocytes, neutrophils, eosinophils, basophils, monocytes, and lymphocytes

- ~~Clinical chemistry: electrolytes (sodium [Na], potassium [K], calcium [Ca], chloride [Cl]), creatinine, alanine and aspartate aminotransferases (ALT, AST), lactate dehydrogenase (LDH), total and direct bilirubin, gamma-glutamyl transferase~~
- HSP-70 antibody

Amended to

The following blood samples will be collected at Screening and Month 6 (or final visit):

- CBC with differential: erythrocytes, hemoglobin, hematocrit, platelets, leukocytes, neutrophils, eosinophils, basophils, monocytes, and lymphocytes
- Serum chemistry (electrolytes (sodium [Na], potassium [K], bicarbonate [CO], chloride [Cl], creatinine, alanine and aspartate aminotransferases [ALT, AST], total bilirubin)

The following blood samples will be collected at Baseline and Month 6 (or final visit):

- HSP-70 antibody (except in subjects <7kg)

Section 7.5.3.4 Inhibitor testing
Original protocol

The FVIII inhibitor testings before study is not applicable for PUPs. ~~However~~, PUPs must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated. ~~The absence of inhibitors will be confirmed with the pre-exposure blood sample at baseline.~~

Subjects participating in the extension study will additionally be tested for inhibitor development every 6 months.

The laboratory analyses will be performed at central laboratories. ~~In addition, spare plasma sample will be collected and frozen at -70°C.~~ Investigators will be provided with a detailed laboratory manual and a copy of the individual results. Inhibitor testing will be done according to the Nijmegen modified Bethesda inhibitor assay. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU in the central lab. Any positive test must be confirmed by a second ~~different~~ sample, ~~for a second titer between 0.3 BU and 0.6 BU, a recovery is required for confirmation.~~

~~The spare 2 mL plasma samples collected at specified study visits will be for immunology or coagulation assays, or for clarification of any clinical or laboratory adverse event and in no case for genetic analyses.~~

Amended to

The requirement for a FVIII inhibitor test before study entry is not applicable for PUPs. The absence of inhibitors will be confirmed at the Baseline evaluation. After treatment is started, PUPs must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated.

Subjects participating in the extension study will additionally be tested for inhibitor development every 6 months.

The laboratory analyses will be performed at central laboratories.

Investigators will be provided with a detailed laboratory manual and a copy of the individual results. Inhibitor testing will be done according to the Nijmegen modified Bethesda inhibitor assay at the central laboratory. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU in the central lab. Any positive test must be confirmed by a second plasma sample.

Section 14.4 Blood draws in subjects weighing less than 10 kg (added)

14.4 Blood draws in subjects weighing less than 10 kg

Every effort has been made to minimize the volumes of blood required for participation in the study. For the majority of subjects in the study, the volumes drawn at any one visit are not expected to exceed more than 1 % of total blood volume, or 3% in any 1 month interval. However, in young infants, Part B of the study may require modification to allow participation by infants or small toddlers.

Table 14.4a shows the estimated total blood volume for children 1-10 kg and the recommended amount of blood for study purposes. These volumes should be considered a guideline, and may be exceeded if determined to be safe by the investigator.

Table 14.4a Recommended Blood Draw Volumes

Body Wt (Kg)	Body Wt (lbs)	Total blood volume (mL)	Allowable volume (mL) in one blood draw (1% of total blood volume)	Total volume (mL) drawn in a 30-day period (3% of total blood volume)
1	2.2	100	1	3
2	4.4	200	2	6
3	6.3	240	2.4	7.2
4	8.8	320	3.2	9.6
5	11	400	4	12
6	13.2	480	4.8	14.4
7	15.4	560	5	16.8
8	17.6	640	6.4	19.2
9	19.8	720	7.2	21.6
10	22	800	8	24

Ernst, D. J. Applied Phlebotomy. Lippincott Williams & Wilkins. 2005

Table 14.4b shows the blood volumes needed for the tubes used for the central laboratory.

Table 14.4b Volume of blood draws in Part B

	Visit 1 Screening	Visit 2 Baseline	Visit 3 ~5 ED	Visit 4 ~10 ED	Visit 5 ~15 ED	Visit 6 20 ED	Interim visit	Final visit 50 ED
Volume of blood (ml)	4.2	5.3	2.7	2.7	2.7	4.1	0	7.7
	7.7							

For infants at least 7 kg at study enrollment, the volumes listed for each individual visit should be well tolerated. As the Screening and Baseline visits can be combined for PUPs, investigators need to be aware that the total volume required could exceed 1% of total blood volume in children 9 kg or less. The total volume at the combined Screening and Baseline visit may be reduced if the CBC and chemistries are processed through the local laboratory using minimal volumes and the results entered in the CRF. The decision whether to use the local laboratory or to divide the blood sampling over more than one draw is at the investigator's discretion, but the total amount of blood drawn should not exceed 3% of total blood volume over a 30 day interval.

For infants who are 7 kg and smaller at study entry, the sampling schedule will be modified. The sample for collection of HSP-70 antibody (1.2 ml) will not be collected. FVIII trough level and inhibitor will be measured using a reduced volume (1.8 ml). Estimated blood volumes based upon these modifications are shown in table 14.4c.

Table 14.4c Modified volume of blood in infants less than 7 kg

	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 ~5 ED**	**Visit 4 ~10 ED**	**Visit 5 ~15 ED**	**Visit 6 20 ED**	**Interim visit**	**Final visit 50 ED**
Volume of blood (ml)	2.4	4.1	2.7	2.7	2.7	4.1	0	6.5
	6.5 (5.2)[a]							

a. (…) Est volume if CBC and chemistries obtained with minimal volumes through local laboratory

For infants less than 7 kg, for whom the Screening and Baseline visits are combined, it is recommended that the screening CBC and chemistries be processed through the local laboratory using minimal volumes, and the results entered in the CRF. Capillary samples may be used if care is used to minimize the risk of hemolysis. It is assumed that the minimal volume needed for both CBC and chemistries is approximately 1.1 ml.

Should an investigator wish to enroll a subject who weighs less than 5 kg, discussion with the sponsor is required.

Section 14.5 Laboratory evaluation for suspected inhibitor (added)

14.5 Laboratory evaluation for suspected inhibitor

If an inhibitor is clinically suspected (a bleed that progresses or does not improve following appropriate therapy), the subject be managed according to local standard of care. The investigator should immediately notify the sponsor and obtain the following information and blood tests:

- time and dose of last infusion
- infused product (if other than BAY 81-8973)

- blood for central laboratory
  - pre and post FVIII level/ aPTT
  - inhibitor to Factor VIII testing by the Nijmegen assay

13.1.2.3 Change 3

Synopsis – Dose(s)
Original protocol

25 -50 IU/kg; prophylaxis with at least 2 ~~injections~~ per week ~~in previously treated patients (PTPs) and at least 1 injection per week in previously untreated patients (PUPs)~~

Amended to

Part A:

PTPs: 25 -50 IU/kg (rounded to nearest size vial); prophylaxis with at least 2 infusions per week and treatment for breakthrough bleeds

Part B:

Previously untreated patients (PUPs): 15-50 IU/kg (rounded to nearest size vial); prophylaxis with at least 1 infusion per week and treatment for bleeds

Synopsis – Duration of treatment
Original protocol

6 months >50 exposure days (ED).
Optional extension study until marketing authorization

Amended to

6 months and/or >50 exposure days (ED).
Optional extension study until marketing authorization

Synopsis – Diagnosis and main criteria for inclusion
Original protocol

Severe hemophilia A (< 1% FVIII:C), age 0-12 years, no inhibitor history, no other bleeding disorder

Amended to

Severe hemophilia A (< 1% FVIII:C),

Part A: male, age 0-12 years, ≥ 50 ED, no inhibitor history, no other bleeding disorder

Part B: male, PUPs, no prior exposure to factor VIII concentrate or plasma

Synopsis - Methodology
Original protocol

The ~~main~~ study consists of ~~a~~ 6-month treatment ~~period with >~~50 ED. After Screening and Baseline visits, all subjects will be evaluated for inhibitor development at Months 1, 2, and 6. ~~PUPs will be tested every 3-5 ED up~~

~~to ED 20 and will have an additional visit at Month 3. During the optional extension study, 6-monthly clinic visits with inhibitor testings are scheduled.~~

The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.

Amended to

Part A:

The study consists of 6-months of treatment in PTPs with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeding events to achieve at least 50 ED. After Screening and Baseline visits, all subjects will be evaluated for inhibitor development and incremental recovery at Months 1, 2, and 6. Enrollment in the study will be staggered, with subjects age >6-12 years entering first, followed by subjects 0-6 years.

Part B:

PUPs will be treated with BAY 81-8973 for all bleeding events and are required to start prophylaxis. Treatment will continue until at least 50 ED. Screening and baseline visits may be combined for this population. Subjects will be tested for inhibitors every 3-5 ED up to ED 20 and again at ED 50. Incremental recovery will be measured at Baseline, ED 20, and ED 50.

In both Part A and Part B, all infusions and bleeding events will be documented in an electronic patient diary (EPD) throughout the study.

Optional extension study:

Subjects in both Part A and B will be offered participation in an optional extension study to continue treatment with BAY 81-8973 to accumulate at least 100 ED or time of market authorization. During the extension study, visits to the treatment center will take place every 6-months for inhibitor screening.

The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.

Original protocol

This is a phase-III multicenter, open-label uncontrolled study to demonstrate safety and efficacy of treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds and surgeries in children with severe hemophilia A. The study will be conducted worldwide.

~~Thirty-five to fifty PTPs (part A) and PUPs (Part B) (20-25 subjects < 6 years, 15-25 subjects 6-12 years; minimum of 35 PTPs) will be included and receive prophylaxis administration of BAY 81-8973.~~

~~The study (part A)~~ will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without ~~any~~ safety concerns. ~~PUPs (Part B) can be included after 10 children have achieved~~ 50 ED. ~~The incremental recovery will be investigated. Participation in pharmacokinetic evaluations is optional and may be obtained in a subset of 6 to 13 subjects in the age group of 6-12 years, if parents consent to it.~~

The total study duration (including screening period) per subject will be approximately 6-~~7~~ months during which the subjects will accumulate at least 50 ED. ~~Thereafter,~~ subjects will be offered the participation in an open-label extension study for ~~at least~~ 6-12 months to ~~accumulate~~ at least 100 ED or until marketing authorization is obtained.

During the study, all subjects will receive treatment only with BAY 81-8973. The dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. ~~Treatment of~~ PUPs may start at a lower dos~~ing frequency with~~ a once per week schedule at the investigator's discretion.

Amended to

This is a phase-III multicenter, open-label uncontrolled study to demonstrate safety and efficacy of treatment with BAY 81-8973 for prophylaxis, breakthrough bleeds, and surgeries in children with severe hemophilia A. The study will be conducted worldwide.

The study is divided into two parts: Part A will investigate a total of 50 PTPs up to 12 years of age. Part B will include 25 PUPs. All subjects will receive prophylactic administration of BAY 81-8973. Subjects in Part A will be treated with 25-50 IU/kg at least 2x a week, or more frequently as needed for prophylaxis. Treatment in Part B may begin with start of prophylaxis with 15-50 IU/kg (minimum dose 250 IU) at least one day a week, or with the subject's first bleeding event. The study drug will be used both for treatment of bleeding events and prevention of bleeds with surgical procedures. Individual subject dose decisions are at the discretion of the investigator.

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns in another study. PTPs ages 7 to 12 years will begin enrollment first, followed by PTPs 6 years and younger. Part B, for PUPs, will begin enrollment after 20 children in Part A have received 50 ED.

The total study duration (including screening period) per subject in Part A will be approximately 6-8 months during which the subjects will accumulate at least 50 ED. For Part B, subjects will continue in the study until achieving 50 ED. Consequently the duration will vary depending upon the frequency of prophylactic infusion and number of bleeding events. All subjects in both Parts A and B will be offered participation in an open-label extension study for an additional 6-12 months to allow observations for at least 100 ED or until marketing authorization is obtained. Enrollment of PUPs in Part B and the extension study may continue after Part A and the extension study for PTPs have been completed.

During the study, all subjects will receive treatment only with BAY 81-8973 for prophylaxis and treatment of bleeds. In Part A, the dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. In Part B, PUPs may start at a lower dose at a once per week schedule at the investigator's discretion.

Section 5.1.1 Inclusion criteria
Original protocol

In order to be included in the study, subjects must ~~meet~~ all of the following criteria upon evaluation at the Screening or Baseline visit:

…

Part B (PUPs) ~~Inclusion~~ of PUPs may start after ~~10~~ children ~~accumulated~~ 50 EDMale,

Amended to

In order to be included in the study, subjects must have all of the following criteria upon evaluation at the Screening or Baseline visit:

Part A

…

- Part B (PUPs) (Enrollment of PUPs may start after safety is evaluated in 20 children in Part A with 50 ED)

Section 5.1.2, Exclusion criteria
Original protocol

Subjects who meet any of the following criteria at Screening or Baseline visits will be excluded from participating in the study:

Part A and B

…

Part B only

…

Amended to

Subjects who meet any of the following criteria at Screening or Baseline visits will be excluded from participating in the study:

Parts A and B

…

Part B only (PUPs):

…

Section 6.1.1 Regular prophylaxis
Original Protocol

Duration:	6 months at least 50 ED at least 100 cumulative ED in subjects participating in the optional extension study~~)~~

Amended to

Duration:	Part A: 6 months and at least 50 ED Part B: 50 ED Extension study: at least 100 cumulative ED in subjects participating in the optional extension study or until market authorization

(Enrollment of PUPs may continue after PTPs have completed participation in Part A and the extension study)

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1	Visit 4 Month 2	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre ~~injection~~ and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after ~~injection~~) [c]		X		X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
~~Injection~~ of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b. Blood samples at the following time points: before, 20-30 min, 4 h, 24 h post-following a washout of 48 h after last dose of FVIII
c. Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6 Month 4 or ED ~20**	**Interim [d] Visit 30-40 ED**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before ~~injection~~ and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after ~~injection~~)		X	X				X		X		
~~Injection~~ of study drug		← continuously in accordance with the prophylaxis regimen →									
Patient diary (EPD) documentation	X	← continuously →									
Healthcare Resources Utilization Questionnaire	X	← monthly →									
Interaction between		← weekly →							← monthly →		

subject/parent and investigator			
Concomitant medication	X	←———	continuously ———→

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > kg at baseline visit
c. Interim visit only if less than 40 ED have been achieved by Month 6.
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Amended to

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator[d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim [d] Visit 30-40 ED**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before infusion and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after infusion)		X	X				X		X		
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →									
Patient diary (EPD) documentation	X	← continuously →									
Healthcare Resources Utilization Questionnaire	X	← monthly →									

Interaction between subject/parent and investigator		← weekly →	← monthly →
Concomitant medication	X	← continuously →	

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Section 7.1.2, Timing of assessments
Original protocol

The main study consists of a screening period of ~~up to 8 weeks and a 6-month treatment period and a minimum of~~ 50 ED per subject ~~will be accumulated. After the Screening and Baseline visits which may be combined to one visit for PUPs, further 3 visits are scheduled at Month 1, Month 2 and Month 6. PUPs will have monthly visits for the first 3 months and blood sampling every 3-5 ED for inhibitor testing~~

~~Thereafter,~~ subjects will be offered ~~to continue~~ treatment in an extension study until a total number of at least 100 ED per subject ~~will be~~ accumulated or until marketing authorisation of the drug~~, with~~ additional visits every 6 months.

Amended to

The main study consists of a Screening period followed by at least 50 ED per subject. The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits.

In Part A, PTPs, a minimum of 50 ED will be accumulated during a 6 month treatment period. Visits are scheduled at Month 1, Month 2 and Month 6.

In Part B, the treatment period will be extended until 50 ED have been accumulated. The duration of Part B will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events. Blood sampling for inhibitor testing is required every 3-5 exposure days up to 20 ED, and again at 50 ED. As most subjects will begin prophylaxis 1x week, study visits during the first 20 ED are expected to occur monthly. However, it is understood that bleeding events resulting in added doses, delayed start of prophylaxis after first bleeds, or missed infusions due to difficult i.v. access may result in some variation in the number of ED a patient has obtained at each visit or the exact interval between visits. Likewise, those patients who receive more frequent infusions, may require study visits more often than once a month.

After completing Part A or B, all subjects will be offered continued treatment in an extension study until a total number of at least 100 ED per subject are accumulated or until marketing authorisation of the drug. Participation will require additional visits every 6 months.

Section 7.1.2.1 Visit 1 – Screening
Original protocol

At the screening visit, the following procedures and assessments will be performed:

- Obtain~~ment of~~ written informed consent from the parents/legal representative. Assent ~~may be~~ obtained from subjects, depending on their age and intellectual status.
  Note: No Screening procedures may be performed unless written informed consent (and assent, if applicable) has been obtained (see Section 11.2)
- ~~Allocation~~ of a unique PID number (see Section 5.3)

- Eligibility check
  No subject may b~~e allocated to treatment~~ unless ~~adherence to~~ all ~~selection~~ criteria as given in Section 5.1 is given. Confirmation of selection criteria may be based on medical records ~~for inclusion~~, but laboratory test results must confirm eligibility ~~except~~ the severity of ~~the disease which is~~ based on ~~the~~ FVIII level at diagnosis.

…

- ~~Explanation~~ and dispense of the EPD

Amended to

At the screening visit, the following procedures and assessments will be performed:

- Obtain written informed consent from the parents/legal representative. Assent should be obtained from subjects, depending on their age and intellectual status or according to local practice.
  Note: No Screening procedures may be performed unless written informed consent (and assent, if applicable) has been obtained. (see Section 11.2)
- Assignment of a unique PID number (see Section 5.3)
- Eligibility check
  No subject may receive treatment with study drug unless all inclusion and exclusion criteria are met as given in Section 5.1. Confirmation of selection criteria may be based on medical records, but laboratory test results must confirm eligibility. The severity of hemophilia may be based on documented FVIII level at diagnosis.

…

- FVIII:C level, inhibitor test (not required for PUPs)
- Training on and dispensing of the EPD

Section 7.1.2.2 Visit 2 - Baseline
Original protocol

This visit will serve as the Baseline visit~~; i~~t will include the first administration of study drug. The Baseline visit should take place within 8 weeks after Screening visit and at least 48 h after last FVIII administration. Baseline may be combined with the screening visit if all selection criteria can be confirmed based on medical records ~~for PUPs without any previous FVIII exposure~~.

This visit should start with the following assessments:

- Confirmation of eligibility including check of laboratory test results.
  Note: Eligible subjects (except PUPs) must be inhibitor negative at Baseline.

~~Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII injection) and HSP-70 antibodiesInjection~~ of the first dose of study drug
Note: ~~If~~ inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated.

- Vital signs (Heart rate, temperature, blood pressure) after ~~injection~~

…

- Documentation of adverse events
- Check of ~~EPD documentation and documentation of interval treatment and bleeding history. Repeated training on the device if required.~~
- Instruction on the prophylaxis regimen to be administered to the subject

Regular weekly contacts between parents and the ~~investigator~~ to check the EPD documentation until next clinic visit.

Amended to

This visit will serve as the Baseline visit. It will include the first administration of study drug.

For subjects in Part A (PTPs), the Baseline visit should take place within 8 weeks after Screening visit and at least 48 h after last FVIII administration.

For subjects in Part B (PUPs), the Baseline visit may be combined with the Screening visit if all selection criteria can be confirmed based on medical records. The first dose of BAY 81-8973 may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment.

This visit should start with the following assessments:

- Confirmation of eligibility including check of laboratory test results.
  Note: Eligible subjects (except PUPs) must be inhibitor negative at Baseline.

Thereafter, the following activities will be performed:

…

- Infusion of the first dose of study drug

Note: For patients in Part B, first exposure to study drug may be either for treatment of an uncomplicated bleed or for start of prophylaxis. Inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated. See discussion on treatment of PUPs in Section 6.1.1.

- Vital signs (Heart rate, temperature, blood pressure) after infusion.

…

- Documentation of adverse events
- Check of understanding of EPD use. Repeat training on the device if required.
- Instruction on the prophylaxis regimen to be administered to the subject

Begin regular weekly contact between parents and the site to check the EPD documentation until next clinic visit. Contacts should be documented in the medical record.

Section 7.1.2.3 Visit 3 – Month 1

Original protocol

7.1.2.3 Visit 3 – Month 1

The following procedures and assessments will be performed:

- Check of EPD ~~documentation~~ and bleeding history

…

- ~~Injection~~ of study drug
- Vital signs ~~(Heart rate, temperature, blood pressure) before and~~ after ~~injection~~

…

Regular weekly contacts between parents and the ~~investigator~~ to check the EPD documentation until next clinic visit.

Amended to

7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B

The following procedures and assessments will be performed:

- Check of EPD entries and bleeding history.

…

- Infusion of study drug (Part A only)
- Vital signs after infusion, if given

…

Regular weekly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.1, Visit 4 – Month 2
Original protocol

7.1.2.4 Visit 4 – Month 2

The following procedures and assessments will be performed:

…

- ~~Injection~~ of study drug
- Vital signs ~~(Heart rate, temperature, blood pressure) before and~~ after ~~injection~~

…

- Check of EPD ~~documentation and documentation~~ of interval treatment and bleeding history.

Regular weekly contacts between parents and the ~~investigator~~ to check the EPD documentation until next clinic visit.

Amended to

7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B

The following procedures and assessments will be performed:

…

- Infusion of study drug (Part A only)
- Vital signs after infusion, if given.

…

- Check of EPD entries of interval treatment and bleeding history.

Regular weekly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (added)

7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1)

The following procedures and assessments will be performed:

…

- Check of EPD entries of interval treatment and bleeding history.

Regular weekly contact between parents and the site to check the EPD entries until next clinic visit.

Section 7.1.2.6 Visit – Month 3, only for PUPs
Original protocol

7.1.2.6 Visit – ~~Month 3, only for PUPs~~

The following procedures and assessments will be performed:

…

- ~~Injection~~ of study drug
- Vital signs ~~(Heart rate, temperature, blood pressure) before and~~ after ~~injection~~

…

- Check of EPD ~~documentation~~ of interval treatment and bleeding history.

Regular weekly contacts between parents and the ~~investigator~~ to check the EPD documentation until next clinic visit.

Amended to

Visit 6 – Part B only; ED 20 (20 ED +/- 1)

The following procedures and assessments will be performed:

…

- Infusion of study drug.
- Vital signs after infusion.

…

- Check of EPD entries of interval treatment and bleeding history.

Regular weekly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.7 Interim visit – Only for Part B (30-40 ED) (added)
7.1.2.7 Interim visit – Only for Part B (30-40 ED)

Visit only required for PUPs who have less than 40 ED, 6 months after the Baseline visit. The intent is to have at least one scheduled visit between completion of 20 ED and the expected date of accumulating 50 ED. The primary purpose of the visit is to assess the well being of the subject, ensure continued compliance with the treatment, and make any needed adjustments in dosage or infusion frequency based upon weight or bleeding events.

The following procedures and assessments will be performed:

- Check of EPD entries of interval treatment and bleeding history.

Regular weekly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.8 Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
Original protocol

7.1.2.8 Visit - ~~Month 6 or final visit~~ (end of the main study and start of the optional extension study)

This visit will take place 6 months after baseline and at least 50 ED were accumulated or in case of early termination.

The following procedures and assessments will be performed:

…

- ~~Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before and after injection~~

…

- Check of EPD ~~documentation and documentation~~ of interval treatment and bleeding history.

For subjects not participating in the optional extension study:

- Return of EPD
- Return of used and unused study ~~medication~~ for final drug accountability
- **Follow-up phone call (1-2 weeks after end of treatment)**
  Call parents/caregiver via telephone and review any new adverse events and changes in concomitant medication since the last study visit.

For subjects participating in the optional extension study:

- Informed consent signed by parents/legal representative must be available
- Continuation of prophylaxis treatment ~~including~~ regular ~~weekly~~ contacts between parents and the ~~investigator~~ to check the EPD documentation until next clinic visit.

Amended to

7.1.2.8 Final Visit - (end of the main study and start of the optional extension study)

For subjects in Part A, this visit will take place 6 months after baseline and at least 50 ED were accumulated, or in case of early termination.

For subjects in Part B, this visit will take place after 50 ED are accumulated, or in the case of early termination. It is expected 50 ED will be achieved for most subjects between 6 and12 months after start of prophylactic treatment.

The following procedures and assessments will be performed:

…

- Infusion of study drug.
- Vital signs after infusion.

…

- Check of EPD entries of interval treatment and bleeding history.

For subjects not participating in the optional extension study:

- Return of EPD
- Return of used and unused study vials for final drug accountability
- **Follow-up phone call (1-2 weeks after end of treatment)**
  Call parents/caregiver via telephone and review any new adverse events and changes in concomitant medication since the last study visit.

For subjects participating in the optional extension study:

- Informed consent signed by parents/legal representative must be available.
- Continuation of prophylaxis treatment
- Begin regular monthly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.9 Visit 7 – Month 12 and every 6 months
Original protocol

7.1.2.9 ~~Visit 7 – Month 12 and every 6 months~~

The following procedures and assessments will be performed:

…

- Check of EPD ~~documentation and documentation~~ of interval treatment and bleeding history

Amended to

7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)

The following procedures and assessments will be performed:

…

- Check of EPD entries of interval treatment and bleeding history

…

- Regular monthly contacts between parents and the site to check the EPD documentation until next clinic visit.

Section 7.1.2.10 Final visit
Original protocol

This visit will take place at the end of the extension period and at least 100 ED (including main study) ~~were~~ accumulated or in case of early termination.

The extension study will be ~~prolonged~~ until marketing authorization.

The final study visit must be performed at the time of switch to commercial drug.

The following procedures and assessments will be performed:

…

- Check of EPD ~~documentation and documentation~~ of interval treatment and bleeding history
- Return of EPD
- Return of used and unused study ~~medication~~ for final drug accountability

Follow-Up Phone Call (1-2 weeks after end of treatment)

Call parents/caregiver via telephone and review any new adverse events since the last study visit.

Amended to

This visit will take place at the end of the extension period and at least 100 ED (including main study) are accumulated, or in case of early termination.

The extension study will be continued until marketing authorization.

The final study visit must be performed at the time of switch to commercial drug.

The following procedures and assessments will be performed:

…

- Check of EPD entries of interval treatment and bleeding history
- Return of EPD
- Return of used and unused study vials for final drug accountability

Follow-Up Phone Call (1-2 weeks after end of treatment)

Call parents/caregiver via telephone and review any new adverse events since the last study visit.

Section 8.5 Planned interim analyses
Original protocol

The main study has a duration of 6 months ~~and~~ the 6-months data will be analyzed for regulatory purposes as an interim analysis. ~~Subjects will continue~~ in the extension trial. The overall study will be closed after all subjects have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

Amended to

The main study has a duration of 6 months. The 6-month data for PTPs will be analyzed for regulatory purposes as an interim analysis. When safety has been assessed in 10-20 PTPs who have received at least 50 ED, enrollment will begin in Part B. All subjects will have the option of continuing in the extension trial. The overall study will be closed after all subjects in Parts A and B have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

The trial data will be reviewed periodically by an independent Data Monitoring Committee (DMC). The DMC will review certain safety and efficacy data sets as defined in the charter, as well as the planned interim analysis, and provide written reports to the sponsor. The decision to open enrollment to each age group will be made following recommendation of the DMC.

Section 8.6 Determination of sample size
Original protocol

~~Therefore~~, this study will include ~~20~~-25 subjects ~~< 6~~ years ~~(PTPs)~~ and ~~15~~-25 subjects aged ~~between 6 and 12 years~~. ~~Thus, the~~ total sample size will be ~~35-50~~ subjects, ~~of whom a minimum of 35 subjects must be PTPs. The number of PUPs is not specified~~.

Amended to

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study consists of two parts. Part A will include a total of 50 PTPs; 25 subjects >6 – 12 years and 25 subjects aged 6 years and less. Part B will enroll 25 PUPs of all ages. Total sample size will be 75 subjects.

13.1.2.4 Change 4

Synopsis – Dose(s)
Original protocol

25 -50 IU/kg; prophylaxis with at least 2 ~~injections~~ per week ~~in previously treated patients (PTPs) and at least 1 injection per week in previously untreated patients (PUPs)~~

Amended to

Part A:

PTPs: 25 -50 IU/kg (rounded to nearest size vial); prophylaxis with at least 2 infusions per week and treatment for breakthrough bleeds

Part B:

Previously untreated patients (PUPs): 15-50 IU/kg (rounded to nearest size vial); prophylaxis with at least 1 infusion per week and treatment for bleeds

Section 6.1.1 Regular prophylaxis
Original Protocol

Test drug:	BAY 81-8973
Dosage:	25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, ≥ 1 ~~injection~~ per week in PUPs.
Route of administration:	Manual intravenous (IV) ~~injection~~ over 1 – 5 minutes according to total volume

Amended to

Test drug:	BAY 81-8973
Dosage:	25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, 15-50 International Unit (IU)/kg; ≥ 1 time per week in PUPs.

