Document Type:	Statistical Analysis Plan
Official Title:	A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy
NCT Number:	NCT01311648
Document Date:	28-JAN-2020

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

BSP study drug	BAY 81-8973		
Study purpose:	To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A		
Clinical study phase:	Phase III	**Date:**	19 Dec 2012
Study No.:	13400	**Version:**	2.1
Authors:	PPD	PPD	

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

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

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Abbreviations

AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
BU	Bethesda unit
CL	clearance
C_{max}	maximum concentration
CS/ADJ	Chromogenic Substrate Assay Adjusted to Label Potency
CS/EP	Chromogenic Substrate Assay / Per European Pharmacopeia
dL	deciliter
DMC	Data Monitoring Committee
CRF	Case Report Form
eCRF	Electronic Case Report Form
ED	exposure day
EPD	Electronic Patient Diary
FVIII	Factor VIII
IU	International Unit
IVR	in vivo recovery
kg	kilogram
LLOQ	lower limit of quantification
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
n/a	not applicable
PDD	Protocol Deviations Document
PPS	Per-Protocol Analysis Set
PTP	previously treated patient
PUP	previously untreated patient
QoL	quality of life
rFVII	recombinant Factor VIII
PP	Per-protocol
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
$t_{1/2}$	half-life
TLF	Tables, Listings, Figures
V_{ss}	steady state volume

1. Introduction

This statistical analysis plan (SAP) is based on Integrated Protocol, Version 3.0, dated 03 Sep 2012.

This protocol version is an integration of the original protocol and the following global amendments:

Original protocol, Version 1.4, 20 Sep 2010
Amendment 1 forming integrated protocol Version 2.0, 31 Mar 2011
Amendment 3 forming integrated protocol Version 3.0, 03 Sep 2012

This SAP describes the study objective, study design, analysis sets, all endpoints, and statistical analysis methods for main evaluation period of previously treated patients (PTPs) in study 13400. Complete details of Tables, Listing and Figures (TLFs) specifications as well as dataset details and data handling specifications will be provided in "TLF specifications" and "Analysis Datasets" documents which are an integral part of this SAP.

The main evaluation period of the study has a duration of 6 months. The 6-month data for PTPs will be analyzed for regulatory purposes as a final analysis of the main study in PTPs, nevertheless, Part B and the extension for both parts will be ongoing. When safety has been assessed in 10-20 PTPs who have received at least 50 EDs, 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 their respective extensions. Additional analyses will summarize data from Part B and the extension trials.

2. Study Objectives

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 a minimum of 6 previously treated patients (PTPs) or previously untreated patients (PUPs)

3. Study Design

From the 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.

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 EDs 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.

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 EDs. 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 EDs 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.

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

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 [Cmax], 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 for 18 months. Treatment will be at the discretion of the treating physician. Data on treatment, FVIII measurements, and inhibitor levels will be collected.

3.1 Sample size calculation

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) and sample sizes have been confirmed on consultation with the European Medicines Agency Pediatric Committee [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 pediatric study consists of two parts. Part A will include a total of 50 PTPs; 25 subjects >6 – 12 years and 25 subjects aged 0-6 years. Part B will enroll at least 25 up to a maximum of approximately 50 PUPs aged 6 years and under. Total sample size will be at least 75 subjects up to a maximum of approximately 100 subjects.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, North Carolina, United States). 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. Unless otherwise noted, any statistical tests will be 2-sided and performed at the 0.05 significance level.

Standard programs such as ADMAP and MOSTO will be used.

There will be a Validity Review Meeting and it is possible that this SAP might be updated based on the Validity Review Report.

The primary variable is the annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and 'other' bleeds) that occur within 48 hours after all prophylaxis infusions. [Note this is a change from the protocol that defined total bleeds to be the sum of spontaneous bleeds and trauma bleeds.]