(Smallest size vial is 250 IU, which may be used for initial treatment of PUPs of any weight)

Route of administration: Manual intravenous (IV) infusion over 1 – 5 minutes according to total volume

Section 6.4 Dosage and administration
Original Protocol

The dose selections for this study are based on the recommended dosage for Kogenate® FS/Bayer.[6] The study medication, BAY 81-8973, has been shown to have similar biological activity to Kogenate® FS/Bayer, which is currently approved in more than 50 countries for the treatment of hemophilia A.

~~All~~ subjects will receive prophylaxis treatment with BAY 81-8973 ~~injections~~ at least 2 times weekly with a dose of 25-50 IU/kg at the choice of the investigator and according to local standards and previous treatment. The dose ~~will always be up-~~rounded to ~~full vials~~. ~~If a subject begins prophylactic treatment, a low frequency may be selected especially in small children. PUPs may start with 1x/week prophylaxis schedule.~~ The frequency as well as the dose may be adapted to the individual needs up to daily ~~injections~~ if needed to accommodate for the subject's activities~~, eg, sports or intensive activities which need a high protection~~. Any ~~instances of breakthrough~~ bleeding occurring in subjects receiving the prophylactic care will be treated according to the ~~current~~ standard of care and severity of the bleed.

Subjects will be injected by parents/caregivers at home ~~or other~~ facility near ~~to~~ subject's home, or by the investigator/delegate during the study visits. Children may also~~ start with~~ self-~~injections after training if they want to do so~~.

During surgery (both major and minor) dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14.1). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide ~~varying~~ instructions based upon the type of surgical procedure to be undertaken.

Amended to

The dose selections for this study are based on the recommended dosage for Kogenate® FS/Bayer.[6] The study medication, BAY 81-8973, has been shown to have similar biological activity to Kogenate® FS/Bayer, which is currently approved in more than 50 countries for the treatment of hemophilia A.

In Part A of this study, subjects will receive prophylaxis treatment with BAY 81-8973 at least 2 times weekly with a dose of 25-50 IU/kg at the choice of the investigator and according to local standards and previous treatment. The dose should be rounded to the appropriate vial size. In Part B, prophylaxis may be started with a low dose, once a week treatment schedule. The recommended dose is 15-50 IU/kg, rounded to the appropriate vial size (minimum 250 IU). For all subjects, the frequency as well as the dose may be adapted to the individual needs up to daily if needed to accommodate for the subject's activities or sports participation.

Any bleeding events occurring in subjects receiving prophylactic care will be treated according to the local standard of care and severity of the bleed.

Subjects will be injected by parents/caregivers at home, at a facility near the subject's home, homecare nurse, or by the investigator/delegate during the study visits. Children may also

self-infuse, if under the supervision of a responsible adult to ensure adherence to the prescribed treatment regimen.

During surgery (both major and minor) dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14.1). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide instructions based upon the type of surgical procedure to be undertaken.

Section 7.1.2.2 Visit 2 - Baseline
Original protocol

~~This visit will serve as the Baseline visit; it will include the first administration of study drug. The Baseline visit should take place within 8 weeks after Screening visit and at least 48 h after last FVIII administration~~. Baseline may be combined with the screening visit if all selection criteria can be confirmed based on medical records ~~for PUPs without any previous FVIII exposure~~.

~~Blood sample for inhibitor test and determination of FVIII:C trough levels (≥ 48 h after last FVIII injection) and HSP-70 antibodiesInjection of the first dose of study drug~~
Note: If inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated

Amended to

For subjects in Part B (PUPs), the Baseline visit may be combined with the Screening visit if all selection criteria can be confirmed based on medical records. The first dose of BAY 81-8973 may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment.

…

Note: For patients in Part B, first exposure to study drug may be either for treatment of an uncomplicated bleed or for start of prophylaxis. Inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated. See discussion on treatment of PUPs in Section 6.1.1.

13.1.2.5 Change 5

Synopsis – Study objectives
Original protocol

Secondary objectives

- To characterize pharmacokinetics in a subset of 6 to 13 ~~the age group of 6-12 years~~, if parents consent to it (participation for PK sampling is optional).

Amended to

Secondary objectives

- To characterize pharmacokinetics in a subset of 6 to 13 previously treated patients ((PTPs) (Part A only)), if parents consent to it (participation for PK sampling is optional).

Synopsis – Methodology

Original protocol

~~Safety laboratory tests, human coagulation factor VIII (FVIII) trough level measurements and recovery will be performed at the clinic visits during the main study only.~~

Amended to:

Pharmacokinetics (PK) samples will be collected in a subset of subjects at pre-infusion and then 20-30 minutes, 4 h, and 24 h post infusion. Participation in the PK portion of the study is voluntary and requires specific consent.

Section 2 Study objectives
Original protocol

Primary objective

Secondary objectives

- To assess pharmacokinetic parameters in a subset of ~~6 to 13~~ children. ~~in the age group of 6-12 years~~ (~~if parents consent to it , participation for pharmacokinetic [PK] sampling is optional,~~).

Amended to

Secondary objectives

- To assess pharmacokinetic parameters in a subset of children. (Part A only - participation in pharmacokinetic [PK] sampling is voluntary and requires consent,).

Section 4 Study Design
Original protocol

Incremental recovery and trough levels will be assessed in all subjects. ~~Other PK parameters (maxiumum concentration [C_{max}], half life, area under curve [AUC], Mean Residence Time [MRT] and clearance) are optional and may be assessed at baseline after the first dose in 6-13 subjects aged 6-12 years using sparse sampling schedule if parents and children (if appropriate) consent to participation.~~ Bleeding and injection information will be collected using an electronic ~~subject~~ diary (EPD), which will be provided to the parents/caregivers.

Amended to

Incremental recovery and trough levels of BAY 94-9027 will be assessed in all subjects. Subjects enrolled in Part A will be offered participation in the pharmacokinetic (PK) evaluation. Participation is optional, and requires consent. PK parameters (maximum concentration [C_{max}], half life, area under curve [AUC], Mean Residence Time [MRT] and clearance) may be assessed using a sparse sampling schedule. Bleeding and injection information will be collected using an electronic patient diary (EPD), which will be provided to the parents/caregivers.

Section 6.1.2 Breakthrough bleeds and surgeries

Original Protocol

BAY 81-8973 will be used for the treatment of breakthrough bleeds. The dosage will be at the discretion of the investigator.

For any surgery that may occur during the course of the study, BAY 81-8973 should be used. During surgery *(both major and minor)* dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14.2). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide varying instructions based upon the type of surgical procedure to be undertaken. Surgery is not allowed as first treatment ~~in a PUP~~.

Amended to

BAY 81-8973 will be used for the treatment of breakthrough bleeds. The dosage will be at the discretion of the investigator. For PUPs in Part B, see Section 6.1.1.

For any surgery that may occur during the course of the study, BAY 81-8973 should be used. During surgery *(both major and minor)* dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14.2). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide varying instructions based upon the type of surgical procedure to be undertaken. For PUPs in Part B, surgery is not allowed as first treatment and should be avoided, when possible, during the first 20 ED.

If the study site routinely measures PK prior to surgical procedures, these results may be used to fulfill the optional PK in Part A, provided that consent is given in advance, the subject undergoes a 48 hour washout, sampling is obtained at the designated time points, and samples are sent to the central laboratory for evaluation.

In case of severe or potentially life threatening bleeding events, or the need for unplanned or emergency surgery, the subject should be managed following local standard of care, using readily available factor products.

Section 6.1.4 Optional pharmacokinetic measurements
Original Protocol

6.1.4 Optional pharmacokinetic measurements

Test drug:	BAY 81-8973
Dosage:	50 IU/kg as a single IV ~~injection~~, at least 48 h after any previous FVIII ~~injection~~.

Amended to

6.1.4 Optional pharmacokinetic measurements (Part A only)

Test drug:	BAY 81-8973
Dosage:	50 IU/kg as a single IV infusion, at least 48 h after any previous treatment with FVIII.

Section 6.1.5 Immune tolerance induction (ITI)
Original Protocol

If a subject develops an inhibitor, ~~an~~ ITI treatment should be considered.

Test drug: BAY 81-8973

Dosage: 200 IU/kg per day as initial dose, either once a day ~~one injection of 200~~ IU/kg or twice a day ~~100 IU/kg~~ at the investigator's discretion until the inhibitor is eradicated successfully or until failure ~~or~~ for a maximum of 18 months. ~~The regimen of 2x100 IU/kg per day is recommended.~~

The following criteria are applied for success:

1. no detectable inhibitor based on Nijmegen assay (< 0.6 BU)
2. normal recovery (> 66% of predicted)
3. normal half life (≥ 6 h~~, absence of anamnestic response~~)

Failure is defined as no response (< 20% decrease in the inhibitor level) within a 6 months period ~~after the first 3 months~~ in the absence of any infection. ~~The detailed treatment plan should be agreed with the Coordinating Investigator.~~

Amended to

If a subject develops an inhibitor, ITI should be considered. All treatments, FVIII measurements, and inhibitor levels will be documented.

Test drug: BAY 81-8973

Dosage: 200 IU/kg per day as initial dose, either once a day or 100 IU/kg twice a day at the investigator's discretion until the inhibitor is eradicated successfully, or until failure, for a maximum of 18 months. The detailed treatment plan should be agreed with the Coordinating Investigator.

The following criteria are applied for success:

1. no detectable inhibitor based on Nijmegen assay (< 0.6 BU)
2. normal recovery (> 66% of predicted)
3. normal half life (≥ 6 h)

Failure is defined as no response (< 20% decrease in the inhibitor level) within a 6 months period in the absence of any infection.

Section 6.4 Dosage and administration
Original Protocol

For the optional PK study, each subject will receive a dose of ~~approximately~~ 50 IU/kg of BAY 81-8973. The dose will be prepared by a pharmacist or nurse at the study ~~center~~. This dose ~~would be~~ expected to increase the plasma level of FVIII to approximately 80-100% FVIII activity ~~in the severe hemophilia subjects~~.

Amended to

For the optional PK study (Part A only), each subject will receive an exact dose of 50 IU/kg of BAY 81-8973. The dose will be prepared by a pharmacist or nurse at the study site. This dose is expected to increase the plasma level of FVIII to approximately 80-100% FVIII activity.

Section 7.1.1 Tabulated overview
Original protocol

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator [d]		← weekly →					
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII.
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Amended to

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator[d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Section 7.1.2 Timing of assessments
Original protocol

The main study consists of a screening period ~~of up to 8 weeks and a 6-month treatment period and a minimum of~~ 50 ED per subject ~~will be accumulated. After the Screening and Baseline visits which may be combined to one visit for PUPs, further 3 visits are scheduled at Month 1, Month 2 and Month 6. PUPs will have monthly visits for the first 3 months and blood sampling every 3-5 ED for inhibitor testing~~

~~Thereafter,~~ subjects will be offered ~~to continue~~ treatment in an extension study until a total number of at least 100 ED per subject ~~will be~~ accumulated or until marketing authorisation of the drug~~, with~~ additional visits every 6 months.

Amended to

The main study consists of a Screening period followed by at least 50 ED per subject. The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits.

In Part A, PTPs, a minimum of 50 ED will be accumulated during a 6 month treatment period. Visits are scheduled at Month 1, Month 2 and Month 6.

In Part B, the treatment period will be extended until 50 ED have been accumulated. The duration of Part B will vary and is dependent upon the frequency of prophylactic infusion and the number of bleeding events. Blood sampling for inhibitor testing is required every 3-5 exposure days up to 20 ED, and again at 50 ED. As most subjects will begin prophylaxis 1x week, study visits during the first 20 ED are expected to occur monthly. However, it is understood that bleeding events resulting in added doses, delayed start of prophylaxis after first bleeds, or missed infusions due to difficult i.v. access may result in some variation in the number of ED a patient has obtained at each visit or the exact interval between visits. Likewise, those patients who receive more frequent infusions, may require study visits more often than once a month.

After completing Part A or B, all subjects will be offered continued treatment in an extension study until a total number of at least 100 ED per subject are accumulated or until marketing authorisation of the drug. Participation will require additional visits every 6 months.

Section 7.1.2.2 Visit 2 - Baseline
Original protocol

- Blood sample for the determination of recovery to be taken at 20-30 min after end of ~~injection~~.

Amended to

- Blood sample for the determination of recovery to be taken at 20-30 min after end of infusion.
- Optional PK (only for subjects participating in Part A): Additional blood samples at 4 h and 24 h post infusion (obtained only once during study).

Section 7.1.2.3 Visit 3 – Month 1
Original protocol

7.1.2.3 Visit 3 – Month 1

The following procedures and assessments will be performed:

- Blood sample for the determination of recovery to be taken at 20-30 min after end of ~~injection~~.

Amended to

7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B

The following procedures and assessments will be performed:

- Blood sample for the determination of recovery to be taken at 20-30 min after end of infusion.

Section 7.1.2.1 Visit 4 – Month 2
Original protocol

7.1.2.4 Visit 4 – Month 2

- Blood sample for the determination of recovery to be taken at 20-30 min after end of ~~injection~~.

Amended to

7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B

- Blood sample for the determination of recovery to be taken at 20-30 min after end of infusion. (Part A only)
- Optional PK (only for subjects participating in Part A): Additional blood samples at 4 h and 24 h post infusion (obtained only once during study).

Section 7.1.2.8 Visit – ~~Month 6 or final visit~~ (end of the main study and start of the optional extension study)
Original protocol

- Blood sample for the determination of recovery to be taken at 20-30 min after end of ~~injection~~.

Amended to

7.1.2.8 Final Visit - (end of the main study and start of the optional extension study)

- Blood sample for the determination of recovery to be taken at 20-30 min after end of infusion.
- Optional (only for subjects participating in Part A): Additional blood samples at 4 h and 24 h post infusion obtained only once during study

Section 7.4 Pharmacokinetics (optional)

Original protocol

7.4 Pharmacokinetics (optional)

Participation in the PK evaluations is optional. The minimal number of subjects in the optional PK is 6. ~~Up to 13 subjects of the age group 6-12 years may participate if parents consent to the PK~~. If ~~parents are~~ consent~~ing to participate in the PK, a sparse sampling approach will be followed with reduced number of~~ sampling time points. The pharmacokinetics of the study drug in plasma ~~will~~ be determined ~~after the 1st administration at Baseline visit~~. There must be a washout of previous FVIII of at least 48 h before the first ~~injection~~ of study drug and the subject must have no signs or symptoms of an acute bleeding episode.

Subjects will be administered a dose of 50 IU/kg. Blood samples will be obtained pre-injection and at 20-30 min, ~~3-5 h, 22-26 h and 46-50 h~~ after the end of ~~injection~~ of study medication. ~~Approximately 5 mL blood will be drawn at each time point.~~ FVIII levels will be determined by the ~~one-stage assay and~~ chromogenic assay. Details of the blood sampling and processing procedures for all laboratory measurements will be provided in the Study Procedure Manual (SPM) that accompanies this protocol.

Based on the plasma concentration time data the following pharmacokinetic parameters will be calculated: C_{max}, recovery, AUC, half-life ($t_{1/2}$), MRT and clearance (CL).

Amended to

7.4 Pharmacokinetics – Part A only (optional – consent required)

Participation in the PK evaluations is optional. The minimal number of subjects in the optional PK is 6. If consent/assent is obtained, PK will be assessed using the sampling time points specified in this protocol. The pharmacokinetics of the study drug in plasma can be determined at any time during the main study, and should be scheduled to coincide with a scheduled visit to measure incremental recovery, if possible. There must be a washout of previous FVIII of at least 48 h before the first infusion of study drug and the subject must have no signs or symptoms of an acute bleeding episode. All samples will be processed in the central laboratory.

Subjects will be administered a dose of 50 IU/kg. Blood samples will be obtained pre-infusion and at 20-30 min, 4 h, and 24 h after the end of infusion of study medication.. FVIII levels will be determined by the chromogenic assay. Details of the blood sampling and processing procedures for all laboratory measurements will be provided in the Study Procedure Manual (SPM) that accompanies this protocol. A dose preparation worksheet will be provided in the Pharmacy manual.

Based on the plasma concentration time data the following pharmacokinetic parameters will be calculated: C_{max}, recovery, AUC, half-life ($t_{1/2}$), MRT and clearance (CL).

Section 8.3 Variables
Original protocol

Pharmacokinetics / pharmacodynamics (Optional)

For investigation of drug exposure and potential relationships to drug effects, selected subjects from selected centers only will participate in pharmacokinetic (PK) sampling. Subject's participation in PK sampling is voluntary and ~~parents have to~~ consent ~~to it~~. PK sampling will be performed in centers which have experience in PK studies and volunteer to participate. ~~For further details of PK sampling, please refer to Section 7.1.1.~~

Based on the known PK ~~variability~~ of FVIII in hemophilia subjects it is expected that a ~~sparse~~ sampling strategy will be sufficient to calculate relevant pharmacokinetic parameters.

Blood samples for population PK analyses will be collected according to a sampling schedule ~~in predefined windows~~. Blood sampling for the determination of FVIII concentration in plasma will be taken at baseline ~~after~~ the ~~first injection~~ at 20-30 minutes, ~~3-5 h, 22-26 h and 46-50 h~~ after end of ~~injection (or at pre dose, the dosing time of the preceding dose will be documented). Samples which are collected outside of the predefined windows will nevertheless be valid for PK analysis. Start and end time of dose and exact sampling times should be documented.~~

A minimal number of 6 subjects is required. The following parameters will be calculated: C_{max}, AUC, recovery, clearance, MRT and t ½ using non-compartmental methods.

Amended to

Pharmacokinetics / pharmacodynamics (Optional)

For investigation of drug exposure and potential relationships to drug effects, selected subjects from selected centers only will participate in pharmacokinetic (PK) sampling. Subject's participation in PK sampling is voluntary and consent/assent is required. PK sampling will be performed in centers which have experience in PK studies and volunteer to participate.

Based on the known PK of FVIII in hemophilia subjects it is expected that a reduced sampling strategy will be sufficient to calculate relevant pharmacokinetic parameters.

Blood samples for population PK analyses will be collected according to a sampling schedule. Blood sampling for the determination of FVIII concentration in plasma will be taken at

baseline before the infusion (pre-infusion) at 20-30 minutes, 4 h, and 24 h after end of infusion. Attempt should be made to collect the sample as close as possible to the times indicated above. If there is a delay in collecting a sample, the sample should still be collected so that there are at least 3 samples post infusion. In all cases the exact time of start and end of infusion and the time of actual sample collection should be noted in the CRF.

A minimal number of 6 subjects is required. The following parameters will be calculated: C_{max}, AUC, recovery, clearance, MRT and t ½ using non-compartmental methods.

13.1.2.6 Change 6

Section 4 Study Design (added)

In the event that any subject acquires an inhibitor to FVIII, Immune Tolerance Induction (ITI) will be offered. The subject may receive BAY 81-8973 up to 200 IU/kg daily for 18 months. Treatment will be at the direction of the treating physician. Data on treatment, FVIII measurements, and inhibitor levels will be collected.

Section 6.1.1 Regular prophylaxis
Original Protocol

Effective prophylaxis requires replacement therapy in order to maintain a FVIII in above 1%. Based on the kinetics 3 week ~~application schedule~~. ~~It is well known that the~~ FVIII clearance is higher in children than in adults~~. In order to maintain a FVIII trough level above 1%~~, the ~~application~~ schedule for children ~~is~~ every other day.

~~Nevertheless, the~~ frequent injections may be difficult for small children and their ~~parents~~. The benefit must be evaluated against ~~the high~~ burden ~~mainly in the first 6 months of treatment~~. ~~In addition, it has been shown, that~~ the first exposures may be critical for the tolerance of the drug. The CANAL study showed that ~~high dosages for~~ surger~~ies and~~ severe bleeds increased the risk for inhibitor development whereas ~~the~~ prophylaxis ~~decreased this~~ risk [17]. This observation was ~~also confirmed by~~ treatment centers in Germany [18].

Taking into account these observations, the following ~~prophylaxis sche~~dule is recommended:

- with a once-a-week schedule and a low dose of 250 IU (15-25 IU/kg)
- ~~,~~increase frequency ~~if required clinically because of~~ bleed~~s or increased~~ physical activity

~~If first treatment is required for a surgery, the subject cannot be included (see Section 5.1)~~

~~If first treatment is required for a bleed, treat the bleed with moderate dosages and continue with prophylaxis once a week, increase frequency if required~~

~~Perform~~ inhibitor testing every 3-5 ED until 20 ED are accumulated or in case of non-response to treatment.

Amended to

Effective prophylaxis requires replacement therapy in order to maintain FVIII activity in the blood above 1%. Based on the kinetics, optimal prophylactic treatment requires infusion at least 3 times a week. As FVIII clearance is higher in children than in adults, the optimal infusion schedule for children may require treatment as frequently as every other day. Frequent injections may be difficult for small children and their caretakers. Consequently, the benefit for each individual child must be evaluated against this burden, particularly in very young children for whom venous access may be difficult.

Recent studies have demonstrated that the timing of the first exposures to FVIII may be critical for the tolerance of the drug. The CANAL study showed that early intensive treatment such as that required for surgery or severe bleeds increased the risk for inhibitor development, whereas regular prophylaxis was associated with a lower risk [17]. This observation was subsequently supported by studies demonstrating lower inhibitor rates in boys treated with low dose early prophylaxis in treatment centers in Germany [18].

Taking into account these observations, the following is recommended for PUPs participating in Part B:

- Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion.
- Begin prophylaxis with a once-a-week schedule low dose of 250 IU (15-25 IU/kg); the starting dose may be tailored to the patient's weight or demonstrated bleeding tendency.
- Avoid starting prophylaxis during febrile illness or other identified inflammatory events.
- Increase frequency of infusion or dose as needed for breakthrough bleeding, increased physical activity, or weight gain.
- Avoid surgery or need for high dose intensive treatment lasting more than 4 days during the first 20 exposure days.
- Do not give FVIII as prophylaxis for vaccinations.

After treatment with BAY 81-8973 begins, inhibitor testing every 3-5 ED is required until 20 ED are accumulated or in case of non-response to treatment (Section 14.5).

Section 5.2.1 Withdrawal
Original protocol

Subjects *must* be withdrawn from the study for ~~the~~ following reasons:

- At their own request or at the request of their legal~~ly acceptable~~ representative
- At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- At the ~~specific~~ request of the sponsor
- A positive inhibitor result at screening or baseline ~~before first injection~~

~~Subjects *may* be withdrawn from the study for the following reasons:~~

- ~~At the specific request of the sponsor~~
- ~~Insufficient response to FVIII treatment~~
- If, in the judgment of the investigator or the sponsor, the subject is not compliant with the protocol.

Amended to

Subjects *must* be withdrawn from the study for ~~the~~ <u>any of the</u> following reasons:

- At their own request or at the request of their <u>parent/</u>legal representative
- At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- A positive inhibitor result at Screening or Baseline <u>visits</u>
- At the request of the sponsor
- If, in the judgment of the investigator or the sponsor, the subject is not compliant with the protocol.

Section 7.5.3.4 Inhibitor testing
Original protocol

Premise for inclusion ~~in this study is the availability of a~~ negative test result of inhibitor at Baseline.

Blood samples for FVIII inhibitor testing will be taken at Screening, Baseline, ~~Month 1, month 2, 3 and Month 6 (or~~ final visit~~)~~. Premise for inclusion of PTPs in this study is the availability of a negative ~~test result of~~ inhibitor as measured in the blood sample at Screening. A further sample will be taken at baseline before the first ~~injection~~. If the inhibitor test result

changed from negative at screening to positive at baseline before the first ~~injection~~ of study medication, the subject must be withdrawn from the trial.

Amended to

Premise for inclusion requires confirmed diagnosis of severe hemophilia A (<1% FVIII) and documentation of a negative test result of inhibitor at Baseline.

Blood samples for FVIII inhibitor testing will be taken at Screening (PTPs only), Baseline, at regularly scheduled intervals throughout the study, and at the final visit. Premise for inclusion of PTPs in this study is the availability of a negative inhibitor result as measured in the blood sample at Screening. A further sample will be taken at baseline before the first infusion. If the inhibitor test result changes from negative at screening to positive at baseline, before the first infusion of study medication, the subject must be withdrawn from the trial.

Section 14.5 Laboratory evaluation for suspected inhibitor (added)

14.5 Laboratory evaluation for suspected inhibitor

If inhibitor is confirmed, the subject may receive immune tolerance therapy using BAY 81-8973. (See section 6.1.4)

If an inhibitor is detected as part of scheduled testing, the investigator will be notified. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU in the central lab. Any positive test must be confirmed by a second plasma sample. Pre and post infusion samples will be required for confirmation.

13.1.2.7 Change 7

Section 6.1.3 Missed infusions due to difficult venous access or family travel (added)

6.1.3 Missed infusions due to difficult venous access or family travel

During the trial, it is expected that all reasonable attempts will be made to ensure that subjects will comply with and adhere to their designated prophylaxis infusion schedule with few interruptions. However, there may be situations when problems related to difficult venous access, or travel to locations where appropriate support for infusions is not available, may necessitate a brief hiatus in the treatment schedule. Parents should inform the investigator of all such situations, and the reason documented in the medical record. Prolonged or repeated breaks in the prophylaxis schedule should be avoided, and could result in the subject being removed from the study.

13.1.2.8 Change 8

Section 7.1.1 Tabulated overview
Original protocol

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire							
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII.
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim [d] Visit 30-40 ED**	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before infusion and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after infusion)		X	X				X		X		
Infusion of study drug	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Amended to

Table7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	Visit 3 Month 1 (+/- 1 week)	Visit 4 Month 2 (+/- 1 week)	Final visit Month 6 (Minimum 50 ED)	Extension Visit every 6 months	Extension Final visit
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	X	X
FVIII baseline level and inhibitor	X						
FVIII level pre infusion and inhibitor		X	X	X	X	X	X
Recovery (20-30 min after infusion) [c]		X	X	X	X		
Pharmacokinetics in up to 13 children (optional)		← X [b] →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare Resources Utilization Questionnaire	X	← monthly →					
Interaction between subject/parent and investigator[d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	Visit 2 Baseline	*Combined Screening and Baseline*	Visit 3 Month 1 or ED ~5	Visit 4 Month 2 or ED ~10	Visit 5 Month 3 or ED ~15	Visit 6, Month 4 or ED ~20	Interim [d] Visit 30-40 ED	Final visit or ED 50	Extension Visit every 6 months	Extension Final visit
Informed consent)	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	X [b]	X [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before infusion and inhibitor [c]				X	X	X	X		X	X	X
Recovery (20-30 min after infusion)		X	X				X		X		
Infusion of study drug	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Healthcare Resources Utilization Questionnaire	X	← monthly →									
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

Section 7.1.2.1 Visit 1 – Screening
Original protocol

- Recording of prior and concomitant medication

Amended to

- Recording of prior and concomitant medication and Healthcare Resources Utilization Questionnaire. (Appendix 14.3). Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature.

Section 7.1.2.2 Visit 2 - Baseline
Original protocol

- Update of concomitant medication and ~~questionnaire on healthcare utilisation~~ (Appendix 14.3)

Amended to

- Update of concomitant medication and Healthcare Resources Utilization Questionnaire. (Appendix 14.3)

Section 7.1.2.3 Visit 3 – Month 1
Original protocol

7.1.2.3 Visit 3 – Month 1

The following procedures and assessments will be performed:

- Check of EPD ~~documentation~~ and bleeding history ~~including~~ adverse events and ~~questionnaire on healthcare utilisation (Appendix 14.3)~~

Amended to

7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B

The following procedures and assessments will be performed:

- Check of EPD entries and bleeding history. Collect information on, adverse events and Healthcare Resources Utilization Questionnaire. (Appendix 14.3).

Section 7.1.2.1 Visit 4 – Month 2
Original protocol

7.1.2.4 Visit 4 – Month 2

- Documentation of interval history including adverse events and concomitant medication and ~~questionnaire on healthcare utilisation~~ (Appendix 14.3)

Amended to

7.1.2.4 Visit 4 – Month 2 <u>for Part A; ED ~10 (9 ED +/- 1) for Part B</u>

- Documentation of interval history including adverse events and concomitant medication and <u>Healthcare Resources Utilization Questionnaire</u> (Appendix 14.3).

Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (added)

<u>7.1.2.5, Visit 5 – Part B only; ED ~15 (14 ED +/- 1)</u>

- <u>Documentation of interval history including adverse events and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3).</u>

Section 7.1.2.6 Visit – Month 3, only for PUPs
Original protocol

7.1.2.6 Visit – ~~Month 3, only for PUPs~~

- Documentation of interval history including adverse events and concomitant medication and ~~healthcare utilisation~~ (Appendix 14.3)

Amended to

7.1.2.6 Visit <u>6 – Part B only; ED 20 (20 ED +/- 1)</u>

- Documentation of interval history including adverse events and concomitant medication and <u>Healthcare Resources Utilization Questionnaire</u> (Appendix 14.3).

Section 7.1.2.7 Interim visit – Only for Part B (30-40 ED) (added)
<u>7.1.2.7 Interim visit – Only for Part B (30-40 ED)</u>

- <u>Documentation of interval history including adverse events and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3).</u>

Section 7.1.2.8 Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
Original protocol

7.1.2.8 Visit - ~~Month 6 or final visit~~ (end of the main study and start of the optional extension study)

- Documentation of interval history including adverse events and concomitant medication

Amended to

7.1.2.8 Final Visit - (end of the main study and start of the optional extension study)

- Documentation of interval history including adverse events and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3).

Section 7.1.2.9 Visit 7 – Month 12 and every 6 months
Original protocol

7.1.2.9 ~~Visit 7 – Month 12 and every 6 months~~

- Documentation of interval history including adverse events and concomitant medication

Amended to

7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)

- Documentation of interval history including adverse events and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3).

Section 7.1.2.10 Final visit
Original protocol

- Documentation of interval history including adverse events and concomitant medication

Amended to

- Documentation of interval history including adverse events and concomitant medication and Healthcare Resources Utilization Questionnaire (Appendix 14.3).

Section 14.3 Healthcare Resources Utilization Questionnaire

Original protocol

~~Dear Parent/Caregiver,~~

~~We appreciate you taking time to complete this questionnaire about your son's health care resource utilization. All your answers are confidential. For the following questions, we would like to ask you to follow the instructions below.~~

- **Only one parent or caregiver, the person with whom the child relates most closely, should answer the questions.**
- **Are you ☐ the Mother? ☐ the Father? ☐ Other: _____**
- **Please read each question carefully.**

Study Center: _____Subject number:_____

_____

1. Did your child have any contact with health professionals this week?
_____NO _____YES (If no, then go to question 2.)

If yes, then
Date(s) of contact_____
Type of contact (Office visit_____ Phone call_____)
Reason for contact_____
Whom did your child see?
Hematologist_____
Family physician_____
Nurse_____
Pharmacist_____
Other (specify)_____

2. Did your child have any procedures performed this week?
_____NO _____YES (If no, then go to question 3.)

If yes, please check below:
Blood test_____ Date:_____ Number of times:_____
Biopsy_____ Date: _____ Number of times:_____
X-ray_____ Date: _____ Number of times:_____
MRI_____ Date: _____ Number of times:_____
CT scan_____ Date:_____ Number of times:_____
Other_____ Date:_____ Number of times:_____

3. Did your child have any lab tests performed this week? _____NO _____YES
_____ (If no, then go to question 4.)

If yes, please list: _____

4. Did your child have any joint-related surgery this week? _____NO _____YES

5. Was your child prescribed any medications this week? _____NO _____YES

(If no, then go to question 6.)

If yes, please list:

~~Name of medication_____ To take for how many days?_____~~
~~Reason for taking medication_____~~

~~6. Was your child hospitalized this week? _____NO _____YES~~

~~(If no, then go to question 7.)~~

~~If yes, Date of hospitalization_____ Date of discharge_____~~
~~Reason for hospitalization?_____~~

~~7. Did your child have an emergency room (ER) visit this week? _____NO _____YES~~

~~(If no, then go to question 8.)~~

~~If yes, Date of ER visit_____~~
~~Reason for ER visit?_____~~

~~8. Was your child in the intensive care unit (ICU) this week? ___NO _____YES~~

~~(If no, then skip to 9)~~

~~If yes, Date of admission to ICU_____~~
~~Date of discharge_____~~
~~Reason for ICU?_____~~

~~9. Work/productivity loss:~~

~~In the past week, how many days of school has your child missed due to Hemophilia?~~
~~_____~~

Amended to

The Healthcare Resources Utilization Questionnaire will be used to collect data on the subject. This will include number of days lost from school, medical procedures or laboratory tests, complications, and hospitalizations due to hemophilia or other medical needs. The questionnaire should be administered by the investigator or delegate monthly throughout the study period by interviewing a parent/caregiver. This can be performed either at scheduled study visits, or during regularly scheduled contact between the study site and the parent/caregiver. The answers will be entered on the paper questionnaire by the study site. The completed questionnaire is a source document subject to review by the monitor.

Healthcare Resources Utilization Questionnaire in LEO Kids (13400)

Instructions for the interviewer:

1. **Only one parent or caregiver, the person with whom the child relates most closely, should answer the questions consistently**
2. **Please record the answers in English.**
3. **Please do not write any other information on the form.**

Study Center: _____ Subject number: _____

Date of interview: _____ (MM/DD/YYYY)
This form is being completed for the month of _____ and year _____.
For example: Month of June and year 2011 (answers include contacts from June 1 to June 30, 2011).

1. Did your son have any contact with health professionals this past month that were not required as part of the LEO Kids study?
_____NO _____YES

If yes, then complete:
Type of contact: _____Office visit _____ Phone call (Check or enter how many if more than one.)
Reason for contact: _____
Whom did your child see? Please check all that apply:

___Hematologist
___Family physician
___Pediatrician
___Nurse
___Pharmacist
___Other, specify: _____

2. Did your son have any procedures or tests performed in the past month that were not required as part of the LEO Kids study?
_____NO _____YES

If yes, please check all that apply:
___ Blood test Number of times blood was drawn: _____ (even if multiple tubes were collected)
___ Urine test Number of times specimen collected: _____
___ Biopsy Number of times: _____
___ X-ray Number of times: _____ (can include multiple views)
___ MRI Number of times: _____
___ CT scan Number of times: _____
___ Joint surgery Number of times: _____

3. Did your son have any hospital visits in the past month?
_____NO _____YES

If yes, check the kind of visit:

___Hospital admission. For how many nights? _____ (Include nights in ICU/PICU)
___Emergency Department visit. For how many nights? _____
___Intensive Care Unit or Pediatric Intensive Care Unit (ICU or PICU).
For how many nights? _____
Reason: _____

4. Did your son miss any days of school due to hemophilia in the past month?
_____NO _____YES If yes, number of days missed? _____

13.1.2.9 Change 9

Section 6.7 Treatment of compliance
Original Protocol

Parents/caregivers will be provided with an electronic patient diary (EPD) for the whole study (for details see Section 7.3.2.2). These logs will be used to collecting the ~~injection~~ data and bleeding episodes ~~by the parents/caregivers and~~ interact ~~on a weekly basis with the Investigator or delegate to verify and complete the weekly injection and bleeds on the EPD.~~

P~~arents/caregivers must transmit the treatment records electronically using the~~ EPD~~device at least once every week~~. EPD will be ~~utilized~~ to assess the compliance with the prophylaxis treatment schedule and with the recording of ~~injection information for~~ bleeding events and medication inventory.

Participation in the study may be terminated at the sponsor's discretion if a subject fails to comply with ~~critical~~ protocol requirements.

Empty vials of study medication must be returned to the study center ~~for drug accountability~~ at each visit ~~during the study~~. At the end of the study, all used and unused study ~~medication must be collected~~ for final drug accountability.

Amended to

Parents/caregivers will be provided with an electronic patient diary (EPD) for the whole study (for details see Section 7.3.2.2). These logs will be used to collecting the treatment data and bleeding episodes. The subject/parent/caregiver will interact with the Investigator or delegate weekly to verify and complete the EPD entries, and monthly during the extension study.

Data on the EPD will be transmitted after each treatment is entered. The EPD will be used to assess the subject's compliance with the prophylaxis treatment schedule and with the recording of treatments and bleeding events, and assist in study medication inventory. See Section 6.1.3 for discussion of missed treatments.

Participation in the study may be terminated at the sponsor's discretion if a subject fails to comply with the above protocol requirements.

Empty vials of study medication must be returned to the study center at each study visit. At the end of the study, all used and unused study drug vials will be counted and collected by the sponsor's representative for final drug accountability.

Section 7.3.1 Efficacy variables
Original protocol

- ~~Physician's /~~ subject~~'s~~/parents' assessment of ~~the~~ response ~~in~~ treatment of ~~mayor~~ bleeding events which is assessed as excellent, good, moderate or ~~none~~.

Amended to

- Subject/parents' assessment of response to treatment of bleeding events, which is assessed as excellent, good, moderate or poor.

Section 7.3.2.1 Incremental recovery
Original protocol

7.3.2.1 Incremental recovery

Samples for FVIII trough levels will be collected in the ~~hospital setting~~ before the next planned ~~injection~~ as scheduled. Recoveries should be performed in conjunction with planned prophylaxis ~~injection~~.

~~FVIII~~ levels will be determined in a central laboratory with ~~both the one-stage and~~ the chromogenic ~~assays~~. T~~he same type of assay should be used throughout the study.~~

FVIII trough levels will be determined in the blood samples collected before the BAY 81-8973 ~~injections~~ at Baseline, Month 1, Month 2, and Month 6 (or final visit). The measurement should be performed ~~after an~~ at least 48-h t~~reatment-free interval.~~

Incremental recovery at 20-30 min after end of ~~injection~~ will be determined at Baseline, Month 1, 2 and Month 6 (or final visit). Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after ~~injection~~ have to be documented in the CRF.

Amended to

7.3.2.1 Incremental recovery <u>of Factor VIII</u>

Samples for FVIII trough levels will be collected in the <u>clinic</u> before the next planned <u>prophylactic infusion</u> as scheduled. Recoveries should be performed in conjunction with planned prophylaxis <u>infusions, using the subjects usual dose (exception, during optional PK in Part A). Infusions given at study visits will not be recorded in the EPD, but in the site patient records, which will be the source document and will be used to enter this information in the CRF.</u>

Levels <u>of BAY 81-8973</u> will be determined in a central laboratory with the chromogenic <u>method</u>.

FVIII trough levels will be determined in the blood samples collected before the <u>scheduled</u> BAY 81-8973 <u>infusions</u> at Baseline, Month 1, Month 2, and Month 6 (or final visit) <u>in Part A; or at Baseline, ED 20, and final visit (ED 50) in Part B</u>. The measurement should be performed at least 48-h <u>after last infusion of BAY 81-8973.</u>

Incremental recovery at 20-30 min after end of <u>infusions</u> will be determined at Baseline, Month 1, 2 and Month 6 (or final visit). Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after <u>infusion</u> have to be documented in the CRF.

Section 7.3.2.2 Injection logs / bleeding verification

Original protocol

7.3.2.2 Injections logs / bleeding verification

~~Injection~~ logs are commonly used for hemophilia subjects for documentation of their home treatment. Home treatment and bleeding frequency are key variables evaluated in this study. Study specific ~~injection~~ logs will be provided in national language. The preferred system for this study will be electronic patient diary (EPD) devices since they are interactive, allow for real time data transmission ~~to the sites~~, record-stamp date and time of fulfillment and facilitate the clarification of data with the site and also the data cleaning process.

Subjects/parents/caregivers will be provided with electronic patient diaries (EPDs) for the whole study. At Screening and Baseline visits, subjects and parents/caregivers will be trained in the use of the device. These logs will be used to collecting the ~~injection~~ data and bleeding episodes by the parents/caregivers or subjects, and interact on a basis with the investigator or delegate to verify and complete the ~~weekly injections and bleeds on~~ the EPD. Thus, the EPD will be considered the source for these data.

For each ~~injection~~ of study medication including the ~~injections~~ administered during a planned visit for evaluation of recovery, information must be recorded on the ~~Injection~~ Logs as follows:

1. Date and time
2. Lot numbers / number of vials administered
3. Reason for ~~injection~~ (~~regular~~ prophylaxis, ~~preventative prophylaxis,~~ spontaneous bleed first treatment, trauma bleed first treatment, follow-up treatment, ~~recovery,~~ surgery, other)

If treatment is for a bleeding episode: site of bleeding, severity (severe, moderate, mild), and response to treatment (excellent, good, moderate~~, none~~).

~~In case of major bleeds or surgery, also the investigator will assess the response to treatment (excellent, good, moderate, none).~~

~~Injections administered in the hospital must be planned in connection with the scheduled prophylactic injection of the study drug.~~

Amended to

7.3.2.2 <u>Treatment</u> logs / bleeding verification

<u>Treatment</u> logs are commonly used for hemophilia subjects for documentation of their home treatment. Home treatment and bleeding frequency are key variables evaluated in this study. Study specific logs will be provided in national language. The preferred system for this study will be electronic patient diary (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 also the data cleaning process.

Subjects/parents/caregivers will be provided with electronic patient diaries (EPDs) for the whole study. At Screening and Baseline visits, subjects and parents/caregivers will be trained

in the use of the device. These logs will be used to collect the treatment data and bleeding episodes by the parents/caregivers or subjects, and interact on a regularly scheduled basis with the investigator or delegate to verify and complete the data on the EPD. Thus, the EPD will be considered the source for these data.

For each use of study medication including the infusions administered during a planned visit for evaluation of recovery, information must be recorded on the Treatment Logs as follows:

1. Date and time
2. Lot numbers / number of vials administered
3. Reason for treatment (prophylaxis, spontaneous bleed first treatment, trauma bleed first treatment, follow-up treatment, surgery, other). (If an infusion is given in response to a fall or identified trauma, such as may occur when a child has an uncomplicated blow to the head and there is no clinical sign or evidence of bleeding, the event should be recorded as prophylaxis.)

If treatment is for a bleeding episode: site of bleeding, severity (severe, moderate, mild), and response to treatment (excellent, good, moderate, poor, too early to tell) are to be recorded. If 'too early to tell' is entered, the subject will be queried for a response the next time they use the device. For guidance to the subject or their caregivers, the following definitions for response to treatment are suggested. Individual subject responses may vary:

- **Excellent**: Abrupt pain relief and /or improvement in signs of bleeding with no additional infusion administered
- **Good:** Definite pain relief and/or improvement in signs of bleeding, but possibly requiring more than one infusion for complete resolution
- **Moderate:** Probable or slight improvement in signs of bleeding, with at least one additional infusion for complete resolution
- **Poor:** No improvement at all between infusions or condition worsens.

13.1.2.10 Change 10
Synopsis – Study objectives
Original protocol

Primary objective

- to demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A

Secondary objectives

- To assess the ~~tolerability profile~~ of BAY 81-8973 ~~during prophylaxis and treatment of breakthrough bleeds and safety and efficacy~~ during surgeries,
- To assess incremental recovery
- To characterize pharmacokinetics in a subset of 6 to 13 ~~the age group of 6-12 years,~~ if parents consent ~~to it~~ (participation for PK sampling is optional).

Amended to

Primary objective

- To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A

Secondary objectives

- To assess the safety and efficacy of BAY 81-8973 during surgeries,
- To assess incremental recovery of BAY 81-8973.
- To characterize pharmacokinetics in a subset of 6 to 13 previously treated patients ([PTPs) (Part A only]), if parents consent (participation for PK sampling is optional).

Section 2 Study objectives
Original protocol

Primary objective

The primary objective is to evaluate the safety and efficacy of the treatment with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeds in children with hemophilia A

Secondary objectives

The secondary objectives are

- To assess the ~~tolerability profile~~ of BAY 81-8973 ~~during prophylaxis and~~
- ~~treatment of breakthrough bleeds and safety and efficacy~~ during surgeries,
- To assess incremental recovery
- To assess pharmacokinetic parameters in a subset of ~~6 to 13~~ children. ~~in the age group of 6-12 years~~ (~~if parents consent to it , participation for pharmacokinetic [PK] sampling is optional,~~).

Amended to

The primary objective is to evaluate the safety and efficacy of the treatment with BAY 81-8973 for prophylaxis and treatment of breakthrough bleeds in children with severe hemophilia A

Secondary objectives

The secondary objectives are

- To assess the safety and efficacy of BAY 81-8973 during surgeries.

- To assess incremental recovery of BAY 81-8973.
- To assess pharmacokinetic parameters in a subset of children. (Part A only - participation in pharmacokinetic [PK] sampling is voluntary and requires consent.).

Section 4 Study Design
Original protocol

Primary variable

~~The primary variable is the response to treatment in relation to~~

~~1. number of bleeds within 48 hour (h) after a prophylaxis injection~~

~~2. assessment of response in treatment of bleeds~~

Amended to

Primary variable

Annualized number of total bleeds (sum of spontaneous bleeds and trauma bleeds) within 48 hours (h) after a prophylactic infusion.

Section 7.3.1 Efficacy variables
Original protocol

The primary variable is the annualized number of ~~all~~ bleeds within 48 h~~ours after a prophylaxis injection.~~

~~The clinical important variable is the number of breakthrough bleeds during prophylaxis, occurring during 48 h after the prophylaxis injection. The bleeding pattern in small children is expected to be different from adults. Joint bleeds are not the primary bleeding site in small children.~~ Additional efficacy parameters include:

- Annualized number of bleeds during prophylaxis treatment
- ~~Physician's / subject's/parents'~~ assessment of ~~response in treatment of bleeds~~ during surgical interventions
- Number of ~~injections~~ infusions for the treatment of a bleed
- Consumption of FVIII

The main surrogate efficacy parameter is the recovery. The complete list of variables to be analyzed for this study will be provided in the statistical analysis plan.

Amended to

The primary variable is the annualized number of total bleeds (sum of spontaneous bleeds and traumatic bleeds) during prophylaxis that occur within 48 h of the last prophylaxis infusion. Both joint and non-joint bleeding will be assessed. Additional efficacy parameters include:

- Annualized number of total bleeds (sum of spontaneous and trauma bleeds) during prophylaxis treatment
- Assessment of adequacy of hemostasis during surgical interventions
- Number of infusions for the treatment of a bleed
- Consumption of FVIII

The main surrogate efficacy parameter is the recovery of FVIII after infusion.

If an infusion is given to control a bleed at the same location within 48 hours of the previous dose for a bleed at that site, it is to be considered a follow-up infusion and not treatment of a new bleed.

Section 8.3 Variables
Original protocol

Extent of Exposure

Extent of exposure to the study drug, including ~~injection~~ characteristics, will be documented in subject diaries and summarized for each subject receiving any amount of drug.

Safety

Safety data will be summarized for all subjects in the safety population. Laboratory findings, adverse events, concomitant medications, and medical history data will be provided in subject listings.

Laboratory values and vital signs will be summarized. Individual listings of AEs [including ~~age, weight, height, body mass index (BMI), gender~~, AEs as reported, start, duration, severity, relation to study drug] will be provided. The incidence of treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Affairs (MedDRA).
Inhibitor development, as measured by Nijmegen assay, will be summarized by time point and presented in subject listings. The frequency of subjects who develop positive inhibitor titers (Bethesda $\geq$ 0.6 BU) will be presented by time point.

The rate of inhibitor development associated with BAY 81-8973 will be determined. Subjects with no inhibitors are required to have at least 50 ED to be counted in the denominator.

Efficacy

Efficacy data will be summarized for all subjects in the ITT population. The primary efficacy variable will be the annualized number of ~~all bleeds~~ within 48 hours after a prophylaxis ~~injection~~. Other variables summarized will be the physician's/parents' assessment of the response to treatment of bleeds (~~none, moderate, good, or~~ excellent) and during surgeries.
The number of treatments required to control bleeds, the ~~number~~ of prophylaxis ~~injections~~ with less than expected therapeutic effect (LETE) (defined as a prophylaxis ~~injection~~ followed

by a bleed within 48 hours), annualized number of ~~all bleeds~~ during prophylaxis, factor VIII usage and recovery will be summarized.

Amended to

Extent of Exposure

Extent of exposure to the study drug, including treatment characteristics, will be documented in subject diaries and summarized for each subject receiving any amount of drug.

Safety

Safety data will be summarized for all subjects in the safety population. Laboratory findings, adverse events, concomitant medications, and medical history data will be provided in subject listings.

Laboratory values and vital signs will be summarized. Individual listings of AEs [including AEs as reported, start, duration, severity, relation to study drug] will be provided. The incidence of treatment-emergent AEs will be summarized using the Medical Dictionary for Regulatory Affairs (MedDRA).

Inhibitor development, as measured by Nijmegen assay, will be summarized by time point and presented in subject listings. The purpose of the listing is to delineate the clinical factors which may be positively associated with development of the inhibitor. The frequency of subjects who develop positive inhibitor titers (Bethesda ≥ 0.6 BU) and confirmed by repeat measurement will be presented by time point. If the inhibitor value drops below 0.6 BU on repeat measure without intervention, the inhibitor will be determined as being transient. We will classify inhibitor patients as being either low titer or high titer based upon persistence of an inhibitor >5 BU.

The rate of inhibitor development associated with BAY 81-8973 will be determined. Subjects with no inhibitors are required to have at least 50 ED to be counted in the denominator.

Efficacy

Efficacy data will be summarized for all subjects in the intent-to-treat (ITT) population. The primary efficacy variable will be the annualized number of total bleeds (sum of spontaneous bleeds and traumatic bleeds) within 48 hours after a prophylaxis infusion. Other variables summarized will be the physician's/subject's/parents' assessment of the response to treatment of bleeds (excellent, good, moderate, poor) and during surgeries. The number of treatments required to control bleeds, the proportion of prophylaxis infusions with less than expected therapeutic effect (LETE) (defined as a prophylaxis infusion followed by a bleed within 48 hours), annualized number of total bleeds (sum of spontaneous bleeds and trauma bleeds) during prophylaxis, factor VIII usage and recovery will be summarized. A detailed Statistical Analysis Plan with be provided.

13.1.2.11 Change 11

Section 5.1.1 Inclusion criteria

Original protocol

In order to be included in the study, subjects must ~~meet~~ all of the following criteria upon evaluation at the Screening or Baseline visit:

1. Male, age~~d~~ ≤ 12 years
2. Severe hemophilia A defined as < 1% factor VIII concentration (FVIII:C) based on ~~medical records~~ and/or screening laboratory
3. ≥ 50 ED with any ~~high purity~~ FVIII;
4. No current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU)/mL] within 2-3 week ~~after~~ of last administration. ~~Subjects~~ may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing.
5. No history of FVIII inhibitor formation. Documentation of negative result in medical records required~~, except for PUPs~~. [Subjects with a maximum historical titer of 1.0 BU on no more than 1 occasion with the classical Bethesda assay but at least 3 successive negative (<0.6 BU) results thereafter are eligible.]
6. Willingness and ability of subjects and/or parents to complete training in the use of the ~~study~~ electronic patient diary (EPD) and to document ~~injection~~ ~~information~~ during the study.
7. Written informed consent by parent/legal representative. Assent should be sought from subjects if appropriate

Part B (PUPs) ~~Inclusion~~ of PUPs may start after ~~10~~ children ~~accumulated~~ 50 ED Male,

Severe hemophilia A defined as < 1% FVIII:C based on ~~medical records and/or~~ screening laboratory

no previous exposure to any FVIII PUPs may be included if they will receive their first FVIII dose ~~as regular~~ prophylaxis ~~or on-demand treatment for bleedings, and are willing to continue with prophylaxis~~.

Amended to

In order to be included in the study, subjects must <u>have</u> all of the following criteria upon evaluation at the Screening or Baseline visit:

<u>Part A</u>

1. Male, age ≤ 12 years. <u>Enrollment will begin with subjects >6-12 years before it is opened to all age groups.</u>
2. Severe hemophilia A defined as < 1% factor VIII concentration (FVIII:C) based on <u>documented prior testing</u> and/or screening laboratory
3. ≥ 50 ED with any FVIII <u>concentrate</u>;

4. No current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.6 Bethesda units (BU)/mL] within 2-3 weeks of last FVIII administration. PTPs may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing at the Screening visit.
5. No history of FVIII inhibitor formation. Documentation of negative result in medical records required. [Subjects with a maximum historical titer of 1.0 BU on no more than 1 occasion with the classical Bethesda assay but at least 3 successive negative (<0.6 BU) results thereafter are eligible.]
6. Willingness and ability of subjects and/or parents to complete training in the use of the electronic patient diary (EPD) and to document infusions during the study.
7. Written informed consent by parent/legal representative. Assent should be sought from subjects if appropriate

Part B (PUPs) (Enrollment of PUPs may start after safety is evaluated in 20 children in Part A with 50 ED)

1. Male, 6 years and under
2. Severe hemophilia A defined as < 1% FVIII:C based on prior documented testing and confirmed on screening laboratory
3. No previous exposure to any FVIII product
4. PUPs may be included if they will receive their first FVIII dose with BAY 81-8973 for treatment of first bleeds and agree to start prophylaxis as part of their care.
5. Willingness and ability of parents to complete training in the use of the electronic patient diary (EPD) and to document all treatment during the study.
6. Written informed consent by parent/legal representative.

13.1.2.12 Change 12

Section 5.1.2 Exclusion criteria
Original protocol

Subjects who meet any of the following criteria at Screening or Baseline visits will be excluded from participating in the study:

Part A and B

1. Any individuals with another bleeding dis~~ease~~ that is different from Hemophilia A (eg, von Willebrand disease, Hemophilia B)
2. Any individual with thrombocytopenia (platelet count < 100 000/mm^3) ~~based on medical records or screening laboratory~~

~~3. Any individual with abnormal renal function (serum creatinine > 2.0 mg/dL) based on medical records or screening laboratory~~

4. Any individual without a~~ny~~ documented negative inhibitor test (except for PUPs)

~~5.~~ Any individual who is receiving ~~or has received other~~ experimental drugs within 3 months ~~prior to study entry or has participated in a FVIII study within the last month~~

6. Any individual who requires any pre-medication to tolerate FVIII ~~injections~~ (eg, antihistamines)

7. Any individual who is unwilling to comply with study visits or other protocol requirements, for example (eg) prophylaxis treatment or is not suitable for participation in this study for any reason, according to the Investigator

8. Known hypersensitivity to active substance, mouse or hamster protein.

9. Previous participation in this study

Part B only

10. For PUPs: first treatment with BAY 81-8973

Amended to

Subjects who meet any of the following criteria at Screening or Baseline visits will be excluded from participating in the study:

Part<u>s</u> A and B

1. Any individual with another bleeding <u>disorder</u> that is different from Hemophilia A (eg, von Willebrand disease, Hemophilia B)

2. Any individual with thrombocytopenia (platelet count < 100 000/mm^3)

3. <u>Creatinine > 2x upper limit of normal or AST/ALT > 5x upper limit of normal</u>

4. Any individual without <u>a</u> documented negative inhibitor test <u>based on medical records or screening laboratory test</u> (except for PUPs)

5. Any individual who is receiving <u>chemotherapy, immune modulatory drugs (IVIG, cyclosporine, chronic use of oral or i.v. corticosteroids), has participated in another FVIII study within the last month, or received another</u> experimental drug within <u>the last</u> 3 months.

6. Any individual who requires any pre-medication to tolerate FVIII <u>treatment</u> (eg, antihistamines).

7. Any individual who is unwilling to comply with study visits or other protocol requirements, for example (eg. prophylaxis treatment) or is not suitable for participation in this study for any reason, according to the Investigator<u>'s judgement</u>.

8. Known hypersensitivity to active substance, mouse or hamster protein.

9. Previous participation in this study

Part B only (PUPs):

10. First treatment with BAY 81-8973 for high risk bleeding situations (eg, surgery, intracranial bleed), or requiring intensive or prolonged treatment.
11. Unable to tolerate volume of blood draws required for study participation (See Section 14.4).

13.1.2.13 Change 13

Section 6.9 Prior and concomitant therapy
Original Protocol

BAY 81-8973 will be used as the sole FVIII source. Pre-medications ~~are not to be administered for injections of BAY 81-8973.~~

All medications and blood products required by the subject during the study will be listed in the ~~appropriate~~ CRF. No other experimental drugs may be taken during the subject's participation in this study.

~~Medications which cause a bleeding diathesis (for example, Aspirin® or any acetylsalicylic acid) are contraindicated in any individual with hemophilia and must not be taken by study subjects. However, non-steroidal anti-inflammatory drugs to treat pain or acute synovitis are allowed.~~

No immunosuppressive/immunomodulatory drugs may be taken during the subject's participation in the study. If such therapy ~~will be deemed necessary for the subject's welfare~~ due to pre-existing illness, the situation should be discussed with the Sponsor before enrollment.

All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements) ~~should~~ be recorded at screening and throughout the treatment and follow-up periods.

Amended to

BAY 81-8973 will be used as the sole FVIII source. Pre-medications to tolerate treatment with BAY 81-8973 are not allowed. Use of topical anesthetics prior to venipuncture is permitted.

All medications and blood products required by the subject during the study will be listed in the CRF. No other experimental drugs may be taken during the subject's participation in this study.

No immunosuppressive/immunomodulatory drugs may be taken during the subject's participation in the study. If such therapy is deemed necessary for the subject's welfare, or due to pre-existing illness, the situation should be discussed with the Sponsor before enrollment. Medications which cause a bleeding diathesis (for example, Aspirin® or acetylsalicylic acid) are contraindicated in any individual with hemophilia and should be

avoided, except as specifically prescribed by a treating physician. Use of non-steroidal anti-inflammatory drugs, COX-2 inhibitors, or brief courses of corticosteroids to treat pain or acute synovitis, or inhaled or topical steroid medications (as for the treatment of asthma or eczema) are allowed.

All concurrent prescription and non-prescription medications including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements) will be recorded in the CRF at screening and throughout the treatment and follow-up periods.

13.1.2.14 Change 14

Section 7.1.2.1 Visit 1 – Screening
Original protocol

At the screening visit, the following procedures and assessments will be performed:

…

- Recording of prior and concomitant medication
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature
- Physical examination including measurement of body height and weight

Amended to

At the screening visit, the following procedures and assessments will be performed:

…

- Recording of prior and concomitant medication and Healthcare Resources Utilization Questionnaire. (Appendix 14.3). Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. Blood pressure may be deferred if appropriate cuff size or equipment is not available.
- Physical examination including measurement of body height/length and weight

Section 7.1.2.2 Visit 2 - Baseline
Original protocol

Thereafter, the following activities will be performed:

- Measurement of body height and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before ~~injection~~

Amended to

Thereafter, the following activities will be performed:

- Measurement of body height/length and weight

- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before infusion. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.3 Visit 3 – Month 1
Original protocol

7.1.2.3 Visit 3 – Month 1

The following procedures and assessments will be performed:

- Measurement of body height and weight

Amended to

7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B

The following procedures and assessments will be performed:

- Measurement of body height/length and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.1 Visit 4 – Month 2
Original protocol

7.1.2.4 Visit 4 – Month 2

The following procedures and assessments will be performed:

- Measurement of body height and weight

Amended to

7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B

The following procedures and assessments will be performed:

- Measurement of body height/length and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (added)

7.1.2.5, Visit 5 – Part B only; ED ~15 (14 ED +/- 1)

The following procedures and assessments will be performed:

- Measurement of body height/length and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.6 Visit – Month 3, only for PUPs
Original protocol

7.1.2.6, Visit – ~~Month 3, only for PUPs~~

The following procedures and assessments will be performed:

- Measurement of body height and weight

Amended to

Visit 6 – Part B only; ED 20 (20 ED +/- 1)

The following procedures and assessments will be performed:

- Measurement of body height/length and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.7 Interim visit – Only for Part B (30-40 ED) (added)
7.1.2.7 Interim visit – Only for Part B (30-40 ED)

The following procedures and assessments will be performed:

- Measurement of body height/length and weight

…

- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.8 Visit – Month 6 or final visit (end of the main study and start of the optional extension study)
Original protocol

7.1.2.8 Visit - ~~Month 6 or final visit~~ (end of the main study and start of the optional extension study)

The following procedures and assessments will be performed:

- Physical examination including measurement of body height and weight

- ~~Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before and after injection~~

Amended to

7.1.2.8 Final Visit - (end of the main study and start of the optional extension study)

The following procedures and assessments will be performed:

- Physical examination including measurement of body height/length and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature. (Blood pressure may be deferred if appropriate cuff size or equipment is not available).

Section 7.1.2.9 Visit 7 – Month 12 and every 6 months
Original protocol

7.1.2.9 ~~Visit 7 – Month 12 and every 6 months~~

The following procedures and assessments will be performed:

- Measurement of body height and weight

Amended to

7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)

The following procedures and assessments will be performed:

- Measurement of body height/length and weight

Section 7.1.2.10 Final visit
Original protocol

The following procedures and assessments will be performed:

- ~~easurement~~ of body height and weight

Amended to

The following procedures and assessments will be performed:

- Measurement of body height and weight

Section 7.5.3.1 Vital signs
Original protocol

Systolic and diastolic blood pressure, heart rate, and body temperature will be measured at ~~Screening, Baseline, Month 1, 2, 3 (PUPs) and Month 6 (or at the final visit).~~

Amended to

Systolic and diastolic blood pressure, heart rate, and body temperature will be measured at all visits. Blood pressure may be deferred in infants if appropriate size cuff or equipment is not available.

Section 7.5.3.2 Physical examination
Original protocol

A complete physical examination including the measurement of body height, weight and temperature will be performed at Screening visit and at Month 6 (or final visit).

~~At the visits at Months 2 and the additional visits of the~~ optional extension study (~~Months 12 and 18,~~ every 6 months until switch to commercial drug), only the subject's body height, temperature and weight will be measured.

Amended to

A complete physical examination including the measurement of body height, weight and temperature will be performed at Screening visit and at Month 6 (or final visit). Body length will be measured instead of height, as age appropriate.

At the other visits, and during the optional extension study (every 6 months until switch to commercial drug), only the subject's body height, temperature and weight will be measured.

13.1.2.15 Change 15

Title page
Original protocol

PPD ~~Bayer Schering Pharma~~

~~Aprather Weg 18 a~~

~~42096 Wuppertal, Germany~~

PPD

Amended to

PPD

Bayer HealthCare Pharmaceuticals, Inc.

P.O. Box 1000

Montville, New Jersey USA

Tel. PPD

Signature of the sponsor's medically responsible person
Original protocol

Name: PPD Role: Global Clinical Leader (GCL)/Medical Expert

Amended to

Name: PPD Role: Global Clinical Leader (GCL)/Medical Expert

Section 3 Investigators and other study participants
Original protocol

Sponsor's Medical Expert

Name: PPD
Title: PPD
Address: ~~Bayer Schering Pharma AG~~
~~Aprather Weg 18 a~~
~~42096 Wuppertal, Germany~~
PPD

Amended to

Sponsor's Medical Expert

Name: PPD
Title: PPD
Address: Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, New Jersey USA
PPD

13.1.2.16 Change 16

Introduction
Original protocol

Background

…

Other significant changes to rFVIII manufacturing have been introduced. Compared to its predecessors, BAY 81-8973 has more complete sialic acid capping of N-terminal glycan groups on the molecular surface, a post-translational modification step that is critical to the

activity and stability of some mammalian proteins. Although pathogen contamination of a recombinant protein product is a theoretical possibility, the BAY 81-8973 purification process achieves a greater level of viral clearance than the current process through the addition of a new viral filtration step. Overall, the complexity of the rFVIII manufacturing process has been substantially simplified for BAY 81-8973 compared to its predecessor products. This allows for a faster production time that may also reduce the buildup of aggregation and breakdown products, which may be linked to suboptimal yields of rFVIII products. In addition, any human or animal additives have been eliminated from the fermentation process. The result of the technological innovations implemented for BAY 81-8973 is the production of a full-length unmodified rFVIII product that more consistently reflects the conformation and glycan structure of the native human FVIII protein

Rationale of the study

The study is planned to demonstrate safety and efficacy of BAY 81-8973 for prophylaxis therapy and treatment of breakthrough bleeds in children with severe hemophilia A.

The overall clinical program ~~will~~ consist of 3 safety and efficacy studies, one study in subjects ≥ 12 years of age (adults and adolescents) including two pharmacokinetic evaluations (baseline and month 6), one study in adults and adolescents ≥ 12 years of age comparing on-demand and prophylaxis treatment and the present study in children from 0-12 years. The first study in adults and adolescents is ongoing. The comparative pharmacokinetic of BAY 81-8973 and Kogenate FS/Bayer has been completed and non-inferiority to the licensed product Kogenate FS/Bayer was demonstrated.

Benefit-risk assessment

…

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

Amended to

Background

…

Other significant changes to rFVIII manufacturing have been introduced. BAY 81-8973 has the same amino acid composition as Kogenate® FS/Bayer. Compared to its predecessors, BAY 81-8973 has more complete sialic acid capping of N-terminal glycan groups on the molecular surface, a post-translational modification step that is critical to the activity and stability of some mammalian proteins. Although pathogen contamination of a recombinant protein product is a theoretical possibility, the BAY 81-8973 purification process achieves a greater level of viral clearance than the current process through the addition of a new viral filtration step. Overall, the complexity of the rFVIII manufacturing process has been substantially simplified for BAY 81-8973 compared to its predecessor products. This allows for a faster production time that may also reduce the buildup of aggregation and breakdown products, which may be linked to suboptimal yields of rFVIII products. In addition, any human or animal additives have been eliminated from the fermentation process. The result of

the technological innovations implemented for BAY 81-8973 is the production of a full-length unmodified rFVIII product that more consistently reflects the conformation and glycan structure of the native human FVIII protein

Based on PK data from 26 subjects who received a single 50 IU/Kg dose of BAY 81-8973 and Kogenate FS in a cross over fashion, it has been demonstrated that BAY 81-8973 is non-inferior to Kogenate® FS/Bayer

Rationale of the study

The study is planned to demonstrate safety and efficacy of BAY 81-8973 for prophylaxis therapy and treatment of breakthrough bleeds in children with severe hemophilia A.

The overall clinical program consists of 3 safety and efficacy studies, one study in subjects ≥ 12 years of age (adults and adolescents) including two pharmacokinetic evaluations (baseline and month 6), one study in adults and adolescents ≥ 12 years of age comparing on-demand and prophylaxis treatment, and the present study in children from 0-12 years. The first study in adults and adolescents is ongoing and has completed enrollment. The comparative pharmacokinetic of BAY 81-8973 and Kogenate FS/Bayer has been completed and non-inferiority to the licensed product Kogenate FS/Bayer was demonstrated. The demonstration of safety in at least 20 adolescents and adults who received a minimum of 50 ED was a necessary requirement to open this study to enrollment of children 12 years of age and younger.

13.1.2.17 Change 17

Abbreviations

Original Protocol

EPD	Electronic ~~Subject~~ Diary
X-linked	A gene on the X chromosome ~~that expresses itself only when there is no different gene present at that locus (spot on the chromosome).~~
~~IVRS~~	~~Interactive voice randomization system~~
~~SAS~~	~~Statistical Analysis System~~
SUSAR	~~Suspected~~ unexpected adverse reaction

Amended to

Amd 1	Amendment 1
DMC	Data Monitoring Committee
EPD	Electronic Patient Diary
X-linked	A gene on the X chromosome
RAVE	Data base for electronic case report form
SUSAR	Serious unexpected suspected adverse reaction

Section 5.2.2 Replacement

Original protocol

Subjects who are withdrawn after start of treatment will not be replaced. Subjects who are withdrawn due to a positive inhibitor result at screening/baseline will be replaced.

Amended to

Subjects who are withdrawn after start of treatment will not be replaced. Subjects who are withdrawn due to failure to met screening criteria, or who have a positive inhibitor result at screening/baseline will be replaced.

Section 6.2.1 Manufacture
Original Protocol

The rFVIII molecule itself is comparable to the current Kogenate® FS/Bayer molecule, with some overall differences, such as reduced high molecular weight proteins. The molecule is highly glycosylated, with increased levels of highly branched glycans and more consistently high sialylation of terminal galactose residues. For further details see ~~Section 1 and~~ Investigator Brochure.

Amended to

The rFVIII molecule itself is comparable to the current Kogenate® FS/Bayer molecule, with some overall differences, such as reduced high molecular weight proteins. The molecule is highly glycosylated, with increased levels of highly branched glycans and more consistently high sialylation of terminal galactose residues. For further details see Investigator Brochure.

Section 6.2.2 Supply and Packaging
Original Protocol

BAY 81-8973 will be supplied lyophilized in BIO-SET® glass vials. Study vials may contain 250 IU, 500 IU or 1000 IU of FVIII activity. The nominal potency of the drug, *as determined by chromogenic assay* will be indicated on the labels of each vial unit pack. The medication is manufactured at Bayer HealthCare in Berkeley, California, United States. The vials of BAY 81-8973 will be packaged together with a pre-filled syringe of the appropriate amount of sterile water for injection, European and US Pharmacopeia (EP) (USP), for reconstitution. For BAY 81-8973, the volume of the solvent is 2.5 mL for all vial sizes. The BAY 81-8973 vials will also be supplied with the following medical devices to facilitate the ~~injection~~: TERUMO Europe NV, SV-S25FL35 infusion set with filter and needle protection, plunger rod, and 10 mL sterile syringe.

Amended to

BAY 81-8973 will be supplied lyophilized in BIO-SET® glass vials. Study vials may contain 250 IU, 500 IU or 1000 IU of FVIII activity. The nominal potency of the drug, *as determined by chromogenic assay,* will be indicated on the labels of each vial unit pack. The medication is manufactured at Bayer HealthCare in Berkeley, California, United States. The vials of BAY 81-8973 will be packaged together with a pre-filled syringe of the appropriate amount of sterile water for injection, European and US Pharmacopeia (EP) (USP), for reconstitution.

For BAY 81-8973, the volume of the solvent is 2.5 mL for all vial sizes. The BAY 81-8973 vials will also be supplied with the following medical devices to facilitate the treatment: TERUMO Europe NV, SV-S25FL35 infusion set with filter and needle protection, plunger rod, and 10 mL sterile syringe.

Section 6.2.5 Instructions for Administration
Original Protocol

The rate of administration can be adapted to the response of the individual subject. Experience with Kogenate® FS/Bayer indicates that a dose may be administered over a period of 1 to 15 minutes. For PK and recovery studies, the entire dose should be administered over a ~~2~~ 5-minute period depending on the total volume.

Parents/caregivers will receive training and detailed information regarding the administration of ~~their~~ study medication.

Amended to

The rate of administration can be adapted to the response of the individual subject. Experience with Kogenate® FS/Bayer indicates that a dose may be administered over a period of 1 to 15 minutes. For PK and recovery studies, the entire dose should be administered over a 5-minute period depending on the total volume.

Parents/caregivers will receive training and detailed information regarding the administration of the study medication.

Section 6.6 Drug logistics and accountability
Original Protocol

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 study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug in writing ~~or via interactive voice randomization system (IVRS)~~ and 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.

Amended to

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 study file; the site-relevant

elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug in writing and 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.

Section 6.8, Post-study therapy
Original Protocol

At the end of the study, all ~~study~~ participants who completed ~~the study~~ will be offered ~~the~~ participation in an extension study ~~with~~ continuation of treatment for at least further 50 ED or until marketing authorization. Documentation ~~of injections is mandatory during the extension study.~~

After completion of the extension study, or if the subjects or their parents/caregivers are not willing to participate in the extension study, ~~the further~~ treatment will be mutually agreed upon by the parents/caregivers and the investigator.

Amended to

At the end of the study, all participants who <u>have</u> completed <u>Part A or B</u> will be offered participation in an extension study. <u>Participation in the extension study will allow</u> continuation of treatment for at least 50 ED or until marketing authorization. <u>The extension study requires continued</u> documentation of <u>infusions, bleeding events, monthly interaction with the treatment center, and visits every 6 months for inhibitor screening</u>.

After completion of the extension study, or if the subjects or their parents/caregivers are not willing to participate in the extension study, <u>treatment with study drug will end. Subsequent</u> treatment will be mutually agreed upon by the parents/caregivers and the investigator.

Section 7.5.1.1 Definitions
Original protocol

<u>Note:</u> Any bleeding event occurring during the study will not be documented as AE, because this is captured in the assessment of efficacy. However, if the bleed requires hospitalization, it must be reported as a Serious Adverse Event (SAE) (see Section 7.5.1.4).

Amended to

<u>Note:</u> Any bleeding event occurring during the study will not be documented as <u>an</u> AE, because this <u>event</u> is captured in the assessment of efficacy. However, if the bleed requires hospitalization, it must be reported as a Serious Adverse Event (SAE) (see Section 7.5.1.4).

Section 8.1 General considerations
Original protocol

~~Statistical analyses will be performed using Statistical Analysis System (SAS); the version used will be specified in the statistical analysis plan.~~

Amended to

Statistical analyses will be performed using SAS release 9.1 or higher (SAS Institute Inc., Cary, North Carolina [NC], United States of America [USA]). The version used will be specified in the Statistical Analysis Plan.

Section 8.2 Analysis sets
Original protocol

~~Efficacy and safety data will be collected from all subjects who received study medication. All subjects given any study drug will be included in the safety and intent-to-treat (ITT) populations.~~

Amended to

Efficacy and safety data will be collected from all subjects who received study medication. The intent-to-treat (ITT) population will include all subjects randomized into the study who received study drug. The per-protocol population will exclude subjects who are deemed invalid in the Validity Review Report. Subjects from Part A and Part B will be summarized separately.

Section 8.6 Determination of sample size
Original protocol

According to the guideline CPMP/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), ~~at least 20 children under the age of 6 years (infants and toddlers) regardless of prior treatment should be included in the investigation. The next age group according to the age classification of International Conference on Harmonization (ICH)/CPMP guideline E11 (Clinical Investigation of Medicinal Products in the Pediatric Population)[19] refers to children up to the age of 11 years.~~ Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973.

~~Therefore,~~ this study will include ~~20~~-25 subjects ~~< 6 years (PTPs)~~ and ~~15~~-25 subjects aged ~~between 6 and 12 years~~. ~~Thus, the~~ total sample size will be ~~35-50~~ subjects, ~~of whom a minimum of 35 subjects must be PTPs. The number of PUPs is not specified~~.

Amended to

Sample size has been determined according to the requirements set forth by guideline CPMP/BPWG/1561/99 (Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and Factor IX Products), and taking into account the revised draft version,

CHMP/BPWP/144533/09. Age groups are in accordance with the International Conference on Harmonization (ICH)/CPMP guideline E11 (Clinical Investigation of Medicinal Products in the Pediatric Population)[19] and sample sizes have been confirmed on consultation with the EMA/PDCO on submission of the Pediatric Investigation Plan.

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study consists of two parts. Part A will include a total of 50 PTPs; 25 subjects >6 – 12 years and 25 subjects aged 6 years and less. Part B will enroll 25 PUPs of all ages. Total sample size will be 75 subjects.

Section 9.1 Data recording
Original protocol

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. ~~The site must implement processes to ensure this happens.~~ A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

The patient reported data may be entered directly into the EPD, for all other data source documentation must be available.

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~~.

Amended to

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. A source document is defined as the first place data are recorded; the CRF is not a source document. The site must ensure the existence of source documents A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

The patient reported data may be entered directly into the EPD, for all other data source documentation must be available.

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.

Section 10 Premature termination of study
Original protocol

For any of the above closures, the following applies:

- Closure~~s~~ should occur only after consultation between involved parties.
- All affected institutions (eg, 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 given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be ~~taken care~~ of in an ethical manner.

Amended to

For any of the above closures, the following applies:

- Closure should occur only after consultation between involved parties.
- All affected institutions (eg, 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 given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post-study follow-up, must be <u>treated</u> of in an ethical manner.

Section 11.2 Subject information and consent
Original protocol

For minors or adults under legal protection, consent shall be given by the legal ~~guardian(s)~~. The ~~consent~~ of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

Amended to

For minors or adults under legal protection, consent shall be given by the <u>parents/</u>legal <u>representative</u>. The <u>assent</u> of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

Section 12 References
Original protocol

18. Kurnik K (Munich, Germany), Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. ~~Haemophilia. 2009:[Epub ahead of print]~~.

Amended to

18. Kurnik K (Munich, Germany), Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. Haemophilia. 2010 Mar;16(2):256-62.

Section 14.1 Instruction for use of Study medication

Original protocol

14. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the subject's comfort, but should not be faster than 2ml\min (maximum rate of ~~injection~~).

Amended to

14. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the subject's comfort, but should not be faster than 2ml\min (maximum rate of infusion).

13.2 Amendment 3

Description of Amendment

The PK sampling is no longer limited to patients in Part A and the limitation to 13 participants has been deleted. All sites and all patients may now participate in the PK sub-study, and PK sampling, if not done earlier, may be done at any visit during the extension phase.

The number of subjects that may be enrolled in Part B (PUPs) has been increased to at least 25, up to a maximum of approximately 50, making the total sample size at least 75, up to a maximum of approximately 100, to allow more subjects to participate in the study.

Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery.

Amendment 3 also implements revisions and clarifications in response to specific questions and comments received from pediatric specialists and investigators. These include an improved explanation of the staggered enrollment by subject age, and clarification of which evaluations are required at which visit. The schedule of evaluations has been revised to reflect changes already made to some text sections in Amendment 1, and the changes in Amendment 3. Inclusion and exclusion criteria were clarified to be more consistent (with pediatric practice). Any gene mutation (if known) has been added to the demographic characteristics to be recorded at Screening.

The possibility of an interim analysis of Part B data has been included, if this should be required for regulatory purposes.

Finally, changes in the study administrative structure, editorial changes, correction of typographical errors, and minor revisions of language were made to ensure clarity and consistency throughout the document.

13.2.1 Overview of changes

Change 1: In order to allow more patients to participate in the optional PK study, it has been opened to patients in Part B as well as those in Part A. The scheduled blood sampling may be done not only at any study visit, but also at any visit during the extension phase. In addition, patients at all centers may now participate in the PK analysis, and there is no restriction on the number of patients who participate in the PK study.

Sections affected include:

- Synopsis, Study objectives
- Section 2, Study objectives
- Section 4, Study design
- Section 6.1.2, Breakthrough bleeds and surgeries
- Section 6.1.4, Optional pharmacokinetic measurements
- Section 6.4, Dosage and administration
- Section 7.1.1, Tabulated overview

- Section 7.1.2.2 – Section 7.1.2.6, Visits
- Section 7.1.2.8, Visit
- Section 7.1.2.9, Visit
- Section 7.4, Pharmacokinetics
- Section 8.3, Variables

Change 2: Adaption/clarification of inclusion criteria concerning age of the subjects in Part A (<6 years and 6-12 years) and Part B (<6 years), number of exposure days with any FVIII concentrate (≥50), definition of severe hemophilia (based on prior documented testing or confirmed on screening laboratory), and the availability of a negative inhibitor result at screening.

Sections affected include:

- Synopsis
- Section 4, Study design
- Section 5.1.1, Inclusion criteria
- Section 5.1.2, Exclusion criteria
- Section 8.6, Determination of sample size

Change 3: Adaptation/clarification of exclusion criterion 5 concerning prior therapy. An exception is made for patients who received Kogenate FS/Bayer (Bayer factor VIII study drugs) in clinical studies within 1 month prior to study entry.

Sections affected include:

- Section 5.1.2, Exclusion criteria
- Section 6.1.1, Regular prophylaxis
- Section 6.9, Prior and concomitant therapy

Change 4: Any gene mutation (if known) has been added to the demographic characteristics to be recorded at Screening.

Sections affected include:

- Section 7.2.1, Demographics

Change 5: Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery.

Sections affected include:

- Section 6.1.5, Immune tolerance induction

Change 6: If an infusion is given to control a bleed at the same location within 72 hours of the previous infusion for a bleed at that site, it is to be considered a follow-up infusion and not treatment of a new bleed, unless both bleeds are skin/mucosa bleeds.

Sections affected include:

- Section 7.3.1, Efficacy variables

Change 7: The option of recruiting more than 25 PUPs has been included.

Sections affected include:

- Synopsis, Number of subjects
- Section 4, Study design
- Section 8.6, Determination of sample size

Change 8: If required for regulatory purposes, Part B data will be described in an interim analysis if at least 5 PUPs have been recruited.

Sections affected include:

- Section 8.5, Planned interim analyses

Change 9: Changes in the study administrative structure have been made, specifically, the Sponsor's Study Medical Expert has been replaced.

Sections affected include:

- Title page
- Signature of the sponsor's medically responsible person
- Section 3, Investigators and other study participants

Change 10: Minor editorial clarifications to ensure consistency, add clarity, and to reflect current practice (highlighted) and the correction of typographical/grammatical errors throughout the protocol (not highlighted).

Sections affected include:

- Section 4, Study design
- Section 6.2.2, Supply and packaging
- Section 7.1.2.1, Visit 1
- Section 7.1.2.3, Visit 3
- Section 7.1.2.9, Extension study visits
- Section 7.1.2.10, Final visit

13.2.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text". Corrections of typing errors or omissions are not highlighted in this amendment.

13.2.2.1 Change 1

Synopsis, Study objectives

Old text:

To characterize pharmacokinetics in a subset of ~~6 to 13~~ previously treated patients (PTPs) ~~(Part A only),~~ if parents consent (participation for PK sampling is optional).

New text:

To characterize pharmacokinetics (PK) in a subset of a minimum of 6 previously treated patients (PTPs) or previously untreated patients (PUPs) if parents consent (participation for PK sampling is optional).

Section 2, Study objectives

Old text

- To assess pharmacokinetic parameters in a subset of children. (***~~Part A only~~ - participation in pharmacokinetic [PK] sampling is voluntary and requires consent***). ***(as of Amd 1)***

New text

- To assess pharmacokinetic parameters in a subset of children. (***PTPs and PUPs - participation in pharmacokinetic [PK] sampling is voluntary and requires consent***). ***(as of Amd 1, Amd 3)***

Section 4, Study design

Old text

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns ~~in another study~~. PTPs ages ***~~7~~ to 12 years*** will begin enrollment first, followed by PTPs ~~6 years and younger~~**.** Part B, for PUPs, will begin enrollment after 20 children in Part A have had 50 ED.

…

Incremental recovery and trough levels of BAY ~~94-9027~~ will be assessed in all subjects. ~~Subjects enrolled in Part A~~ will be offered participation in the pharmacokinetic (PK) evaluation. Participation is optional, and requires consent. PK parameters (maximum concentration [C_{max}], half-life, area under curve [AUC], Mean Residence Time [MRT] and clearance) may be assessed using a sparse sampling schedule.

New text

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns in previous studies with BAY 81-8973. PTPs age 6 to 12 years will begin enrollment first, followed by PTPs ≤6 years**.** Part B, for PUPs, will begin enrollment after 20 children in Part A have had 50 ED.

…

Incremental recovery and trough levels of BAY 81-8973 will be assessed in all subjects. Suitable subjects will be given the opportunity to participate in the pharmacokinetic (PK) evaluation. Participation is optional, and requires consent. PK parameters (maximum concentration [C_{max}], half-life, area under curve [AUC], Mean Residence Time [MRT] and clearance) may be assessed using a sparse sampling schedule.

Section 6.1.2, Breakthrough bleeds and surgeries

Old text:

If the study site routinely ~~measures~~ pharmacokinetic (PK) prior to surgical procedures, these results may be used to fulfill the optional PK ~~in Part A~~, provided that consent is given in advance, the subject undergoes a 48 hour washout, sampling is obtained at the designated time points, and samples are sent to the central laboratory for evaluation.

New text:

If the study site routinely takes pharmacokinetic (PK) measurements prior to surgical procedures, these results may be used to fulfill the optional PK, provided that consent is given in advance, the subject undergoes a 48 hour washout, sampling is obtained at the designated time points, and samples are sent to the central laboratory for evaluation.

Section 6.1.4, Optional pharmacokinetic measurements (~~Part A only~~)

Additional text:

Suitable subjects will be given the opportunity to participate in the PK sub-study, either during the main study, or during the extension period.

Section 6.4, Dosage and administration

Old text:

For the optional PK study ***(~~Part A only~~)***, each subject will receive ***an exact*** dose of 50 IU/kg of BAY 81-8973.

New text:

For the optional PK study, each subject will receive ***an exact*** dose of 50 IU/kg of BAY 81-8973.

Section 7.1.1, Tabulated overview

Old text:

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1** *(+/- 1 week) (as of Amd 1)*	**Visit 4 Month 2** *(+/- 1 week) (as of Amd 1)*	**Final visit Month 6** *(Minimum 50 ED (as of Amd 1))*	**Extension Visit every 6 months**	**Extension Final visit**
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X	~~X~~	~~X~~
FVIII baseline level and inhibitor	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	*X*	X	X		
Pharmacokinetics in up to 13 children (optional)		~~X~~ [b]					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation	X	← continuously →					
Healthcare *Resources* Utilization *Questionnaire (as of Amd 1)*	*X (as of Amd 1)*	← monthly →					
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. CBC, Chemistries

b Blood samples at the following time points: before, 20-30 min, 4 h, ***and*** 24 h post-***infusion*** following a washout of 48 h after last dose of FVIII. ***Exact times need to be entered into CRF***

c Measured at least 48 h after last dose of FVIII (as of Amd 1)

d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim [d] Visit *30-40 ED (as of Amd 1)***	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent	X		X								
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events		X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]	~~X~~ [b]	~~X~~ [b]
FVIII baseline level and inhibitor		X	X								
FVIII level before *infusion* and inhibitor [c] *(as of Amd 1)*				X	X	X	X		X	X	X
Recovery (20-30 min after *infusion*) *(as of Amd 1)*		X	X				X		X		
Infusion of study drug *(as of Amd 1)*	← continuously in accordance with the prophylaxis regimen →										
Patient diary (EPD) documentation	X	← continuously →									
Healthcare Resources Utilization Questionnaire (as of Amd 1)	*X (as of Amd 1)*	← monthly →									
Interaction between subject/parent and investigator		← weekly →							← monthly →		
Concomitant medication	X	← continuously →									

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.

New text:

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1** *(+/- 1 week) (as of Amd 1)*	**Visit 4 Month 2** *(+/- 1 week) (as of Amd 1)*	**Final visit Month 6** *(Minimum 50 ED [as of Amd 1])*	**Extension Visit every 6 months**	**Extension Final visit**
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events *(as of Amd 3)*	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies *(as of Amd 3)*		X			X		
FVIII baseline level and inhibitor(one stage) (*Amd 3*)	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	X	X	X		
Pharmacokinetics (optional) *(as of Amd 3)*		←----------			X [b]		----------→
***Infusion* of study drug**		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation		← continuously →					
Healthcare *Resources* Utilization *Questionnaire* *(as of Amd 1)*	*X (as of Amd 1)*	← monthly →					
Interaction between subject/parent and investigator[d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

a. Complete Blood Count (CBC), Chemistries

b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF

c. Measured at least 48 h after last dose of FVIII (as of Amd 1)

d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension; min: minute

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6, Month 4 or ED ~20**	**Interim [d] Visit *30-40 ED (as of Amd 1)***	**Final visit or ED 50**	**Extension Visit every 6 months**	**Extension Final visit**
Informed consent)	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X		
Laboratory examination [a]	X		X						X		
HSP-70 antibodies *(as of Amd 3)*		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) *(as of Amd 3)*		X	X								
FVIII level before *infusion* and inhibitor [c] *(as of Amd 1)*				X	X	X	X		X	X	X
Recovery (20-30 min after *infusion*) *(as of Amd 1)*		X	X				X		X		
Pharmacokinetics (optional)		←	----------	----------	----------	----------	X [e]	----------	----------	----------	→
Infusion of study drug *(as of Amd 1)*		←	continuously in accordance with the prophylaxis regimen								→
Patient diary (EPD) documentation		←	----------	continuously							→
Healthcare Resources Utilization Questionnaire(as of Amd 1)	*X (as of Amd 1)*	←	----------	monthly							→
Interaction between subject/parent and investigator		←	weekly	→					←	monthly	→
Concomitant medication	X	←	----------	continuously							→

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d. Interim visit only if less than 40 ED have been achieved by Month 6.
e. Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF

Section 7.1.2.2 – Section 7.1.2.6, Visits, and Section 7.1.2.8, Visits

Additional text:

Optional PK: Additional blood samples at 4 h and 24 h post infusion, for Part B patients also at 20-30 min after end of infusion (can also be performed at a later visit; to be obtained only once during study).
Note to investigators: In compliance with EMA guidance and for patient safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg who must therefore be excluded from the PK sub-study.

Section 7.1.2.9, Visits

Additional text:

Optional PK: Additional blood samples at 20-30 min, 4 h and 24 h post infusion (can also be performed at a later visit; to be obtained only once during study).
Note to investigators: In compliance with EMA guidance and for patient safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study.

Section 7.4, Pharmacokinetics

Old text

Details of the blood sampling and processing procedures for all laboratory measurements will be provided in the ~~Study Procedure~~ Manual ~~(SPM) that~~ accompanies this protocol.

New text

Details of the blood sampling and processing procedures for all laboratory measurements will be provided in the Laboratory Manual, developed by the central laboratory**,** which accompanies this protocol.

…

Note to investigators: In compliance with EMA guidance and for patient safety, no more than 1% blood volume may be obtained at any one visit, and no more than 3% may be taken in one month (see Section 14.4). If additional PK samples are taken, the total volume of blood drawn in 24 h will be too high for infants weighing less than 9 kg, who must therefore be excluded from the PK sub-study.

Section 8.3, Variables

The following text is deleted:

~~PK sampling will be performed in centers which have experience in PK studies and volunteer to participate.~~

13.2.2.2 Change 2

Synopsis, Methodology, Number of subjects

Old text:

Enrollment in the study will be staggered, with subjects age ~~>6-~~12 years entering first, followed by subjects ~~0-6 years~~.

New text:

Enrollment in the study will be staggered, with subjects age 6-12 years entering first, followed by subjects <6 years.

Synopsis, Number of subjects

Old text:

age group ~~>6-12 years~~: N=25

age group ~~0-6 years~~: N=25

Part B: N=25

Total = 75 (includes both Part A and B)

New text:

age group 6-12 years: N=25

age group <6 years: N=25

Part B: N= at least 25, up to a maximum of approximately 50 PUPs

Age group <6 years

Total = at least 75, up to a maximum of approximately 100 (includes both Part A and B)

Section 4, Study design

Old text:

Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns ~~in another study~~. PTPs ages ~~7~~ to 12 years will begin enrollment first, followed by PTPs ~~6 years and younger~~.

New text:

Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns in previous studies with BAY 81-8973. PTPs age 6 to 12 years will begin enrollment first, followed by PTPs <6 years.

Section 5.1.1, Inclusion criteria

Old text:

Part A

1. Male, age ≤ 12 years. Enrollment will begin with subjects ~~≥6-~~12 years before it is opened to all age groups.

2. Severe hemophilia A defined as < 1% factor VIII concentration (FVIII:C) based on documented prior testing ~~and/~~or screening laboratory

3. ~~≥~~ 50 ED with any FVIII concentrate;

New text:

Part A

1. Male, age ≤ 12 years. Enrollment will begin with subjects 6-12 years before it is opened to all age groups.

2. Severe hemophilia A defined as < 1% factor VIII concentration (FVIII:C) based on documented prior testing or screening laboratory

3. ≥ 50 ED with any FVIII concentrate;

Old text:

Part B

Part B (PUPs) (Enrollment of PUPs may start after safety is evaluated in 20 children in Part A with 50 ED)

1. Male, ~~6 years and under~~

2. Severe hemophilia A defined as < 1% FVIII:C based on prior documented testing ~~and~~ confirmed on screening laboratory.

New text:

Part B (PUPs) (Enrollment of PUPs may start after safety is evaluated in 20 children in Part A with 50 ED)

1. Male, ≤6 years

2. Severe hemophilia A defined as < 1% FVIII:C based on prior documented testing or confirmed on screening laboratory.

Section 5.1.2, Exclusion criteria

Old text:

4. Any individual without a ~~documented~~ negative inhibitor test ~~based on medical records or~~ screening ~~laboratory test~~ (except for PUPs)

New text:

4. Any individual without a negative inhibitor test at screening (except for PUPs)

Section 8.6, Determination of sample size

Old text:

This study consists of two parts. Part A will include a total of 50 PTPs; 25 subjects ~~≥ 6 –~~ 12 years and 25 subjects ~~aged 6 years and less~~. Part B will enroll 25 PUPs ~~of all ages~~. The total sample size will be 75 subjects.

New text:

This study consists of two parts. Part A will include a total of 50 PTPs; 25 subjects age 6 – 12 years and 25 subjects age <6 years. Part B will enroll at least 25, up to a maximum of approximately 50 PUPs age <6 years. The total sample size will be at least 75, up to a maximum of approximately 100 subjects.

13.2.2.3 Change 3

Section 5.1.2

Old text:

5. Any individual who is receiving chemotherapy, immune modulatory drugs (IVIG, cyclosporine, chronic use of oral or i.v. corticosteroids), ~~has participated in another FVIII study~~ within the last month, or received another experimental drug within the last 3 months.

New text:

5. Any individual who is receiving chemotherapy, immune modulatory drugs (IVIG, cyclosporine, chronic use of oral or i.v. corticosteroids), has received another investigational FVIII product within the last month, or received another experimental drug within the last 3 months.

Section 6.1.1

Additional text:

Note: PTPs will continue their previous treatment up to 48 h before the first dose of BAY 81-8973.

Section 6.9

Old text:

BAY 81 8973 will be used as the sole FVIII source. Pre-medications to tolerate treatment with BAY 81 8973 are not allowed. Use of topical anesthetics prior to venipuncture is permitted.

New text:

BAY 81 8973 will be used as the sole FVIII source. Pre-medications to tolerate treatment with BAY 81 8973 are not allowed. Use of topical anesthetics prior to venipuncture is

permitted. Note: PTPs will continue their previous treatment up to 48 hours before the first dose of BAY 81-8973.

13.2.2.4 Change 4

Section 7.2.1, Demographics

Old text:

Demographic characteristics to be recorded at Screening will include age and race. In addition, a complete physical examination including pulse, blood pressure, body temperature, height, weight, and a review of body systems will be performed and the results documented.

New text:

Demographic characteristics to be recorded at Screening will include age and race. In addition, a complete physical examination including pulse, blood pressure, body temperature, height, weight, and a review of body systems will be performed and the results documented. If known, any gene mutation should be noted.

13.2.2.5 Change 5

Section 6.1.5, Immune tolerance induction

Old text:

If a subject develops an inhibitor, ITI should be considered. All treatments, FVIII measurements, and inhibitor levels will be documented.

New text:

If a subject develops an inhibitor, ITI should be considered. Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery. All treatments, FVIII measurements, and inhibitor levels will be documented.

13.2.2.6 Change 6

Section 7.3.1, Efficacy variables

Old text:

If an infusion is given to control a bleed at the same location ~~within 48 hours~~ of the previous dose for a bleed at that site, it is to be considered a follow-up infusion and not treatment of a new bleed.

New text:

If an infusion is given to control a bleed at the same location within 72 hours of the previous dose for a bleed at that site, it is to be considered a follow-up infusion and not treatment of a new bleed, unless both bleeds are skin/mucosa bleeds.

13.2.2.7 Change 7

Synopsis, Number of subjects

Old text

Part B
N= 25 PUPs
age group <6 years
Total = 75 (includes both Part A and B)

New text

Part B
N= at least 25, up to a maximum of approximately 50 PUPs
age group <6 years
Total = at least 75, up to a maximum of approximately 100 (includes both Part A and B)

Section 4, Study design

Old text

Part B will include 25 PUPs.

New text

Part B will include at least 25, up to a maximum of approximately 50 PUPs.

Section 8.6, Determination of sample size

Old text

Part B will enroll 25 PUPs age <6 years. The total sample size will be 75 subjects.

New text

Part B will enroll at least 25, up to a maximum of approximately 50 PUPs age <6 years. The total sample size will be at least 75, up to a maximum of approximately 100 subjects.

13.2.2.8 Change 8

Section 8.5, Planned interim analyses

Old text

The main study has a duration of 6 months. The 6-month data for PTPs will be analyzed for regulatory purposes as an interim analysis. The overall study will be closed after all subjects in Parts A and B have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

New text

The main study has a duration of 6 months. The 6-month data for PTPs will be analyzed for regulatory purposes as an interim analysis. If required for regulatory purposes, Part B data will be described in an interim analysis if at least 5 PUPs have been recruited. The overall study will be closed after all subjects in Parts A and B have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

13.2.2.9 Change 9

Title page

Old text:

Sponsor's medical expert: PPD
Bayer Healthcare Pharmaceuticals Inc.
P.O. Box 1000
Montville, New Jersey, USA
~~Tel.~~ PPD

New text:

Sponsor's medical expert: PPD
Bayer Healthcare Pharmaceuticals Inc.
P.O. Box 1000
Montville, New Jersey, USA
Tel. PPD

Signature of the sponsor's medically responsible person

Old text:

Name: PPD Role: Global Clinical Leader (GCL)/Medical Expert

New text:

Name: PPD Role: Global Clinical Leader (GCL)/Medical Expert

Section 3, Investigators and other study participants

Old text:

Name: PPD
Title: PPD
Address: Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, New Jersey USA
PPD

New text:

Sponsor's Medical Expert
Name: PPD
Title: PPD

Address: Bayer HealthCare Pharmaceuticals, Inc.
P.O. Box 1000
Montville, New Jersey USA
PPD

13.2.2.10 Change 10

Section 4, Study design

Old text:

Incremental recovery and trough levels of ~~BAY 94-9027~~ will be assessed in all subjects.

New text:

Incremental recovery and trough levels of BAY 81-8973 will be assessed in all subjects.

Section 6.2.2, Supply and packaging

Old text:

BAY 81-8973 will be supplied lyophilized in ~~BIO-SET~~® glass vials. Study vials may contain 250 IU, 500 IU or 1000 IU of FVIII activity. The nominal potency of the drug, *as determined by chromogenic assay,* will be indicated on the labels of each vial unit pack. The medication is manufactured at Bayer HealthCare in Berkeley, California, United States. The vials of BAY 81-8973 will be packaged together with a pre-filled syringe of the appropriate amount of sterile water for injection, European and US Pharmacopeia (EP) (USP), for reconstitution. For BAY 81-8973, the volume of the solvent is 2.5 mL for all vial sizes. The BAY 81-8973 vials will also be supplied with the following medical devices to facilitate the treatment: ~~TERUMO Europe NV, SV-S25FL35~~ infusion set with filter and needle protection, plunger rod, and 10 mL sterile syringe.

New text:

BAY 81-8973 will be supplied lyophilized in glass vials. Study vials may contain 250 IU, 500 IU or 1000 IU of FVIII activity. The nominal potency of the drug, *as determined by chromogenic assay,* will be indicated on the labels of each vial unit pack. The medication is manufactured at Bayer HealthCare in Berkeley, California, United States. The vials of BAY 81-8973 will be packaged together with a pre-filled syringe of the appropriate amount of sterile water for injection, European and US Pharmacopeia (EP) (USP), for reconstitution. For BAY 81-8973, the volume of the solvent is 2.5 mL for all vial sizes. The BAY 81-8973 vials will also be supplied with the following medical devices to facilitate the treatment: an infusion set with filter and needle protection, plunger rod, and 10 mL sterile syringe. Before infusion, the product should be filtered using the infusion set provided or another approved filtration device.

Section 7.1.2.1, Visit 1

Old text:

- Training on and dispensing of the EPD

New text:

- Training on and dispensing of the EPD. Note: the EPD may be given to the patients to take home at any time between Screening and Baseline, but no entries are to be made before the first injection at Baseline.

Section 7.1.2.3, Visit 3

Old text:

- Check of EPD entries and bleeding history. Collect information on adverse events and Healthcare Resources Utilization Questionnaire. (Appendix 14.3).

New text:

- Check of EPD entries and bleeding history. Collect information on adverse events, update of concomitant medication and completion of Healthcare Resources Utilization Questionnaire. (Appendix 14.3).

Section 7.1.2.9, Extension study visits

Old text:

- Regular monthly contacts between parents and the site to check the EPD documentation ~~until~~ next clinic visit.

New text:

- Regular monthly contacts between parents and the site to check the EPD documentation, update information on adverse events and concomitant medication, completion of Healthcare Resources Utilization Questionnaire before next clinic visit.

Section 7.1.2.10, Final visit

Old text:

This visit will take place at the end of the extension period ~~and at least 100 ED (including main study) are accumulated~~, or in ~~case~~ of early termination.

New text:

This visit will take place at the end of the extension period, or in the event of early termination.

13.3 Amendment 4

Description of Amendment

Amendment 4 involved the following changes:

- Optional biomarker (pharmacogenetic) analysis was added to collect data to evaluate genetic differences, to better understand the causes and risk factors for potential development of inhibitors in haemophilia A patients on recombinant FVIII. This information will be collected only in PUPs.
- Epitope mapping of samples from subjects confirmed positive for inhibitor antibodies was added to identify the binding sites of the FVIII inhibitor.
- Specification of the need to document ITI therapy was added.
- Text describing the duration of treatment in the extension study was added to ensure consistency throughout the document.
- Typographic error on time for infusion was corrected.
- The time-window for final and extension visits was specified to provide guidance.

13.3.1 Overview of changes

Change 1: To collect data to evaluate genetic information in subjects (pharmacogenetics).

Sections affected:

- Section 7.1.1 Tabulated overview
- Section 7.1.2 Timing of assessments
- Section 7.6 Other procedures and variables – *subsection added*

Change 2: To collect data to perform epitope mapping in subjects who develop inhibitors.

Sections affected:

- Section 7.1.1 Tabulated overview
- Section 7.5.3.4 Inhibitor testing
- Section 7.6 Other procedures and variables – *subsection added*

Change 3: To specify the need to document ITI therapy in subjects who develop inhibitors.

Sections affected:

- Section 6.1.5 Immune tolerance induction (ITI)

Change 4: To describe the duration of treatment in the extension study consistently.

Sections affected:

- Synopsis
- Section 7.1.2.10 Final visit

Change 5: To correct a typographic error on the time for infusion.

Sections affected:

- Section 6.1.1

Change 6: To specify the time-window for the final and extension visits.

Sections affected:

- Section 7.1.1

13.3.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text".

13.3.2.1 Change 1

Additional text:

Section 7.1.1 Tabulated overview

Table 7-2b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6 Month 4 or ED ~20**	**Interim [d] Visit *30-40 ED (as of Amd 1)***	**Final Visit or 50 ED [g]**	**Extension Visit every 6 months [g]**	**Extension Final Visit [g]**
Informed consent)	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X		
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)		X	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X	X
Epitope mapping (inhibitor positive patients) *(Amd 4)*				←	←	←	←	X [f]	→	→	→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X		
Pharmacokinetics (optional) (Amd 3)			←	←	←	←	←	X [e]	→	→	→
Biomarker investigation (optional) *(Amd 4)*			←	←	←	←	←	X [h]	→	→	→
Infusion of study drug *(Amd 1)*			←	←	←	←	←	continuously in accordance with the prophylaxis regimen	→	→	→
Patient diary (EPD) documentation			←	←	←	←	←	continuously	→	→	→
Healthcare Resources Utilization Questionnaire(Amd 1)	*X (Amd 1)*			←	←	←	←	monthly	→	→	→
Interaction between subject/parent and investigator				←	←	←	←	weekly	→	← monthly	→
Concomitant medication	X			←	←	←	←	continuously	→	→	→

CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
Measured at least 48 h after last dose of FVIII

Interim visit only if less than 40 ED have been achieved by Month 6.
Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies *(as of Amd 4)*
The Final Visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained *(as of Amd 4)*
The optional biomarker investigation (pharmacogenetics) requires a separate signed informed consent. The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw. (*as of Amd 4)*

Additional text for the-below visits:

Section 7.1.2 Timing of assessments

Section 7.1.2.2 Visit 2 – Baseline

- Optional pharmacogenetics in PUPs (Part B and extension):
  collect blood sample for biomarker investigation – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amd 4)

Section 7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B (as of Amd 1),
Section 7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B (as of Amd 1),
Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (as of Amd 1),
Section 7.1.2.6 Visit 6 – Part B only; ED 20 (20 ED +/- 1) (as of Amd 1),
Section 7.1.2.8 Final Visit (end of the main study and start of the optional extension study,
Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months) (as of Amd 1)
Section 7.1.2.10 Final visit

- Optional pharmacogenetics in PUPs (Part B and extension):
  collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amd 4)

Additional text:

Section 7.6.2 Biomarker investigation (pharmacogenetics) (optional – consent required) (as of Amd 4)

The purpose of this genetic analysis is to identify markers for risk of inhibitor development in subjects treated with BAY 81-8973. The markers to be analyzed are type of FVIII gene mutation if not available, single nucleotide polymorphisms (SNPs) in immunoregulators (eg, IL-10), HLA genotype, and FVIII polymorphisms. This biomarker analysis is exploratory and will be analyzed for previously untreated patients (PUPs) only. (as of Amd 4)

A separate informed consent for pharmacogenetic sampling is required and participation is optional. (as of Amd 4)

If a subject elects to participate, a blood sample can be collected at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw. Samples will be prepared and labeled according to laboratory specifications. Details of the sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

A subject does not need to agree to participate in the pharmacogenetic sub-study to be enrolled in the main study. (as of Amd 4)

13.3.2.2 Change 2

Additional text

Section 7.1.1 Tabulated overview

Additional text is shown in the tabulated overview together with Change 1 (see Section 13.3.2.1).

Section 7.5.3.4 Inhibitor testing

For any subject confirmed positive for inhibitors, epitope mapping will be performed (see Section 7.6.1 for details). (as of Amd 4)

Section 7.6 Other procedures and variables (as of Amd 4)

~~Not applicable~~.

Section 7.6.1 Epitope mapping (as of Amd 4)

In the event a subject tested positive for inhibitor, additional blood, up to a maximum allowable as described in Table 14-4a, should be taken to confirm the result (retesting). If the result upon retesting is also positive, epitope mapping will be performed with the additional blood sample that was taken. Details of sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

13.3.2.3 Change 3

Section 6.1.5 Immune tolerance induction (ITI)

Additional text

Dosage: Details on ITI therapy should be documented. Technical guidance on how to document this information will be provided in the study manual. (as of Amd 4)

13.3.2.4 Change 4

Synopsis

Old text:

Duration of treatment	6 months ***and/or*** >50 exposure days (ED). ***(as of Amd 1)*** Optional extension study until marketing authorization

New text:

Duration of treatment	6 months ***and/or*** >50 exposure days (ED). ***(as of Amd 1)*** Optional extension study for at least 100 cumulative ED or (as of Amd 4) until marketing authorization

Section 7.1.2.10 Final visit

Old text:

The extension study will be continued (as of Amd 1) until marketing authorization.

New text:

The extension study will be continued (as of Amd 1) for at least 100 cumulative ED or (as of Amd 4) until marketing authorization.

13.3.2.5 Change 5

Section 6.1.1 Regular prophylaxis

Old text:

Route of administration: Manual intravenous (IV) infusion over 1 – ~~5~~ minutes according to total volume (as of Amd 1)

New text:

Route of administration: Manual intravenous (IV) infusion over 1 – 15 minutes (as of Amd 4) according to total volume (as of Amd 1)

13.3.2.6 Change 6

Additional text

Section 7.1.1 Tabulated overview

Additional text affecting Part A is shown below.

Additional text affecting Part B is shown together with Change 1 (see Section 13.3.2.1).

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1** ***(+/- 1 week) (as of Amd 1)***	**Visit 4 Month 2** ***(+/- 1 week) (as of Amd 1)***	**Final visit Month 6** ***(Minimum 50 ED [as of Amd 1])***	**Extension Visit every 6 months** [e]	**Extension Final Visit** [e]
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X		
FVIII baseline level and inhibitor(one stage) (*Amd 3*)	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	X	X	X		
Pharmacokinetics (optional)		←---------- X [b] ----------→					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation		← continuously →					
Healthcare *Resources* Utilization *Questionnaire (as of Amd 1)*	*X (as of Amd 1)*	← monthly →					
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← continuously →					

Complete Blood Count (CBC), Chemistries

Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF

Measured at least 48 h after last dose of FVIII *(as of Amd 1)*

Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension min: minute

For the regular Extension Visit every 6 months, a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained *(as of Amd 4)*

13.4 Amendment 6

Description of Amendment

Amendment 6 involved the following changes:

- Requirements for inhibitor testing during the extension phase clarified.
- FVIII:C determination at screening.
- Transfer device (Vial adapter) to be used for reconstitution.
- Clarification of Part B visit schedule.
- Update synopsis to reflect that plasma exposure is not exclusion criteria.
- Addition of recovery measurement is required at the first extension visit at 6 months and at final visit.
- Inclusion of minimally treated patients (MTPs) now possible in Part B.
- Addition of inhibitor evaluation at screening in MTPs only (ie, unnecessary to evaluate in PUPs) (include retention sample for inhibitor assessment by ELISA for MTPs) in Part B.
- Use of remaining rest of plasma samples.
- Interim analysis in Part B when 25 PUPs have reached 50 ED clarified.
- Addition of further details on choice of on-demand vs prophylaxis for initiation of treatment in PUPs.
- Addition of further information on monitoring of subjects commenced on ITI therapy in extension study.
- Changes in the study administrative structure.
- Minor editorial changes made (not listed in detail).

13.4.1 Overview of changes

Change 1: Requirements for inhibitor testing during the extension phase are clarified. Inhibitor testing is required every 6 months after start of the extension, until finalization of the study.

Rationale: Clarification.

Sections affected include:

- Section 7.1.1 Tabulated overview
- Section 7.5.3.4 Inhibitor testing

Change 2: FVIII:C is to be determined at screening to confirm the diagnosis if necessary.

Rationale: FVIII:C determination at screening should confirm the diagnosis if the local result does not clearly confirm the required inclusion criterion.

Sections affected include:

- Section 7.1.1 Tabulated overview
- Section 7.1.2.1 Visit 1 – Screening

Change 3: Vial adapter to be used for reconstitution.

Rationale: To allow reconstitution of the medication if necessary, this vial adapter is provided as an option.

Sections affected include:

- Section 6.2.2 Supply and packaging
- Section 14.1.2 Presentation of vial and the vial adapter – new section

Change 4: Clarification of visit scheduling in Part B

Rationale: Since visits in Part B are scheduled according to ED, giving informative approximate time frames for visits in months has led to confusion. In order to improve clarity, those visits are now listed by their ED threshold only.

Section affected includes:

- Section 7.1.1 Tabulated overview

Change 5: Update synopsis to reflect exposure to plasma is not exclusion criteria

Rationale: Exclusion limited to exposure to FVIII concentrate to keep it consistent to section 5.1.1 Inclusion criteria.

Section affected includes:

- Synopsis

Change 6: Addition of recovery measurement is required at the first extension visit at 6 months and at final visit.

Rationale: As per Guideline, addition of recovery measurements following a positive inhibitor test, as well as at the first extension visit at 6 months and at final visit.

Sections affected include:

- Section 6.8 Post-study therapy
- Section 7.1.1 Tabulated overview
- Section 7.1.2.2 Visit 2 – Baseline
- Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)
- Section 7.1.2.10 Extension final visit
- Section 7.3.2.1 Incremental recovery of Factor VIII (as of Amd 1)
- Section 7.5.3.4 Inhibitor testing

Change 7: Addition of MTPs into the protocol now possible in Part B. In addition to PUPs, MTPs are now eligible to participate in Part B. MTPs are defined as patients who have not previously received more than 3 injections with any FVIII product and who have no current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay assessed by central laboratory prior to first exposure in this study. In case of MTPs, the screening visit should only take place after a washout period of at least 48 h following any previous treatment with any FVIII replacement product.

Rationale: Emergency treatment of a bleed or trauma as first treatment is frequent in this very rare population and results in non-eligibility of subjects for the study according to the current protocol. Treatment with up to 3 injections does not affect the objective of the study and may support recruitment.

Sections affected include:

- Synopsis
- Section 1 Introduction
- Section 2 Study objectives
- Section 4 Study design
- Section 5.1.1 Inclusion criteria
- Section 5.1.2 Exclusion criteria
- Section 6.1.1 Regular prophylaxis
- Section 6.1.2 Breakthrough bleeds and surgeries
- Section 7.1.1 Tabulated overview
- Section 7.1.2 Timing of assessments
- Section 7.1.2.1 Visit 1 – Screening
- Section 7.1.2.2 Visit 2 – Baseline
- Section 7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B
- Section 7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B

- Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1)
- Section 7.1.2.6 Visit 6 – Part B only; ED 20 (20 ED +/- 1)
- Section 7.1.2.7 Interim visit - Only for Part B (30-40 ED) (as of Amd 1)
- Section 7.1.2.8 Final Visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months)
- Section 7.1.2.10 Final visit
- Section 7.5.3.4 Inhibitor testing
- Section 7.6.2 Biomarker investigation (pharmacogenetics) (optional – consent required)
- Section 8.6 Determination of sample size

Change 8: Addition of inhibitor evaluation at screening in MTPs only (ie, unnecessary to evaluate in PUPs) (include retention sample for inhibitor assessment by ELISA for MTPs) in Part B.

Rationale: Inhibitor testing only needed for MTPs as they have had prior exposure to FVIII.

Sections affected include:

- Section 7.1.1 Tabulated overview
- Section 7.1.2.1 Visit 1 – Screening
- Section 7.1.2.2 Visit 2 – Baseline

Change 9: Use of remaining rest of plasma samples collected.

Rationale: Usage for immunology or additional coagulation analysis, or for clarification of any clinical or laboratory adverse event.

Sections affected include:

- Section 7.5.3.4 Inhibitor testing

Change 10: Clarification of the interim analysis for 25 PUPs after they have completed Part B.

Rationale: Further detail added to the protocol to clarify that interim analysis will be undertaken in 25 PUPs after they will have completed Part B for regulatory purposes.

Sections affected include:

- Section 8.5 Planned interim analyses

Change 11: Additional information added to clarify that on-demand treatment is an option, as well as initiating prophylaxis directly.

Rationale: Either on-demand treatment or prophylaxis are options for PUPs starting in the study, and further emphasis has been added to the protocol.

Section affected includes:

- Section 6.1.1 Regular prophylaxis
- Section 7.1.2.2 Visit 2 – Baseline

Change 12: Subjects who commence ITI therapy in Part B will be followed up within the extension study.

Rationale: Further clarification on how to monitor subjects who have inhibitors and plan to start ITI therapy, as subjects will leave the main study but require documented visits within the extension study.

Sections affected include:

- Section 4 Study design
- Section 6.1.5 Immune tolerance induction

Change 13: Changes in the study administrative structure have been made, specifically, the Sponsor's Medical Expert has been replaced.

Sections affected include:

- Title Page
- Signature of the sponsor's medically responsible person
- Section 3 Investigators and other study participants

13.4.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text".

13.4.2.1 Change 1

Section 7.1.1 Tabulated overview

Old text:

Table 7-1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1** ***(+/- 1 week) (as of Amd 1)***	**Visit 4 Month 2** ***(+/- 1 week) (as of Amd 1)***	**Final visit Month 6** ***(Minimum 50 ED [as of Amd 1])***	**Extension Visit every 6 months** [e]	**Extension Final Visit** [e]
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events	*X*	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X		
FVIII baseline level and inhibitor(one stage) (*Amd 3*)	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	*X*	X	X		
Pharmacokinetics (optional)		← ---------- X [b] ---------- →					
Infusion of study drug		← continuously in accordance with the prophylaxis regimen →					
Patient diary (EPD) documentation		← ---------- continuously ---------- →					
Healthcare *Resources* Utilization *Questionnaire (as of Amd 1)*	*X (as of Amd 1)*	← ---------- monthly ---------- →					
Interaction between subject/parent and investigator [d]		← weekly →				← monthly →	
Concomitant medication	X	← ---------- continuously ---------- →					

Complete Blood Count (CBC), Chemistries
Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
Measured at least 48 h after last dose of FVIII *(as of Amd 1)*
Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension min: minute
For the regular Extension Visit every 6 months, a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 EDs is achieved or until market authorization is obtained. *(as of Amd 4)*

Table 7-2 b: Schedule of evaluations (Part B – PUPs; no prior FVIII exposure)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	***Combined Screening and Baseline***	**Visit 3 Month 1 or ED ~5**	**Visit 4 Month 2 or ED ~10**	**Visit 5 Month 3 or ED ~15**	**Visit 6 Month 4 or ED ~20**	**Interim [d] Visit *30-40 ED (as of Amd 1)***	**Final Visit or 50 ED [g]**	**Extension Visit every 6 months [g]**	**Extension Final Visit [g]**
Informed consent)	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X		
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)		X	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X	X
Epitope mapping (inhibitor positive patients) (Amd 4)				←	———	———	———	X [f]	———	———	→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X		
Pharmacokinetics (optional) (Amd 3)			←	———	———	———	X [e]	———	———	———	→
Biomarker investigation (optional) (Amd 4)			←	———	———	———	X [h]	———	———	———	→
Infusion of study drug *(Amd 1)*			←	———	continuously in accordance with the prophylaxis regimen	———	———	———	———	———	→
Patient diary (EPD) documentation			←	———	———	continuously	———	———	———	———	→
Healthcare Resources Utilization Questionnaire(Amd 1)	*X (Amd 1)*		←	———	monthly	———	———	———	———	———	→
Interaction between subject/parent and investigator			←	———	weekly	———	→		←	monthly	→
Concomitant medication	X		←	———	———	continuously	———	———	———	→	

CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
Measured at least 48 h after last dose of FVIII
~~Interim visit only if less than 40 ED have been achieved by Month 6.~~

Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF

Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies *(as of Amd 4)*

The Final Visit can be performed as soon as a minimum of 50 EDs is achieved, but no later than 2 weeks after achieving 50 EDs. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 EDs is achieved or until market authorization is obtained *(as of Amd 4)*

The optional biomarker investigation (pharmacogenetics) requires a separate signed informed consent. The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw *(as of Amd 4)*

New text:

Table 7–1a: Schedule of evaluations (Part A – PTPs; >50 ED)

Assessments and procedures	Main study					Optional extension study	
	Visit 1 Screening	**Visit 2 Baseline**	**Visit 3 Month 1 *(+/- 1 week) (as of Amd 1)***	**Visit 4 Month 2 *(+/- 1 week) (as of Amd 1)***	**Final visit Month 6 *(Minimum 50 ED [as of Amd 1])***	**Extension Visit every 6 months [e]**	**Extension Final Visit [e]**
Inclusion (date of written informed consent)	X				X		
Inclusion / exclusion criteria	X	X					
Demographic data	X						
Height, weight	X	X	X	X	X	X	X
Medical and surgical history	X						
Previous medication (medication history)	X						
Physical examination	X				X		
Adverse events	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X		
Laboratory examination [a]	X				X		
HSP-70 antibodies		X			X		
FVIII baseline level and inhibitor (one stage) (*Amd 3*)	X						
FVIII level *pre infusion* and inhibitor *(as of Amd 1)*		X	X	X	X	X	X
Recovery (20-30 min after *infusion*) [c] *(as of Amd 1)*		X	X	X	X	X [f] *(Amd 6)*	X *(Amd 6)*
Pharmacokinetics (optional)		←	----------	----------	X [b]	----------	---------- →
Infusion of study drug		←	continuously in accordance with the prophylaxis regimen				→
Electronic patient diary (EPD) documentation		←	----------	continuously		----------	→
Healthcare *Resources* Utilization *Questionnaire (as of Amd 1)*	*X (as of Amd 1)*	←	----------	monthly		----------	→
Interaction between subject/parent and investigator [d]		←	weekly	→		← monthly	→
Concomitant medication	X	←	----------	continuously		----------	→

a. Complete Blood Count (CBC), Chemistries
b Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
c. Measured at least 48 h after last dose of FVIII ***(as of Amd 1)***
d Weekly contact during Part A, monthly during extension and 1-2 weeks after last study visit extension ~~min: minute~~
e. For the regular Extension Visit every 6 months, a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained. ***(as of Amd 4)***
f. At the first extension visit 6 months after the start of the extension and at any time in case of inhibitor development (***as of Amd 6***)

Table 7–2b: Schedule of evaluations (Part B – PUPs/MTPs)

Assessments and procedures	Main study									Optional extension study	
	Visit 1 Screening [k]	**Visit 2 Baseline**	***Combined Screening and Baseline*** *(PUPs only)* *(as of Amd 6)*	**Visit 3 ED ~5** *(as of Amd 6)*	**Visit 4 ED ~10** *(as of Amd 6)*	**Visit 5 ED ~15** *(as of Amd 6)*	**Visit 6 ED ~20** *(as of Amd 6)*	**Interim[d] Visit** ***30-40 ED*** *(as of Amd 1)*	**Final Visit or 50 ED** [f]	**Extension Visit every 6 months** [f]	**Extension Final Visit** [f]
Informed consent	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X		
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X[b]	X[b]						X[b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)	X [h] (*Amd 6*)	X	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X[j]	X
Epitope mapping (inhibitor positive patients) (Amd 4)				←				X[e]			→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X	X[j] (*Amd 6*)	X (*Amd 6*)
Pharmacokinetics (optional) (Amd 3)		←					X[d]				→
Biomarker investigation (optional) (Amd 4)		←					X[g]				→
Infusion of study drug *(Amd 1)*		←	continuously in accordance with the prophylaxis regimen								→
Electronic patient diary (EPD) documentation		←				continuously					→
Healthcare Resources Utilization Questionnaire(Amd 1)	X *(Amd 1)*		←			monthly					→
Interaction between subject/parent and investigator		←		weekly	→				← monthly		→
Concomitant medication	X	←			continuously						→

For footnotes please see next page

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
e Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies *(as of Amd 4)*
f The Final Visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained *(as of Amd 4)*
g The optional biomarker investigation (pharmacogenetics) requires a separate signed informed consent. The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw *(as of Amd 4)*
h *Inhibitor to be evaluated at screening in MTPs only (ie, unnecessary to evaluate in PUPs) (as of Amd 6, include retention sample for inhibitor assessment by ELISA for MTPs)*
j *At the first extension visit 6 months after the start of the extension, and at any time in case of inhibitor development (as of Amd 6)*
k In case of MTPs, the screening visit should only take place after a washout period of at least 48 hours following any previous treatment with any FVIII replacement product (as of Amd 6).

Section 7.5.3.4 Inhibitor testing

Old text:

[…]

~~T~~he ***requirement for a (as of Amd 1)*** FVIII inhibitor test before study ***entry (as of Amd 1)*** is not applicable for PUPs. ***The absence of inhibitors will be confirmed at the Baseline evaluation. After treatment is started (as of Amd 1),*** PUPs must be tested for inhibitor development every 3-5 EDs until 20 EDs are accumulated.

~~Subjects participating in the extension study will additionally be tested for inhibitor development every 6 months.~~

[…]

New text:

[…]

In Part B, the ***requirement for a (as of Amd 1)*** FVIII inhibitor testing before study ***entry (as of Amd 1)*** is not applicable for PUPs ***but is applicable for MTPs (as of Amd 6).The absence of inhibitors will be confirmed at the Baseline evaluation. After treatment is started (as of Amd 1),*** PUPs***/MTPs*** must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated ***(as of Amd 6). Afterwards, blood samples for inhibitor testing and determination of FVIII:C trough level (>48 h after last FVIII treatment) are to be taken:***

- ***every 6 months in the extension study until finalization of the study, and at the final visit (as of Amds 1 and 6).***

[…]

13.4.2.2 Change 2

Section 7.1.1 Tabulated overview

Additional text in this section is detailed in the respective section in Change 1.

Section 7.1.2.1 Visit 1 – Screening

Old text:

- ***FVIII:C level, inhibitor test (not required for PUPs) (as of Amd 1)***

New text:

- ***FVIII:C level for PUPs and MTPs, inhibitor testing (not required for PUPs but required for MTPs incl. a retention sample for ELISA) (as of Amds 1 and 6)***

13.4.2.3 Change 3

Section 6.2.2 Supply and packaging

Additional text:

For preparing reconstitution, BAY 81-8973 will be provided in either of two presentations:

1) ***Vial with BIO-SET reconstitution cap: See Section 14.1.1 for Instructions for Use. Before infusion, the product should be filtered using the infusion set provided or another approved filtration device (as of Amds 3 and 6).***
2) ***Vial and vial adapter: (see section 14.1.2 for Instructions for Use). (as of Amd 6).***

Section 14 Appendices

Additional text:

14 Appendices

14.1 Instruction for use of study medication

14.1.1 Presentation of vials with Bio-SET reconstruction cap

[…]

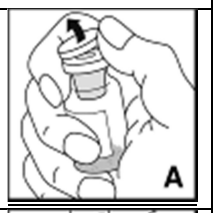
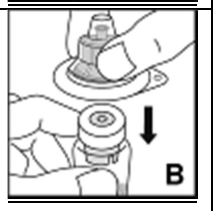
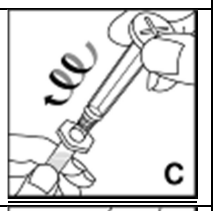
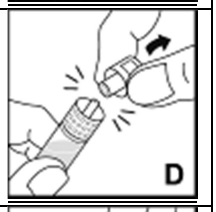
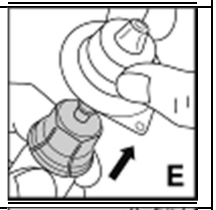
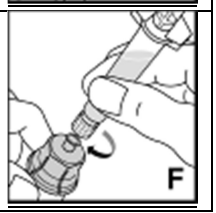
14.1.2 Presentation of vial and vial adapter (as of Amd 6)

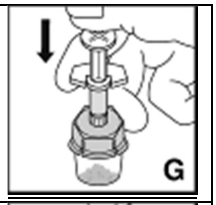
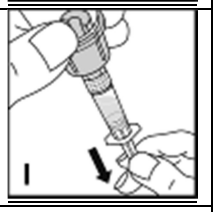
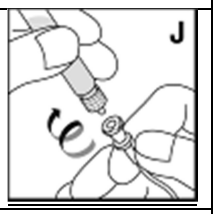
Note: This section was introduced by amendment 6.

How to use BAY 81-818973

- This medicine is intended for injection into a vein only and should be used within 3 hours after reconstitution.
- Use only the items (vial adapter, pre-filled syringe containing solvent and venipuncture set) that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.
- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. **You are filtering by using the vial adapter.**
- This medicine must **not** be mixed with other infusion solutions. Follow the directions given by your doctor closely and use the **detailed instructions for reconstitution and administration provided in the Annex of this leaflet below.**
- You will need alcohol swabs, gauze pads and plasters.

ANNEX: Detailed instructions for reconstitution and administration for presentation with vial adapter:

1. Wash your hands thoroughly using soap and warm water.	
2. Warm both an unopened vial and a syringe in your hands to a comfortable temperature (do not exceed 37°C).	
3. Remove the protective cap from the vial **(A)** and wipe the rubber stopper on the vial with an alcohol swab and allow it to air dry before use.	
4. Place **product vial** on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do **not** remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down **(B)**. The adapter will snap over the vial cap. Do **not** remove the adapter housing at this point.	
5. Hold the pre-filled water for injections syringe upright, grasp the plunger rod as per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper **(C)**.	
6. Holding the syringe by the barrel, snap the syringe cap off the tip **(D)**. Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	
7. Now remove and discard the adapter housing **(E)**.	
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise **(F).**	

9. Inject the diluent by slowly pushing down on the plunger rod **(G)**.	
10. Swirl vial gently until all material is dissolved **(H)**. Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.	
11. Hold the vial on end above the vial adapter and syringe **(I)**. Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.	
12. Apply a tourniquet.	
13. Determine the point of injection and clean the skin with an alcohol swab.	
14. Puncture the vein and secure the venipuncture set with a plaster.	
15. Holding the vial adapter in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe **(J)**.	
16. Remove tourniquet.	
17. Inject the solution into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of administration should be based on your comfort, but should not be faster than 2 mL per minute.	
18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.	
19. If no further dose is required, remove the venipuncture set and syringe. Hold a pad firmly over the injection site on your outstretched arm for approximately 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.	

13.4.2.4 Change 4

Section 7.1.1 Tabulated overview

Additional text in this section is detailed in the respective section in Change 1.

13.4.2.5 Change 5

Synopsis

Old text:

Diagnosis and main criteria for inclusion	Severe hemophilia A (< 1% Factor VIII concentration [FVIII:C]), ***Part A: male,*** age 0-12 years, ***≥ 50 ~~Exposure days (ED)~~ (as of Amd 1),*** no inhibitor history, no other bleeding disorder ***Part B: male, PUPs, no prior exposure to factor VIII concentrate ~~or plasma~~ (as of Amd 1)***

New text:

Diagnosis and main criteria for inclusion	Severe hemophilia A (< 1% Factor VIII concentration [FVIII:C]), ***Part A: male,*** age 0-12 years, ***≥ 50 ED (as of Amd 1),*** no inhibitor history, no other bleeding disorder ***Part B: male, PUPs, no prior exposure to factor VIII (FVIII) concentrate (as of Amds 1 and 6)*** [...]

13.4.2.6 Change 6

Section 6.8 Post-study therapy

Additional text:

At the end of the study, all participants who ***have*** completed ***Part A or B (as of Amd 1)*** will be offered participation in an extension study. ***Participation in the extension study will allow (as of Amd 1)*** continuation of treatment for at least 100 ED or until marketing authorization. ***The extension (as of Amd 1)*** study requires continued documentation of ***infusions, bleeding events, monthly interaction with the treatment center, and visits every 6 months for inhibitor testing and recovery measurements. (as of Amds 1 and 6)***

Section 7.1.1 Tabulated overview

Additional text in this section is detailed in the respective section in Change 1.

Section 7.1.2.2 Visit 2 – Baseline

Additional text:

Blood sample for the determination of recovery to be taken at 20-30 min after end of ***infusion***. ***(as of Amd 1)*** ***(Only for subjects who start prophylaxis at Baseline, for others, recovery should be done when prophylaxis is started [as of Amd 6].)***

Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months) (as of Amd 1)

Additional text:

- ***Blood sample for recovery measurement to be collected only at the first extension visit at 6 months. Blood sample to be taken at 20-30 min after end of infusion (as of Amd 6).***

Section 7.1.2.10 Extension final visit

Additional text:

- ***Recovery measurement, blood sample to be taken at 20-30 min after end of infusion. (as of Amd 6)***

Section 7.3.2.1 Incremental recovery of Factor VIII (as of Amd 1)

Old text:

[…]

Incremental recovery at 20-30 min after end of ***infusions (as of Amd 1)*** will be determined at Baseline, Month 1, 2 ~~and~~ Month 6 (or final visit). Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after ***infusion (as of Amd 1)*** have to be documented in the CRF.

New text:

[…]

Incremental recovery at 20-30 min after end of ***infusions (as of Amd 1)*** will be determined at Baseline, Month 1, 2, Month 6 (or final visit)***, 1st extension visit and final extension visit (as of Amd 6).*** Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after ***infusion (as of Amd 1)*** have to be documented in the CRF.

Section 7.5.3.4 Inhibitor testing

Old text.

[…]

Investigators will be provided with a detailed laboratory manual and a copy of the individual results. Inhibitor testing will be done according to the Nijmegen modified Bethesda inhibitor assay ***at the central laboratory (as of Amd 1)***. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU in the central lab. Any positive test must be confirmed by a second ***plasma (as of Amd 1)*** sample.

[…]

New text:

[…]

Investigators will be provided with a detailed laboratory manual and a copy of the individual results. Inhibitor testing will be done according to the Nijmegen modified Bethesda inhibitor assay ***at the central laboratory (as of Amd 1)***. A positive inhibitor testing is defined with a threshold of ≥ 0.6 BU in the central laboratory. Any positive test must be confirmed by a second ***plasma (as of Amd 1)*** sample ***and a determination of recovery should be performed. (as of Amd 6)***

[…]

13.4.2.7 Change 7

Synopsis

Old text:

[…]	
Study objective(s)	**Primary objective** • To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A **Secondary objectives** • To assess the ***safety and efficacy (as of Amendment 1 [Amd 1])*** of BAY 81-8973 during surgeries, • To assess incremental recovery ***of BAY 81-8973. (as of Amd 1)*** • To characterize pharmacokinetics in a subset of ***a minimum of 6*** previously treated patients (PTPs) ***or previously untreated patients (PUPs)*** if parents' consent (participation for pharmacokinetic (PK) sampling is optional). ***(as of Amd 3)***
[…]	

Dose(s)	***Part A:*** *PTPs:* 25 -50 International Units (IU)/kilogram (kg) *(rounded to nearest size vial)*; prophylaxis with at least 2 *infusions* per week *and treatment for breakthrough bleeds (as of Amd 1)* ***Part B:*** ***PUPs: 15-50 IU/kg ~~(rounded to nearest size vial)~~; prophylaxis with at least 1 infusion per week and treatment for bleeds (as of Amd 1)***
[…]	
Diagnosis and main criteria for inclusion	Severe hemophilia A (< 1% Factor VIII concentration [FVIII:C]), ***Part A: male,*** age 0-12 years, ***≥ 50 ~~Exposure days (ED)~~ (as of Amd 1),*** no inhibitor history, no other bleeding disorder ***Part B: male, PUPs, no prior exposure to factor VIII concentrate ~~or plasma~~ (as of Amd 1)***
[…]	
Methodology	***Part A (as of Amd 1):*** The study consists of 6-months *of treatment in PTPs with BAY 81-8973 for prophylaxis and* treatment *of breakthrough bleeding events to achieve at least* 50 EDs. *All subjects will be evaluated for inhibitor development and incremental recovery at Baseline*, Months 1, 2, and 6. *Enrollment in the study will be staggered, with subjects age 6-12 years entering first, followed by subjects <6 years. (as of Amd 3)* ***Part B (as of Amd 1):*** ***PUPs will be treated with BAY 81-8973 for all bleeding events and are required to start prophylaxis. Treatment will continue until at least 50 EDs. Screening and baseline visits may be combined for ~~this population~~. Subjects will be tested for inhibitors every 3-5 EDs up to ED ~~20~~ and again at ED ~~50~~. Incremental recovery will be measured at Baseline, ED ~~20~~, and ED ~~50~~.*** ***Pharmacokinetics (PK) samples will be collected in a subset of subjects at pre-infusion and then 20-30 minutes, 4 hours (h), and 24 h post infusion. Participation in the PK portion of the study is voluntary and requires specific consent. (as of Amd 1)*** ***In both Part A and Part B, all infusions and bleeding events will be documented in an electronic patient diary (EPD) throughout the study. (as of Amd 1)*** ***Optional extension study (as of Amd 1):*** ***Subjects in both Part A and B will be offered participation in an optional extension study to continue treatment with BAY 81-8973, to accumulate at least 100 ED or until the time of market authorization. During the extension study, visits to the treatment center will take place every 6 months ~~for inhibitor screening~~. (as of Amd 1)*** The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.
[…]	

Number of subjects	***Part A:*** ***Total Number (N) = 50 PTPs~~)~~*** ***age group 6-12 years: N=25*** ***age group <6 years: N=25*** ***Part B*** ***N= at least 25, ~~up to a maximum of approximately 50 PUPs~~ (as of Amd 3)*** ***age group <6 years*** ***Total = at least 75, up to a maximum of approximately 100 (includes both Part A and B) (as of Amd 1~~, Amd~~ 3)***
[…]	

New text:

[…]	
Study objective(s)	**Primary objective** • To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A **Secondary objectives** • To assess the ***safety and efficacy (as of Amendment 1 [Amd 1])*** of BAY 81-8973 during surgeries • To assess incremental recovery ***of BAY 81-8973 (as of Amd 1)*** • To characterize pharmacokinetics in a subset of ***a minimum of 6*** previously treated patients (PTPs), ***previously untreated patients (PUPs)<u>, or Minimally Treated Patients (MTPs) (as of Amd 6)</u>*** if parents' consent (participation for pharmacokinetic (PK) sampling is optional). ***(as of Amd 3)***
[…]	
Dose(s)	***Part A:*** *PTPs:* 25 -50 International Units (IU)/kilogram (kg) *(rounded to nearest size vial)*; prophylaxis with at least 2 *infusions* per week *and treatment for breakthrough bleeds (as of Amd 1)* ***Part B:*** ***PUPs/<u>MTPs</u> 15-50 IU/kg; prophylaxis with at least 1 infusion per week and treatment for bleeds (as of Amds 1 <u>and 6</u>)***
[…]	
Diagnosis and main criteria for inclusion	Severe hemophilia A (< 1% Factor VIII concentration [FVIII:C]), ***<u>Part A</u>: male,*** age 0-12 years, ***<u>≥</u> 50 ED (as of Amd 1),*** no inhibitor history, no other bleeding disorder ***<u>Part B</u>: male, PUPs, no prior exposure to factor VIII <u>(FVIII)</u> concentrate (as of Amd<u>s</u> 1 <u>and 6</u>) <u>or MTPs who have not previously received more than 3 injections with any FVIII concentrate and no current evidence of inhibitor antibody (as of Amd 6)</u>***

[…]	
Methodology	***Part A (as of Amd 1):*** The study consists of 6-months *of treatment in PTPs with BAY 81-8973 for prophylaxis and* treatment *of breakthrough bleeding events to achieve at least* 50 ED. *All subjects will be evaluated for inhibitor development and incremental recovery at Baseline*, Months 1, 2, and 6. *Enrollment in the study will be staggered, with subjects age 6-12 years entering first, followed by subjects <6 years. (as of Amd 3)* ***Part B (as of Amds 1 and 6):*** ***PUPs/MTPs will be treated with BAY 81-8973 for all bleeding events and are required to start prophylaxis. Treatment will continue until at least 50 ED. Screening and baseline visits may be combined for PUPs. Subjects will be tested for inhibitors every 3-5 ED up to 20 ED and again at 50 ED. Incremental recovery will be measured at Baseline, 20 ED, and 50 ED.*** ***Pharmacokinetics (PK) samples will be collected in a subset of subjects at pre-infusion and then 20-30 minutes, 4 hours (h), and 24 h post infusion. Participation in the PK portion of the study is voluntary and requires specific consent. (as of Amd 1)*** ***In both Part A and Part B, all infusions and bleeding events will be documented in an electronic patient diary (EPD) throughout the study. (as of Amd 1)*** ***Optional extension study (as of Amd 1):*** ***Subjects in both Part A and B will be offered participation in an optional extension study to continue treatment with BAY 81-8973, to accumulate at least 100 ED or until the time of market authorization. During the extension study, visits to the treatment center will take place every 6 months. (as of Amds 1 and 6)*** The study is designed according the requirements defined in the European "Note for Guidance on the clinical investigation of recombinant FVIII and FIX products" CPMP/BPWG/1561/99.
[…]	
Number of subjects	***Part A:*** ***Total Number (N) = 50 PTPs*** ***age group 6-12 years: N=25*** ***age group <6 years: N=25*** ***Part B*** ***N= at least 25 PUPs, plus up to additional 25 PUPs/MTPs/ (as of Amds 3 and 6)*** ***age group <6 years*** ***Total = at least 75, up to a maximum of approximately 100 (includes both Part A and B) (as of Amds 1 and 3)***
[…]	

Section 1. Introduction

Additional text:

All subjects will receive a replacement therapy at the highest level of standard of care. For previously untreated patients (PUPs), ***and minimally treated patients (MTPs) (as of Amendment 6 [Amd 6])***, there is a well-known risk for inhibitor development during the first 20 exposure days (ED) with any FVIII product which decreases with increasing exposure.

Section 2. Study objectives

Additional text:

- To assess pharmacokinetic parameters in a subset of children. (***PTPs and PUPs/MTPs -participation in pharmacokinetic [PK] sampling is voluntary and requires consent***). ***(as of Amds 1, 3 and 6)***

Section 4. Study design

Old text:

The study is divided into two parts: Part A will investigate a total of 50 PTPs up to 12 years of age. Part B will include at least 25, ~~up to a maximum of approximately 50 PUPs.~~ All subjects will receive prophylactic administration of BAY 81-8973…

[…]

New/ Additional text:

The study is divided into two parts: Part A will investigate a total of 50 PTPs up to 12 years of age. Part B will include at least 25 PUPs, plus up to additional 25 PUPs/MTPs (as of Amd 6). All subjects will receive prophylactic administration of BAY 81-8973. Subjects in Part A will be treated with 25-50 IU/kg at least 2 times per week, or more frequently as needed for prophylaxis. Treatment in Part B may begin with start of prophylaxis with 15-50 IU/kg (minimum dose 250 IU) at least one day a week, or with the subject's first bleeding event. The study drug will be used both for treatment of bleeding events and prevention of bleeds and with surgical procedures. Individual subject dose decisions are at the discretion of the investigator. (as of Amds 1 and 3)

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns ***in previous studies with BAY 81-8973***. PTPs age ***6 to 12 years*** will begin enrollment first, followed by PTPs ***<6 years (as of Amd 3).*** Part B, for PUPs***/MTPs*** (***as of Amd 6***) will begin enrollment after 20 children in Part A have had 50 ED.

The total study duration (including screening period) per subject ***in Part A (as of Amd 1)*** will be approximately 6***-8*** months ***(as of Amd 1)*** during which the subjects will accumulate at least 50 ED. ***For Part B, subjects will continue in the study until achieving 50 ED. Consequently the duration will vary depending upon the frequency of prophylactic infusion and number of bleeding events. All*** subjects ***in both Parts A and B (as of Amd 1)*** will be offered participation in an open-label extension study for ***an additional*** 6-12 months ***to allow observations for (as of Amd 1)*** at least 100 ED or until marketing authorization is obtained. ***Enrollment of PUPs/MTPs (as of Amd 6) in Part B and the extension study may continue after Part A and the extension study for PTPs have been completed. (as of Amd 1)***

During the study, all subjects will receive treatment only with BAY 81-8973 ***for prophylaxis and treatment of bleeds. In Part A, the (as of Amd 1)*** dosage range for prophylaxis treatment will be 25-50 IU/kg administered at least 2 times per week at the investigator's discretion. In Part B, PUPs***/MTPs (as of Amd 6)*** may start at a lower ***dose at (as of Amd 1)*** once per week schedule at the investigator's discretion. ***(as of Amd 1)***

Section 5.1.1 Inclusion criteria

Old text:
[…]

- Part B (PUPs) ~~(~~*Enrollment* ~~of PUPs~~ may start after *safety is evaluated in 20* children *in Part A with* 50 ED~~)~~ *(as of Amd 1)*

1. Male, <6 ***years (as of Amd 3)***

2. Severe hemophilia A defined as < 1% FVIII:C based on ***prior documented testing or confirmed on (as of Amd 1, Amd 3) screening*** laboratory.

3. No previous exposure to any FVIII ***product (as of Amd 1)***

4. PUPs may be included if they will receive their first FVIII dose ***with BAY 81-8973 for treatment of first bleeds and agree to start*** prophylaxis ***as part of their care. (as of Amd 1)***
[…]

New text:
[…]

- Part B (PUPs***/MTPs***): *Enrollment* may start after *safety is evaluated in 20* children *in Part A with* 50 ED ***(as of Amds 1 and 6)***.

1. Male, <6 ***years (as of Amd 3)***

2. Severe hemophilia A defined as < 1% FVIII:C based on ***prior documented testing or confirmed on (as of Amd 1, Amd 3) screening*** laboratory.

3a. PUPs: No previous exposure to any FVIII ***product (as of Amd 1)***

3b. MTPs: Have previously received not more than 3 injections with any FVIII product and who have no current evidence of inhibitor antibody measured using the Nijmegen-modified Bethesda assay [<0.2 Bethesda units (BU)/mL]. MTPs may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing at the Screening visit. (as of Amd 6)

3c. MTPs: No history of FVIII inhibitor formation. (as of Amd 6)

4. PUPs may be included if they will receive their first FVIII dose ***with BAY 81-8973 for treatment of first bleeds and agree to start*** prophylaxis ***as part of their care. (as of Amd 1) MTPs may be included if they agree to start prophylaxis as part of their care (as of Amd 6).***
[…]

Section 5.1.2 Exclusion criteria

Additional text:
[…]

Part B only ***(PUPs/MTPs [as of Amd 6])***:

[…]

Section 6.1.1 Regular prophylaxis

Additional text:

Test drug:	BAY 81-8973
Dosage:	25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, ***15-50 International Unit (IU)/kg;*** ≥ 1 ***time*** per week in PUPs***/MTPs***. ***(as of Amds 1 and 6)***

(Smallest size vial is 250 IU, which may be used for initial treatment of PUPs/MTPs of any weight) (as of Amds 1 and 6)

Route of administration:	Manual intravenous (IV) ***infusion*** over 1 – ***15 minutes (as of Amd 4)*** according to total volume ***(as of Amd 1)***

Note: PTPs will continue their previous treatment up to 48 h before the first dose of BAY 81-8973 (as of Amd 3).

Duration:	***Part A:*** 6 months ***and*** at least 50 ED ***Part B: 50 ED*** ***Extension study:*** at least 100 cumulative ED in subjects participating in the optional extension study ***or until market authorization (as of Amd 1)***

(Enrollment of PUPs/MTPs may continue after PTPs have completed participation in Part A and the extension study) (as of Amds 1 and 6)

[…]

Taking into account these observations, the following is recommended ***for PUPs/MTPs participating in Part B (as of Amds 1 and 6):***

[…]

Section 6.1.2 Breakthrough bleeds and surgeries

Additional text:

BAY 81-8973 will be used for the treatment of breakthrough bleeds. The dosage will be at the discretion of the investigator. ***For PUPs/MTPs in Part B, see Section 6.1.1. (as of Amds 1 and 6)***

For any surgery that may occur during the course of the study, BAY 81-8973 should be used. During surgery *(both major and minor)* dosing with BAY 81-8973 will follow the same standard practice as followed for Kogenate® FS/Bayer (Appendix 14). The guidelines are designed to maintain adequate hemostatic FVIII levels and provide varying instructions based upon the type of surgical procedure to be undertaken. ***For PUPs /MTPs in Part B (as of Amds 1 and 6),*** surgery is not allowed as first treatment ***and should be avoided, when possible, during the first 20 ED. (as of Amd 1)***

Section 7.1.1 Tabulated overview

Old text and new text in this section is detailed in the respective section in Change 1.

Section 7.1.2 Timing of assessments

Additional text:

The main study consists of a Screening period ***followed by at least*** 50 ED per subject. ***The Screening and Baseline visits may be combined to one visit for PUPs. There is no minimum interval between the Screening and Baseline visits for PUPs/MTPs (as of Amd 6) or PTPs. For PTPs, no longer than 8 weeks should pass between Screening and Baseline visits. (as of Amd 1)***

Section 7.1.2.1 Visit 1 - Screening

Additional text:

[…]

In case of MTPs, the screening visit should only take place after a washout period of at least 48 h following any previous treatment with any FVIII replacement product (as of Amd 6).

Section 7.1.2.2 Visit 2 - Baseline

Additional text:

[…]

For PUPs, the Baseline ***visit (as of Amds 1)*** may be combined with the Screening visit if all selection criteria can be confirmed based on medical records…

[…]

Note: ***For subjects in Part B (PUPs/MTPs), first exposure to study drug may be either for treatment of an uncomplicated bleed or for start of prophylaxis***. Inhibitor testing is mandatory every 3-5 ED until 20 ED are accumulated. ***See discussion on treatment of PUPs/MTPs in Section 6.1.1. (as of Amds 1 and 6)***

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amds 4 and 6)***

[…]

Section 7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B (as of Amd 1)

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B (as of Amd 1)

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (as of Amd 1)

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.6 Visit 6 – Part B only; ED 20 (20 ED +/- 1) (as of Amd 1)

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.7 Interim visit – Only for Part B (30-40 ED) (as of Amd 1)

Additional text:

Visit only required for PUPs and MTPs who have less than 40 ED, 6 months after the Baseline visit. The intent is to have at least one scheduled visit between completion of 20 ED and the expected date of accumulating 50 ED. The primary purpose of the visit is to assess the well being of the subject, ensure continued compliance with the treatment, and make any needed adjustments in dosage or infusion frequency based upon weight or bleeding events.

Section 7.1.2.8 Visit 8 – Final Visit (end of the main study and start of the optional extension study)

Additional text:

[…]

For PUPs and MTPs in Part B, this visit will take place after 50 ED with study medication are accumulated, or in the case of early termination (as of Amd 6). It is expected 50 ED will be achieved for most subjects between 6 and12 months after start of prophylactic treatment. (as of Amd 1)

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months) (as of Amd 1)

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.1.2.10 Extension final visit

Additional text:

[…]

- ***Optional pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

Section 7.5.3.4 Inhibitor testing

Additional text:

Blood samples for FVIII inhibitor testing will be taken at Screening ***(PTPs and MTPs only)***, Baseline, ***at regularly scheduled intervals throughout the study, and at the (as of Amds 1 and 6)*** final visit. The premise for inclusion of PTPs ***and MTPs*** in this study is the availability of a negative inhibitor ***result (as of Amds 1 and 6)*** as measured in the blood sample at Screening. A further sample will be taken at baseline before the first ***infusion (as of Amd 1)***. If the inhibitor testing result changes from negative at screening to positive at baseline, before the first ***infusion (as of Amd 1)*** of study medication, the subject must be withdrawn from the trial.

[…]

Section 7.6.2 Biomarker investigation (pharmacogenetics) (optional – consent required) (as of Amd 4)

Old text:
…This biomarker analysis is exploratory and will be analyzed for ~~previously untreated patients (~~PUPs~~)~~ only. (as of Amd 4)

New text:
…This biomarker analysis is exploratory and will be analyzed for PUPs and MTPs only. (as of Amds 4 and 6)

Section 8.6 Determination of sample size

Additional text:

[…]

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study c***onsists of two parts. Part A (as of Amd 1)*** will include ***a total of 50 PTPs (as of Amd 1)***; 25 subjects age ***6*** – 12 years ***(as of Amd 3)*** and 25 subjects age <6 ***years. Part B will enroll at least 25, up to a maximum of***

approximately 50 PUPs/MTPs age <6 ***years. (as of Amd 3)*** The total sample size will be ***at least 75, up to a maximum of approximately 100*** subjects. (***as of Amds 3 and 6***)

13.4.2.8 Change 8

Section 7.1.1 Tabulated overview

Additional text in this section is detailed in the respective section in Change 1.

Section 7.1.2.1 Visit 1 – Screening

Old text:

- ***FVIII:C level, inhibitor test (not required for PUPs) (as of Amd 1)***

New text:

- ***FVIII:C level for PUPs and MTPs, inhibitor testing (not required for PUPs but required for MTPs incl. a retention sample for ELISA) (as of Amds 1 and 6)***

Section 7.1.2.2 Visit 2 – Baseline

Additional text:

[…]

This visit should start with the following assessments:

> Confirmation of eligibility including check of laboratory test results.
> Note: Eligible subjects (except PUPs) must be inhibitor negative at Baseline. ***MTPs must be inhibitor negative as evaluated at Screening Visit (as of Amd 6).***

[…]

13.4.2.9 Change 9

Section 7.5.3.4 Inhibitor testing

Additional text:

[…]

Remaining rest of the plasma samples collected at specified study visits could be used for immunology or additional coagulation analysis, or for clarification of any clinical or laboratory adverse event and in no case for genetic analyses. (as of Amd 6)

13.4.2.10 Change 10

Section 8.5 Planned interim analyses

Additional text:

The main study has a duration of 6 months. The 6-month data ***for PTPs (as of Amd 1)*** will be analyzed for regulatory purposes as an interim analysis. ***An interim analysis will be performed for 25 PUPs after they will have completed in Part B (as of Amd 6). If required for regulatory purposes, Part B data will be described in an interim analysis if at least 5 PUPs have been recruited (as of Amd 3). The overall study will be closed after all subjects in Parts A and B (as of Amd 1)*** have completed the extension trial and an additional analysis will include all data from the main trial and the extension part.

13.4.2.11 Change 11

Section 6.1.1 Regular prophylaxis

Old text:

- ***Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion. (as of Amd 1)***
- ***~~Begin~~ prophylaxis*** with a once-a-week schedule low dose of 250 IU (15-25 IU/kg)***; the starting dose may be tailored to the ~~patient's~~ weight or demonstrated bleeding tendency. (as of Amd 1)***

New text:

- ***Treatment can be initiated with an on-demand regimen. Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion. (as of Amd 1 and 6)***
- ***Alternatively, prophylaxis can be started directly*** with a once-a-week schedule low dose of 250 IU (15-25 IU/kg)***; the starting dose may be tailored to the subject's weight or demonstrated bleeding tendency. (as of Amd 1 and 6)***

Section 7.1.2.2 Visit 2 – Baseline

Additional text:

[…]

- ***Infusion*** of the first dose of study drug ***or dispensation of study drug for on-demand treatment in Part B (as of Amd 6).***

[…]

13.4.2.12 Change 12

Section 4. Study design

Old text:

[…]

In the event that any subject acquires an inhibitor to FVIII, Immune Tolerance Induction (ITI) will be offered. The subject may receive BAY 81 8973 up to 200 IU/kg daily for 18 months. Treatment will be at the discretion of the treating physician. Data on treatment, FVIII measurements, and inhibitor levels will be collected. (as of Amd 1)

New text:

[…]

In the event that any subject acquires an inhibitor to FVIII, Immune Tolerance Induction (ITI) will be offered. The subject may receive BAY 81-8973 up to 200 IU/kg daily or 100 IU/kg twice a day for 18 months. Treatment will be at the discretion of the treating physician. Subject commences on ITI therapy will be followed up within the extension study. Data on treatment, FVIII measurements, and inhibitor levels will be collected. (as of Amds 1 and 6)

Section 6.1.5 Immune tolerance induction ~~(ITI)~~

Old text:

If a subject develops an inhibitor, ITI should be considered. ***Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery (as of Amd 3). All treatments, FVIII measurements, and inhibitor levels will be documented. (as of Amd 1)***

New text:

If a subject develops an inhibitor, ITI should be considered. ***Clinically relevant inhibitor development is defined as the occurrence of at least 2 positive inhibitor titers combined with a decreased recovery (as of Amd 3). Subject commences on ITI therapy will be followed up within the extension study. All treatments, FVIII measurements, and inhibitor levels will be documented. (as of Amds 1 and 6)***

13.4.2.13 Change 13

Title page

Old text:

Sponsor's medical expert: PPD

Bayer HealthCare ~~AG, D-51368 Leverkusen, Germany~~

Tel. PPD ***(as of Amd 4)***

New text:

Sponsor's medical expert: PPD

Bayer Healthcare, 67 Whippany Road, Whippany, NJ 07981, USA

Tel. PPD ***(as of Amd 6)***

Signature of the sponsor's medically responsible person

Old text:

Name:	PPD (***as of Amd 4***)	Role:	Global Clinical Leader (GCL) /Medical Expert

New text:

Name:	PPD (***as of Amd 6***)	Role:	Global Clinical Leader (GCL) /Medical Expert

Section 3 Investigators and other study participants

Old text:

Name: PPD
Title: PPD
Address: ***Bayer HealthCare ~~AG,~~***
~~D-51368 Leverkusen, Germany~~
Tel. PPD ***(as of Amd 4)***

New text:

Name: PPD
Title: PPD
Address: ***Bayer Healthcare, 67 Whippany Road,***
Whippany, NJ 07981, USA
Tel. PPD ***(as of Amd 6)***

13.5 Amendment 7

Description of Amendment

Amendment 7 involved the following changes:

- Change of sponsorship information
- Changes in the study administrative structure
- Increase of the number of subjects that may be enrolled in Part B (PUPs/MTPs)
- Addition of inhibitor evaluation at baseline using local laboratory testing in MTPs in Part B
- Adoption of a staggered approach for subject enrollment
- Minor editorial changes and corrections made to ensure clarity and consistency (not listed in detail).

13.5.1 Overview of changes

Change 1: Change of sponsorship information.

Rationale: The Sponsor was changed from Bayer Healthcare AG to Bayer AG for non-US territory and sponsor information for Bayer HealthCare Pharmaceuticals Inc. was added for US-territory. Bayer HealthCare AG merged with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceased to exist and Bayer AG became its legal successor and automatically took over all of the Bayer HealthCare AG's rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor.

Sections affected include:

- Title page

Change 2: Changes in the study administrative structure.

Rationale: The Sponsor's study medical expert has changed. Instead of PPD , PPD has taken over this task.

Sections affected include:

- Title page
- Signature of the sponsor's medically responsible person
- Section 3 Investigators and other study participants

Change 3: The option of recruiting more than 25 PUPs/MTPs in Part B has been included.

Rationale: The number of subjects that may be enrolled in Part B (PUPs/MTPs) has been increased, making the total sample size approximately 100, to allow more subjects to participate in the study.

Sections affected include:

- Synopsis Number of subjects
- Section 8.6 Determination of sample size

Change 4: Addition of inhibitor evaluation at baseline using local laboratory testing in MTPs, as part of inclusion criterion 3b in Part B.

Rationale: The inclusion criterion 3b for Part B has been amended to add further information on the inhibitor antibody testing for MTPs. A clause has been added introducing the evaluation of the absence of evidence (<0.6 Bethesda unit [BU/mL]) of inhibitor antibody for MTPs at baseline, using local laboratory testing. This further testing will confirm that patient has negative inhibitor titer before starting treatment. Also, a clause has been added to clarify that the administration of the study drug should start upon availability of results of local testing that confirm the inclusion criterion. The criterion for withdrawal from the study has also been adapted to better reflect the above change, and clarify the requirement of study participation.

Sections affected include:

- Section 5.1.1 Inclusion criteria
- Section 5.2.1 Withdrawal
- Section 7.1.1 Tabulated overview
- Section 7.1.2.2 Visit 2 – Baseline
- Section 7.5.3.4 Inhibitor testing

Change 5: Adoption of a staggered approach for subject enrollment as inclusion criterion 7 in Part B (PUPs/MTPs):

Rationale: Additional safety measure to be implemented.

Sections affected include:

- Section 4 Study design

Change 6: Minor editorial changes and corrections made to ensure clarity and consistency.

Rationale: Minor editorial clarifications and corrections have been included to add clarity, consistency, and to reflect current practice.

Sections affected include:

- Section 4 Study design
- Section 6.1.1 Regular prophylaxis
- Section 7.1.1 Tabulated overview

- Section 7.1.2.2 Visit 2 – Baseline
- Section 7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B (as of Amd 1)
- Section 7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B (as of Amd 1)
- Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (as of Amd 1)
- Section 7.1.2.6 Visit 6 – Part B only; ED ~20 (20 ED +/- 1) (as of Amd 1)
- Section 7.1.2.8 Final Visit (end of the main study and start of the optional extension study)
- Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months (as of Amd 1)
- Section 7.1.2.10 Extension final visit
- Section 7.3.2.1 Incremental recovery of Factor VII
- Section 7.5.3.4 Inhibitor testing
- Section 7.6.2 Biomarker investigation (pharmacogenetics) (optional – consent required) (as of Amd 4).

13.5.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the "old text" refers to the protocol version preceding this amendment. Deletions are crossed out in the "old text". Additions are underlined in the "new text".

13.5.2.1 Change 1

Title Page

Old text:

[…]

Clinical study phase:	III	Date:	**~~19 FEB 2016~~**
EudraCT no.:	2010-021781-29	Version no.:	**~~5~~.0**
Study no.:	BAY 81-8973 / 13400		
Sponsor:	**Bayer ~~HealthCare~~ AG, D-51368 Leverkusen, Germany**		

[…]

New text:

[…]

Clinical study phase:	III	Date:	**30 MAY 2017**
EudraCT no.:	2010-021781-29	Version no.:	**6.0**
Study no.:	BAY 81-8973 / 13400		
Sponsor:	**Non-US territory: Bayer AG, D-51368 Leverkusen, Germany** **US territory: Bayer HealthCare Pharmaceuticals Inc.,** **100 Bayer Boulevard, P.O. Box 915,** **Whippany NJ 07981-0915, US *(as of Amd 7)***		

[…]

13.5.2.2 Change 2

Title page

Old text:

Sponsor's medical expert: PPD

Bayer Healthcare, ~~67 Whippany Road, Whippany, NJ 07981, USA~~
Tel. PPD ***(as of Amd ~~6~~)***

New text:

Sponsor's medical expert: PPD

Bayer Healthcare, Rua Domingos Jorge, 1100, Predio 9301 2o andar, 04779-900 São Paulo – SP Brasil
Tel. PPD ***(as of Amd 7)***

Signature of the sponsor's medically responsible person

Old text:

Name: PPD (***as of Amd 6***) Role: Global Clinical Leader (GCL)~~/Medical Expert~~

New text:

Name: PPD (***as of Amd 6***) Role: Global Clinical Leader (GCL) (***as of Amd 7***)

Section 3 Investigators and other study participants

Old text:

Name: PPD
Title: PPD
Address: ***Bayer Healthcare, ~~67 Whippany Road, Whippany, NJ 07981, USA~~***
Tel. PPD ***(as of Amd ~~6~~)***

New text:

Name: PPD
Title: PPD
Address: ***Bayer Healthcare, Rua Domingos Jorge, 1100, Predio 9301 2o andar, 04779-900 São Paulo – SP Brasil***
Tel. PPD ***(as of Amd 7)***

13.5.2.3 Change 3

Synopis – Number of subjects

Old text:

[…]	
Number of subjects	***Part A:*** ***Total Number (N) = 50 PTPs*** ***age group 6-12 years: N=25*** ***age group <6 years: N=25*** ***Part B*** ***N= at least 25 PUPs, plus ~~up to~~ additional 25 PUPs/MTPs (as of Amds 3, and 6)*** ***age group <6 years*** ***Total = ~~at least 75, up to a maximum of~~ approximately 100 (includes both Part A and B) (as of Amds 1 and 3)***
[…]	

New text:

[…]	
Number of subjects	***Part A:*** ***Total Number (N) = 50 PTPs*** ***age group 6-12 years: N=25*** ***age group <6 years: N=25*** ***Part B:*** ***N= at least 25 PUPs, plus approximately an additional 25 PUPs/MTPs (as of Amds 3, 6 and 7)*** ***age group <6 years*** ***Total = approximately 100 (includes both Part A and B) (as of Amds 1, 3 and 7)***
[…]	

Section 8.6 Determination of sample size

Old text:

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study c***onsists of two parts. Part A (as of Amd 1)*** will include ***a total of 50 PTPs (as of Amd 1)***; 25 subjects age ***6*** – 12 years ***(as of Amd 3)*** and 25 subjects age <6 ***years. Part B will enroll at least 25~~, up to a maximum of approximately 50~~ PUPs/MTPs*** age <6 ***years. (as of Amd 3)*** The total sample size will be ***~~at least 75, up to a maximum of~~ approximately 100*** subjects. (***as of Amds 3 and 6***)

[…]

New text:

Adolescents and adults are included in 2 ongoing efficacy and safety studies of the clinical development program of BAY-81-8973. This study c***onsists of two parts. Part A (as of Amd 1)*** will include ***a total of 50 PTPs (as of Amd 1)***; 25 subjects age ***6*** – 12 years ***(as of Amd 3)*** and 25 subjects age <6 ***years. Part B will enroll at least 25, plus approximately an additional 25 PUPs/MTPs*** age <6 ***years. (as of Amd 3 and Amd 7)*** The total sample size will be ***approximately 100*** subjects. (***as of Amds 3, 6 and 7***)

[…]

13.5.2.4 Change 4

Section 5 Inclusion criteria

Additional text:

[…]

- **Part B (PUPs*/MTPs*):** *Enrollment **s*** may start after *safety is evaluated in 20* children *in Part A with* 50 ED ***(as of Amds 1 and 6)***.

1. Male, <6 ***years (as of Amd 3)***

2. Severe hemophilia A defined as < 1% FVIII:C based on ***prior documented testing or confirmed on (as of Amd 1, Amd 3) screening*** laboratory.

3a. PUPs: No previous exposure to any FVIII ***product (as of Amd 1)***

3b. MTPs: Have previously received not more than 3 injections with any FVIII product and who have no current evidence of inhibitor antibody measured centrally using the Nijmegen-modified Bethesda assay [<0.2 Bethesda units (BU)/mL] at screening, with confirmation using local laboratory testing at baseline (<0.6 Bethesda unit [BU/mL]) (as of Amd 7). MTPs may not receive FVIII within 48 h prior to the collection of samples for inhibitor testing at the Screening and Baseline visits. (as of Amd 6 and Amd 7).

[…]

Section 5.2.1 Withdrawal

Additional text:

[…]

- A positive inhibitor result at Screening or Baseline ***visits (as of Amd 1). Evidence of inhibitor formation in MTPs prior to starting treatment with study drug ([defined as ≥0.2 BU/mL by central laboratory testing at screening, and/or ≥0./6 BU/mL by local laboratory testing at baseline) (as of Amd 7)***

[…]

Section 7.1.1 Tabulated overview

Old text:

[…]

Table 7-2b: Schedule of evaluations (Part B – PUPs/MTPs)

	Visit 1 Screening [k]	Visit 2 Baseline	*Combined Screening and Baseline (PUPs only) (as of Amd 6)*	Visit 3 ED ~5 *(as of Amd 6)*	Visit 4 ED ~10 *(as of Amd 6)*	Visit 5 ED ~15 *(as of Amd 6)*	Visit 6 ED ~20 *(as of Amd 6)*	Interim Visit *30-40 ED (as of Amd 1)*	Final Visit or 50 ED [f]	Extension Visit every 6 months [f]	Extension Final Visit [f]
Informed consent	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X		
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)	X [h] (*Amd 6*)	X	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X [j]	X
Epitope mapping (inhibitor positive patients) (Amd 4)				←				X [e]			→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X	X [j] (*Amd 6*)	X (*Amd 6*)
Pharmacokinetics (optional) (Amd 3)		←					X [d]				→
Biomarker investigation (~~optional~~) (Amd 4)		←					X [g]				→
Infusion of study drug *(Amd 1)*		←	continuously in accordance with the prophylaxis regimen								→
Electronic patient diary (EPD) documentation		←	continuously								→
Healthcare Resources Utilization Questionnaire(Amd 1)	*X (Amd 1)*		← monthly								→

Interaction between subject/parent and investigator		← weekly →	← monthly →
Concomitant medication	X	← continuously →	

For footnotes please see next page

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
e Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies ***(as of Amd 4)***
f The Final Visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained ***(as of Amd 4)***
g The ~~optional~~ biomarker investigation (pharmacogenetics) requires a separate signed informed consent. The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw ***(as of Amd 4)***
h *Inhibitor to be evaluated at screening in MTPs only (ie, unnecessary to evaluate in PUPs) (**as of Amd 6**, include retention sample for inhibitor assessment by ELISA for MTPs).*
j *At the first extension visit 6 months after the start of the extension, and at any time in case of inhibitor development **(as of Amd 6)***
*k In case of MTPs, the screening visit should only take place after a washout period of at least 48 hours following any previous treatment with any FVIII replacement product **(as of Amd 6).***

New text:

[…]

Table 7-2b: Schedule of evaluations (Part B – PUPs/MTPs)

	Visit 1 Screening [k]	Visit 2 Baseline	*Combined Screening and Baseline (PUPs only) (as of Amd 6)*	Visit 3 ED ~5 *(as of Amd 6)*	Visit 4 ED ~10 *(as of Amd 6)*	Visit 5 ED ~15 *(as of Amd 6)*	Visit 6 ED ~20 *(as of Amd 6)*	Interim Visit *30-40 ED (as of Amd 1)*	Final Visit or 50 ED [f]	Extension Visit every 6 months [f]	Extension Final Visit [f]
Informed consent	X		X						X		
Inclusion / exclusion criteria	X	X	X								
Demographic data	X		X								
Height, weight	X	X	X	X	X	X	X	X	X	X	X
Medical and surgical history	X		X								
Previous medication (medication history)	X		X								
Physical examination	X		X						X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	***X* (*Amd 7*)**	***X* (*Amd 7*)**
Laboratory examination [a]	X		X						X		
HSP-70 antibodies		X [b]	X [b]						X [b]		
FVIII baseline level and inhibitor (one stage) (Amd 3)	X [h] (*Amd 6*)	**X[h] (*Amd 7*)**	X								
FVIII level before *infusion* and inhibitor [c] *(Amd 1)*				X	X	X	X		X	X [j]	X
Epitope mapping (inhibitor positive patients) (Amd 4)				←	←	←	←	*X* [e]	→	→	→
Recovery (20-30 min after *infusion*) *(Amd 1)*		X	X				X		X	X [j] (*Amd 6*)	X (*Amd 6*)
Pharmacokinetics (optional) (Amd 3)		←	←	←	←	←	*X* [d]	→	→	→	→
*Biomarker investigation (**recommended**) (Amd 4 **and Amd 7**)*		←	←	←	←	←	*X* [g]	→	→	→	→
Infusion of study drug *(Amd 1)*		←	←	←	←	←	continuously in accordance with the prophylaxis regimen	→	→	→	→
Electronic patient diary (EPD) documentation		←	←	←	←	←	continuously	→	→	→	→

Healthcare Resources Utilization Questionnaire(Amd 1)	*X (Amd 1)*	← monthly →
Interaction between subject/parent and investigator		← weekly → | ← monthly →
Concomitant medication	X	← continuously →

For footnotes please see next page

a. CBC, chemistries; local labs as needed to reduce blood volume (Section 14.4)
b. In subjects > 7 kg at baseline visit. See recommendations for blood draws in subjects <10 kg (Section 14.4)
c. Measured at least 48 h after last dose of FVIII
d Blood samples at the following time points: before, 20-30 min, 4 h, and 24 h post-infusion following a washout of 48 h after last dose of FVIII. Exact times need to be entered into CRF
e Epitope mapping to be performed in combination with confirmatory retest for inhibitory antibodies ***(as of Amd 4)***
f The Final Visit can be performed as soon as a minimum of 50 ED is achieved, but no later than 2 weeks after achieving 50 ED. For the regular Extension Visit (performed every 6 months), a window of ±2 weeks is allowed. The Extension Final Visit should take place no later than 2 weeks after 100 ED is achieved or until market authorization is obtained ***(as of Amd 4)***
g The ***recommended*** biomarker investigation (pharmacogenetics) requires a separate signed informed consent ***(as of Amd 7)***. The single blood sample for this analysis can be taken at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw ***(as of Amd 4)***
h *Inhibitor to be evaluated at screening* ***(central laboratory testing), and at t baseline (central and local laboratory testing),*** *in MTPs only (ie, unnecessary to evaluate in PUPs)* ***(as of Amd 6, include retention sample for inhibitor assessment by ELISA for MTPs). Study drug administration should start upon availability of result from local laboratory testing. (as of Amd 6 and Amd 7)***
j *At the first extension visit 6 months after the start of the extension, and at any time in case of inhibitor* ***development (as of Amd 6)***
k *In case of MTPs, the screening visit should only take place after a washout period of at least 48 hours following any previous treatment with any FVIII replacement product* ***(as of Amd 6).***

Section 7.1.2.2 Visit 2 – Baseline

Additional text:

[…]

This visit should start with the following assessments:

Confirmation of eligibility including check of laboratory test results.
Note: Eligible subjects (except PUPs) must be inhibitor negative at Baseline. ***MTPs must be inhibitor negative as evaluated via central laboratory testing at Screening visit (as of Amd 6). A confirmatory inhibitor test must be taken at Baseline visit. Results from local laboratory testing must be negative (<0.6 BU/mL) prior to administration of study drug. (as of Amd 7)***

[…]

Section 7.5.3.4 Inhibitor testing

Old text:

[…]

In Part B, the ***requirement for a*** FVIII inhibitor testing before study ***entry (as of Amd 1)*** is not applicable for PUPs ***but is applicable for MTPs (as of Amd 6). The absence of inhibitors will be ~~confirmed~~ at ~~the~~ Baseline ~~evaluation~~. After treatment is started (as of Amd 1),*** PUPs***/MTPs*** must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated ***(as of Amd 6). Afterwards, blood samples for inhibitor testing and determination of FVIII:C trough level (>48 h after last FVIII treatment) are to be taken:***

[…]

New text:

[…]

In Part B, the ***requirement for a*** FVIII inhibitor testing before study ***entry (as of Amd 1)*** is not applicable for PUPs ***but is applicable for MTPs (as of Amd 6). The absence of inhibitors will be assessed using central laboratory testing at Screening (<0.2 BU/mL), with confirmation using local laboratory testing at Baseline (<0.6 BU/mL) (as of Amd 7). After treatment is started (as of Amd 1),*** PUPs***/MTPs*** must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated ***(as of Amd 6). Afterwards, blood samples for inhibitor testing and determination of FVIII:C trough level (>48 h after last FVIII treatment) are to be taken:***

[…]

13.5.2.5 Change 5

Section 4 Study design

Additional text:

[…]

Enrollment will be staggered. Part A will start after 20 adult/adolescent subjects have received 50 ED with BAY 81-8973 without safety concerns ***in previous studies with BAY 81-8973***. PTPs age ***6 to 12 years*** will begin enrollment first, followed by PTPs ***<6 years (as of Amd 3).*** Part B, for PUPs***/MTPs*** (***as of Amd 6***) will begin enrollment after 20 children in Part A have had 50 ED. ***As of Amd 7, enrollment will occur in staggered approach. 10 patients will be enrolled, and will commence treatment for 20 ED. Enrollment of next sequence will start if no safety concerns are identified in the first group. Enrollment will be suspended if the inhibitor rate in the first cohort exceeds 50% following discussion with an independent Data Monitoring Committee (DMC). (as of Amd 7)***

[…]

13.5.2.6 Change 6

Section 4 Study design

Additional text:

[…]

In the event that any subject acquires an inhibitor to FVIII, Immune Tolerance Induction (ITI) will be offered. The subject may receive BAY 81-8973 up to 200 IU/kg daily or 100 IU/kg twice a day for 18 months. Treatment will be at the discretion of the treating physician, although the detailed treatment plan should be agreed with the Coordinating Investigator (as of Amd 7). Subject commences on ITI therapy will be followed up within the extension study. Data on treatment, FVIII measurements, and inhibitor levels will be collected. (as of Amds 1 and 6).

Section 6.1.1 Regular prophylaxis

Old text:

[…]

Test drug:	BAY 81-8973
Dosage:	25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, ***15-50 International Unit (IU)/kg;*** ≥ 1 ***time*** per week in PUPs***/MTPs***. ***(as of Amds 1 and 6).***

[…]

- ***Treatment can be initiated with an on-demand regimen. Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion. (as of Amd 1 and 6)***

- ***Alternatively, prophylaxis can be started directly*** with a once-a-week schedule low dose of 250 IU (15-25 IU/kg)***; the starting dose may be tailored to the subject's weight or demonstrated bleeding tendency. (as of Amd 1 and 6)***
- ***Avoid starting prophylaxis during febrile illness or other identified inflammatory events. (as of Amd 1)***
- ~~Increase frequency ***of infusion or dose as needed for breakthrough bleeding, increased*** physical activity, ***or weight gain. (as of Amd 1)***~~
- ***Avoid surgery or need for high dose intensive treatment lasting more than 4 days during the first 20 ED. (as of Amd 1)***
- ***Do not give FVIII as prophylaxis for vaccinations. (as of Amd 1)***

[…]

New text:

[…]

Test drug:	BAY 81-8973
Dosage:	25-50 International Unit (IU)/kg; ≥ 2 times per week in PTPs, ***15-50 International Unit (IU)/kg;*** ≥ 1 ***time*** per week in PUPs***/MTPs***. ***(as of Amds 1 and 6). <u>Recommendations for starting prophylaxis in PUPs/MTPs are described below. (as of Amd 7)</u>***

[…]

<u>Treatment recommendations (as of Amd 7)</u>

- ***Treatment can be initiated with an on-demand regimen. Prophylaxis should begin after a minimal number of on-demand FVIII exposures with BAY 81-8973 (no more than 2-3 bleeding events) or when the child is large enough to tolerate weekly infusion. (as of Amd 1 and 6)***
- ***Alternatively, prophylaxis can be started directly*** with a once-a-week schedule low dose of 250 IU (15-25 IU/kg)***; the starting dose may be tailored to the subject's weight or demonstrated bleeding tendency. (as of Amd 1 and 6)***
- <u>Increase frequency ***of infusion or dose as needed for breakthrough bleeding, increased***</u> physical activity, <u>***or weight gain. (as of Amd 1)***</u>
- ***Avoid starting prophylaxis during febrile illness or other identified inflammatory events. (as of Amd 1)***
- ***Avoid surgery or need for high dose intensive treatment lasting more than 4 days during the first 20 ED. (as of Amd 1)***
- ***Do not give FVIII as prophylaxis for vaccinations. (as of Amd 1)***

[…]

Section 7.1.1 Tabulated overview

Additional text is shown in the tabulated overview together with Change 4 (see Section 13.5.2.4).

Section 7.1.2.2 Visit 2 - Baseline

Old text:

[…]

For PUPs, the Baseline ***visit (as of Amd 1)*** may be combined with the Screening visit if all selection criteria can be confirmed based on medical records. ***The first dose of BAY 81-8973 may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment. (as of Amd 1)***

[…]

~~Thereafter,~~ the following activities will be performed:

- Measurement of body height***/length (as of Amd 1)*** and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before ***infusion. (Blood pressure may be deferred if appropriate cuff size or equipment is not available)***. ***(as of Amd 1)***
- Update of concomitant medication and ***Healthcare Resources Utilization Questionnaire (as of Amd 1)***. (Appendix 14.3)
- HSP-70 antibodies ***(in children > 7kg) (as of Amd 1)***
- ~~***Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment). (as of Amd 1)***~~
- ***Infusion*** of the first dose of study drug ***or dispensation of study drug for on-demand treatment in Part B (as of Amd 6).***

[…]

- ~~***Optional***~~ ***pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amds 4 and 6)***

[…]

New text:

[…]

For PUPs, the Baseline ***visit (as of Amd 1)*** may be combined with the Screening visit if all selection criteria can be confirmed based on medical records. ***The first dose of BAY 81-8973 may be for treatment of a bleed. First treatment should not occur during high risk situations, surgery, or bleeds requiring prolonged or intensive treatment (see Section 6.1.1). (as of Amd 1 and Amd 7)***

[…]

The following activities will be performed ***(as of Amd 7)***:

- ***Blood sample for inhibitor testing and determination of FVIII:C trough levels (≥ 48 h after last FVIII treatment). (as of Amd 1)***
- Measurement of body height***/length (as of Amd 1)*** and weight
- Measurement of vital signs: Systolic and diastolic blood pressure, heart rate, and body temperature before ***infusion. (Blood pressure may be deferred if appropriate cuff size or equipment is not available)***. ***(as of Amd 1)***
- Update of concomitant medication and ***Healthcare Resources Utilization Questionnaire (as of Amd 1)***. (Appendix 14.3)
- HSP-70 antibodies ***(in children > 7kg) (as of Amd 1)***
- ***Infusion*** of the first dose of study drug ***or dispensation of study drug for on-demand treatment in Part B (as of Amd 6).***

[…]

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw (as of Amds 4 and 6). Additional informed consent is required (as of Amd 7).***

[…]

Section 7.1.2.3 Visit 3 – Month 1 for Part A; ED ~5 (4 ED +/- 1) for Part B (as of Amd 1)

Old text:

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

New text:

[…]

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.4 Visit 4 – Month 2 for Part A; ED ~10 (9 ED +/- 1) for Part B (as of Amd 1)

Old text:

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

New text:

[…]

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.5 Visit 5 – Part B only; ED ~15 (14 ED +/- 1) (as of Amd 1)

Old text:

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

New text:

[…]

- ***<u>Recommended (as of Amd 7)</u> pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.6 Visit 6 – Part B only; ED ~20 (20 ED +/- 1) (as of Amd 1)

Old text:

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

New text:

[…]

- ***<u>Recommended (as of Amd 7)</u> pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.8 Final Visit (end of the main study and start of the optional extension study)

Old text:

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

New text:

[…]

- ***<u>Recommended (as of Amd 7)</u> pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.9 Extension study visits – 6 months after completion of Part A or B; then every 6 months) (as of Amd 1)

Old text:

[…]

The following procedures and assessments will be performed:

- Measurement of body height***/length (as of Amd 1)*** ~~and~~ weight

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

New text:

[…]

The following procedures and assessments will be performed:

- Measurement of body height***/length,*** weight***, and vital signs (as of Amd 1 and Amd 7)***

[…]

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.1.2.10 Extension final visit

Old text:

[…]

The following procedures and assessments will be performed:

- ***Measurement (as of Amd 1)*** of body height ~~and~~ weight

[…]

- ***~~Optional~~ pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed***

informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)

[…]

New text:

[…]

The following procedures and assessments will be performed:

- ***Measurement (as of Amd 1)*** of body height**,** weight ***and vital signs (as of Amd 7)***

[…]

- ***Recommended (as of Amd 7) pharmacogenetics in PUPs/MTPs (Part B and extension): collect blood sample for biomarker investigation, if not taken previously – requires signed informed consent. This blood draw will be done once only, and can be performed at any visit except Screening (as of Amds 4 and 6)***

[…]

Section 7.3.2.1 Incremental recovery of Factor VIII (as of Amd 1)

Additional text:

[…]

Incremental recovery at 20-30 min after end of ***infusions (as of Amd 1)*** will be determined at Baseline, Month 1, 2, Month 6 (or final visit)***, 1st extension visit and final extension visit (as of Amd 6).*** Incremental recovery should only be measured when the subject is not actively bleeding. The exact sampling times before and after ***infusion (as of Amd 1)*** have to be documented in the CRF.

A determination of recovery should also be performed with the confirmatory inhibitor test. (as of Amd 7)

Section 7.5.3.4 Inhibitor testing

Additional text:

[…]

After treatment is started (as of Amd 1), PUPs***/MTPs*** must be tested for inhibitor development every 3-5 ED until 20 ED are accumulated ***(as of Amd 6), and at the final visit (50 ED) (as of Amd 7). Afterwards, blood samples for inhibitor testing and determination of FVIII:C trough level (>48 h after last FVIII treatment) are to be taken:***

[…].

Section 7.6.2 Biomarker investigation (pharmacogenetics) (optional – consent required) (as of Amd 4)

Old text:

Section 7.6.2 Biomarker investigation (pharmacogenetics) (~~optional –~~ consent required) (*as of Amd 4*)

The purpose of this genetic analysis is to identify markers for risk of inhibitor development in subjects treated with BAY 81-8973. The markers to be analyzed are type of FVIII gene mutation if not available, single nucleotide polymorphisms (SNPs) in immunoregulators (eg, IL 10), HLA genotype, and FVIII polymorphisms. This biomarker analysis is exploratory and will be analyzed for PUPs and MTPs only. (as of Amds 4 and 6)

A separate informed consent for pharmacogenetic sampling is required and participation is ~~optional~~. (as of Amd 4)

If a subject elects to participate, a blood sample can be collected at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw. Samples will be prepared and labeled according to laboratory specifications. Details of the sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

A subject does not need to agree to participate in the pharmacogenetic sub-study to be enrolled in the main study. (as of Amd 4).

New text:

Section 7.6.2 Biomarker investigation (pharmacogenetics) (*recommended* – consent required) (*as of Amd 4 and Amd 7)*

The purpose of this genetic analysis is to identify markers for risk of inhibitor development in subjects treated with BAY 81-8973. The markers to be analyzed are type of FVIII gene mutation if not available, single nucleotide polymorphisms (SNPs) in immunoregulators (eg, IL 10), HLA genotype, and FVIII polymorphisms. This biomarker analysis is exploratory and will be analyzed for PUPs and MTPs only. (as of Amds 4 and 6)

A separate informed consent for pharmacogenetic sampling is required and participation is recommended. (as of Amd 4 and Amd 7)

If a subject elects to participate, a blood sample can be collected at any visit except Screening, ideally at Visit 3 or whenever the subject's body weight/condition is suitable for an additional blood draw. Samples will be prepared and labeled according to laboratory specifications. Details of the sample collection and shipment procedures will be provided in the Laboratory Manual. (as of Amd 4)

A subject does not need to agree to participate in the pharmacogenetic sub-study to be enrolled in the main study. (as of Amd 4). However, as this analysis provides important information about inhibitor development, participation is the sub study is recommended. (as of Amd 7)

13.6 Amendment 8

Amendment 8 is the sixth global amendment dated 01 FEB 2019, and is presented using a different approach from the previous amendments. The rationale for this amendment with an overview of the affected sections is provided in the "Protocol Amendment Summary of Changes Table" which can be found directly before the Table of contents in this document.

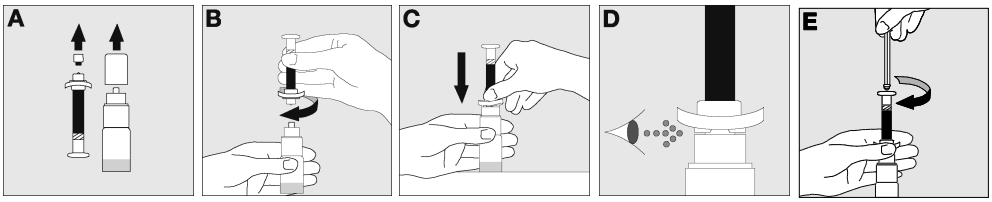
Changes in this document are made without annotations. A separate file with tracked changes against the last integrated protocol version is available upon request.

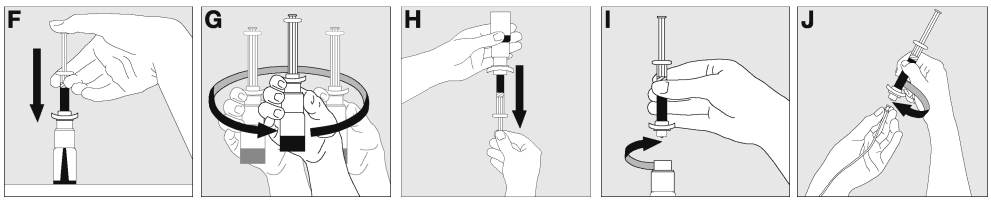
14. Appendices

14.1 Instruction for use of study medication

14.1.1 Presentation of vials with Bio-SET reconstitution cap

- Study medication is intended for intravenous administration only and must be administered immediately after reconstitution.
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of study medication.
- Study medication must not be mixed with other infusion solutions. Follow the directions given by your doctor closely and use the instructions below as a guide:





1. Wash your hands thoroughly using soap and warm water. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set.

   This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).

7. Inject the solvent by slowly pushing the syringe's plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.
10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the subject's comfort, but should not be faster than 2ml\min (maximum rate of ***infusion***). ***(as of Amd 1)***
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

NOTE: See accompanying instructions for Injection Set with Filter for injections after blood withdrawal.

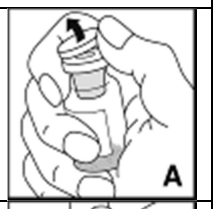
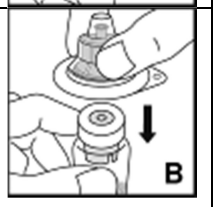
14.1.2 *Presentation of vial and vial adapter (as of Amd 6)*

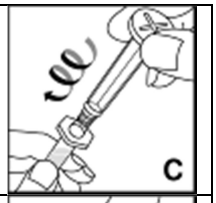
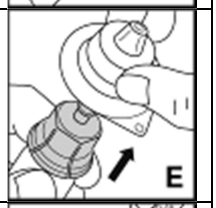
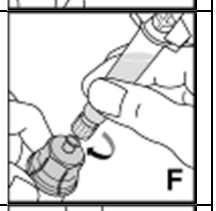
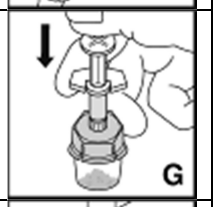
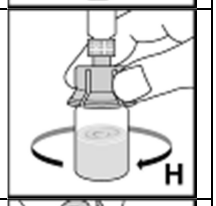
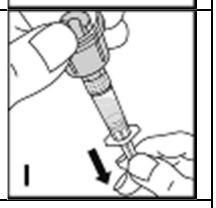
Note: This section was introduced by amendment 6.

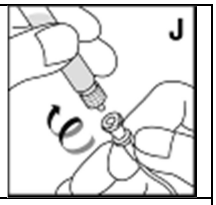
How to use BAY 81-818973

- This medicine is intended for injection into a vein only and should be used within 3 hours after reconstitution.
- Use only the items (vial adapter, pre-filled syringe containing solvent and venipuncture set) that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.
- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. **You are filtering by using the vial adapter.**
- This medicine must **not** be mixed with other infusion solutions. Follow the directions given by your doctor closely and use the **detailed instructions for reconstitution and administration provided in the Annex of this leaflet below.**
- You will need alcohol swabs, gauze pads and plasters.

ANNEX: Detailed instructions for reconstitution and administration for presentation with vial adapter:

1.	Wash your hands thoroughly using soap and warm water.	
2.	Warm both an unopened vial and a syringe in your hands to a comfortable temperature (do not exceed 37°C).	
3.	Remove the protective cap from the vial **(A)** and wipe the rubber stopper on the vial with an alcohol swab and allow it to air dry before use.	
4.	Place **product vial** on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do **not** remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down **(B)**. The adapter will snap over the vial cap. Do **not** remove the adapter housing at this point.	

5.	Hold the pre-filled water for injections syringe upright, grasp the plunger rod as per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper **(C)**.	
6.	Holding the syringe by the barrel, snap the syringe cap off the tip **(D)**. Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.	
7.	Now remove and discard the adapter housing **(E)**.	
8.	Attach the pre-filled syringe to the threaded vial adapter by turning clockwise **(F).**	
9.	Inject the diluent by slowly pushing down on the plunger rod **(G)**.	
10.	Swirl vial gently until all material is dissolved **(H)**. Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.	
11.	Hold the vial on end above the vial adapter and syringe **(I)**. Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.	
12.	Apply a tourniquet.	
13.	Determine the point of injection and clean the skin with an alcohol swab.	
14.	Puncture the vein and secure the venipuncture set with a plaster.	

15. Holding the vial adapter in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe **(J)**.	
16. Remove tourniquet.	
17. Inject the solution into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of administration should be based on your comfort, but should not be faster than 2 mL per minute.	
18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.	
19. If no further dose is required, remove the venipuncture set and syringe. Hold a pad firmly over the injection site on your outstretched arm for approximately 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.	

14.2 Standard of Care

The dosage necessary to achieve hemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines: (Source: Package Insert Kogenate Bayer). In this protocol, minor surgical procedures are defined as any surgical procedure (elective or emergent) that does not involve general anesthesia and/or respiratory assistance (eg, minor dental extractions, incision and drainage of abscess, or simple excisions). Major surgical procedures are defined as any surgical procedure (elective or emergent) that involves general anesthesia and/or respiratory assistance in which a major body cavity is penetrated and exposed, or a substantial impairment of physical or physiological functions is produced (eg, laparotomy, thoracotomy, craniotomy, fracture).

Degree of hemorrhage/ Type of surgical procedure	**Factor VIII level required (%) (IU/dL)**	**Frequency of doses (hours)/ Duration of therapy (days)**
Hemorrhage		
Early hemarthrosis, muscle bleed or oral bleed	20 – 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.

Degree of hemorrhage/ Type of surgical procedure	**Factor VIII level required (%) (IU/dL)**	**Frequency of doses (hours)/ Duration of therapy (days)**
More extensive hemarthrosis, muscle bleed or hematoma	30 – 60	Repeat infusion every 12 – 24 hours for 3 – 4 days or more until pain and disability are resolved.
Life threatening bleeds such as intracranial bleed, throat bleed, severe abdominal bleed	60 – 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Minor including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	80 – 100 (pre- and postoperative)	a) By bolus injections Repeat infusion every 8 – 24 hours until adequate wound healing occurs, then continue with therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60%

14.3 Healthcare Resources Utilization Questionnaire

The Healthcare Resources Utilization Questionnaire will be used to collect data on the subject. This will include number of days lost from school, medical procedures or laboratory tests, complications, and hospitalizations due to hemophilia or other medical needs. The questionnaire should be administered by the investigator or delegate monthly throughout the study period by interviewing a parent/caregiver. This can be performed either at scheduled study visits, or during regularly scheduled contact between the study site and the parent/caregiver. The answers will be entered on the paper questionnaire by the study site. The completed questionnaire is a source document subject to review by the monitor.

Healthcare Resources Utilization Questionnaire in LEO Kids (13400)

Instructions for the interviewer:

- ***Only one parent or caregiver, the person with whom the child relates most closely, should answer the questions consistently***

- ***Please record the answers in English.***
- ***Please do not write any other information on the form.***

Study Center: _____ Subject number: _____
Date of interview: _____ (MM/DD/YYYY)
This form is being completed for the month of _____ and year _____.
For example: Month of June and year 2011 (answers include contacts from June 1 to June 30, 2011).

1. Did your son have any contact with health professionals this past month that were not required as part of the LEO Kids study?
_____NO ____YES

If yes, then complete:
Type of contact: _____Office visit _____ Phone call (Check or enter how many if more than one.)
Reason for contact: _____
Whom did your child see? Please check all that apply:

___Hematologist
___Family physician
___Pediatrician
___Nurse
___Pharmacist
___Other, specify: _____

2. Did your son have any procedures or tests performed in the past month that were not required as part of the LEO Kids study?
_____NO _____YES

If yes, please check all that apply:
___ Blood test Number of times blood was drawn: _____ (even if multiple tubes were collected)
___ Urine test Number of times specimen collected: _____
___ Biopsy Number of times: _____
___ X-ray Number of times: _____ (can include multiple views)
___ MRI Number of times: _____
___ CT scan Number of times: _____
___ Joint surgery Number of times: _____

3. Did your son have any hospital visits in the past month?
_____NO _____YES

If yes, check the kind of visit:

___Hospital admission. For how many nights? _____ (Include nights in ICU/PICU)
___Emergency Department visit. For how many nights? _____
___Intensive Care Unit or Pediatric Intensive Care Unit (ICU or PICU).
For how many nights? _____
Reason: _____

4. Did your son miss any days of school due to hemophilia in the past month?

_____NO _____YES If yes, number of days missed? _____ (as of Amd 1)

14.4 Blood draws in subjects weighing less than 10 kg (as of Amd 1)

Every effort has been made to minimize the volumes of blood required for participation in the study. For the majority of subjects in the study, the volumes drawn at any one visit are not expected to exceed more than 1 % of total blood volume, or 3% in any 1 month interval. However, in young infants, Part B of the study may require modification to allow participation by infants or small toddlers. (as of Amd 1)

Table 14.4a shows the estimated total blood volume for children 1-10 kg and the recommended amount of blood for study purposes. These volumes (as of Amd 1) should be considered a guideline, and may be exceeded if determined to be safe by the investigator.

Table 14.4a Recommended Blood Draw Volumes (as of Amd 1)

Body Wt (Kg)	*Body Wt (lbs)*	*Total blood volume (mL)*	*Allowable volume (mL) in one blood draw (1% of total blood volume)*	*Total volume (mL) drawn in a 30-day period (3% of total blood volume)*
1	*2.2*	*100*	*1*	*3*
2	*4.4*	*200*	*2*	*6*
3	*6.3*	*240*	*2.4*	*7.2*
4	*8.8*	*320*	*3.2*	*9.6*
5	*11*	*400*	*4*	*12*
6	*13.2*	*480*	*4.8*	*14.4*
7	*15.4*	*560*	*5*	*16.8*
8	*17.6*	*640*	*6.4*	*19.2*
9	*19.8*	*720*	*7.2*	*21.6*
10	*22*	*800*	*8*	*24*

Wt: Body weight/ ***Ernst, D. J. Applied Phlebotomy. Lippincott Williams & Wilkins. 2005***

Table 14.4b shows the blood volumes needed for the tubes used for the central laboratory. (as of Amd 1)

Table 14.4b Volume of blood draws in Part B (as of Amd 1)

	Visit 1 Screening	***Visit 2 Baseline***	***Visit 3 ~5 ED***	***Visit 4 ~10 ED***	***Visit 5 ~15 ED***	***Visit 6 20 ED***	***Interim visit***	***Final visit 50 ED***
Volume of blood (ml)	*4.2*	*5.3*	***2.7***	***2.7***	***2.7***	***4.1***	***0***	***7.7***
	7.7							

For infants at least 7 kg at study enrollment, the volumes listed for each individual visit should be well tolerated. As the Screening and Baseline visits can be combined for PUPs, investigators need to be aware that the total volume required could exceed 1% of total blood

volume in children 9 kg or less. The total volume at the combined Screening and Baseline visit may be reduced if the CBC and chemistries are processed through the local laboratory using minimal volumes and the results entered in the CRF. The decision whether to use the local laboratory or to divide the blood sampling over more than one draw is at the investigator's discretion, but the total amount of blood drawn s***hould not exceed 3% of total blood volume over a 30 day interval. (as of Amd 1)***

For infants who are 7 kg and smaller at study entry, the sampling schedule ***will be modified. The sample for collection of HSP-70 antibody (1.2 ml) will not be collected. (as of Amd 1)*** FVIII trough level and inhibitor will be measured using a reduced volume (1.8 ml). ***Estimated blood volumes based upon these modifications are shown in table 14.4c. (as of Amd 1)***

Table 14.4c Modified volume of blood in infants less than 7 kg (as of Amd 1)

	Visit 1 Screening	***Visit 2 Baseline***	***Visit 3 ~5 ED***	***Visit 4 ~10 ED***	***Visit 5 ~15 ED***	***Visit 6 20 ED***	***Interim visit***	***Final visit 50 ED***
Volume of blood (ml)	***2.4***	***4.1***	***2.7***	***2.7***	***2.7***	***4.1***	***0***	***6.5***
	6.5 (5.2)[a]							

a. (…) Est volume if CBC and chemistries obtained with minimal volumes through local laboratory

For infants less than 7 kg, for whom the Screening and Baseline visits are combined, it is recommended that the screening CBC and chemistries be processed through the local laboratory using minimal volumes, and the results entered in the CRF. Capillary samples may be used if care is used to minimize the risk of hemolysis. It is assumed that the minimal volume needed for both CBC and chemistries is approximately 1.1 ml. (as of Amd 1)

Should an investigator wish to enroll a subject who weighs less than 5 kg, discussion with the sponsor is required. (as of Amd 1)

14.5 Laboratory evaluation for suspected inhibitor (as of Amd 1)

If an inhibitor is clinically suspected (a bleed that progresses or does not improve following appropriate therapy), the subject be managed according to local standard of care. The investigator should immediately notify the sponsor and obtain the following information and blood tests:

- ***time and dose of last infusion***
- ***infused product (if other than BAY 81-8973)***
- ***blood for central laboratory***
  - ***pre and post FVIII level/ Activated Partial Thromboplastine Time (aPTT)***

- *inhibitor to Factor VIII testing by the Nijmegen assay*

If inhibitor is confirmed, the subject may receive immune tolerance therapy using BAY 81-8973. (See section 6.1.4)

If an inhibitor is detected as part of scheduled testing, the investigator will be notified. A positive inhibitor test is defined with a threshold of ≥ 0.6 BU in the central laboratory. Any positive test must be confirmed by a second plasma sample. Pre and post infusion samples will be required for confirmation. (as of Amd 1)