Secondary efficacy parameters are:

- Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and 'other' bleeds) during prophylaxis treatment
- Hemostatic outcome of surgeries (both major and minor) including blood loss, transfusion, and/or hemostatic-related surgical complications
- FVIII recovery values
  [note: recovery = (post-infusion FVIII – pre-infusion FVIII) * body weight / IU]

Additional efficacy parameters are:

- Annualized number of joint bleeds, spontaneous bleeds, and trauma bleeds that occur within 48 hours after all prophylaxis infusions
- Annualized number of joint bleeds, spontaneous bleeds, and trauma bleeds

- % of joint bleeds in target joint for subjects with target joint
- Number of infusions for the treatment of bleeds per bleed
- For all infusions and prophylaxis infusions, FVIII usage calculation expressed in number of infusions, IU, IU/kg, IU/infusion, IU/year, IU/kg/infusion, and IU/kg/year.
- For bleed infusions, FVIII usage calculation expressed in number of infusions, IU, IU/bleed, IU/kg/bleed, IU/bleed (first infusion), IU/kg/bleed (first infusion), IU/infusion, IU/year, IU/kg/infusion, and IU/kg/year.
- For surgery infusions, FVIII usage calculation expressed in number of infusions, IU, IU/kg, IU/infusion, and IU/kg/infusion.
- Description of bleeding according to type, severity, and location as indicated on EPD
- Subject's assessment of response to treatment of bleeds, with the hemostatic outcome of bleeding episodes expressed as "poor", "moderate", "good", and "excellent".
- Healthcare Resources Utilization Questionnaire (Within a subject, sum over all responses to obtain number of visits, procedures, and other events.)

The following pharmacokinetic parameters will be calculated and summarized: Based on the plasma concentration time data the following pharmacokinetic parameters will be calculated:

- maximum concentration (Cmax)
- Cmaxnorm
- area under the curve (AUC)
- half-life (t1/2)
- mean residence time (MRT)
- clearance (CL)

All data will be listed and summary tables will be provided.

4.2 Handling of Dropouts

Annualized number of total bleeds will be calculated for all subjects, including dropouts. See formula in Section 4.5. Subjects who drop from the study will be included in a listing.

4.3 Handling of Missing Data

Each subject's start and stop date will be needed to compute the annualized bleeding rate. If a bleed date is missing, but an infusion date is available, infusion date will be used as the bleed date. Otherwise, use imputation rules as specified in "Analysis Datasets" document.

Missing or incomplete AE start and end date or time: For the purpose of treatment emergent flags, missing AE start day will be imputed as the 15th of the month. However, if the AE start day is missing, but the AE starts during the same month as the first dose, or if the AE starts on the same day as the first dose, but the AE start time is missing, the AE start day (and time in the

second case) will be taken from first dose start day (and time). If both day and month of AE start date are missing, day and month will be imputed as July 1st, or the date of the first dose, whichever comes later.

Drug-related AE tables will include AEs with missing values of causality.

Imputation rules for AE durations (days) are described in the analysis datasets specifications.

When computing age at diagnosis, age at start of therapy, and time since start of therapy; if day is missing, use 15. If month and day are missing, use July 1. If necessary, adjust imputed dates so they are not before the birth date.

4.4 Interim Analyses and Data Monitoring

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.

Although not considered an interim analysis, the 6-month data for PTPs will be analyzed for regulatory purposes as a final analysis of the main study. Safety will be assessed in 10-20 PTPs before enrollment of PUPs begins.

4.5 Data Rules

All bleed and infusion data will be entered into the EPD (hospital infusions will be entered into an eCRF) and imported into SAS. If an infusion is given for a bleed and the bleed information is not provided, the infusion date will be used as the bleed date. Total bleeds is the sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and 'other' bleeds. Bleeds occurring before start of prophylaxis treatment with study medication will not be counted.

Bleeding rate will be annualized using the following formula:

Annualized bleed rate under prophylaxis =
(number of bleeds) * 365.25 / (last datetime in study – 1st datetime in study) / (60*24)

where:

- 1st datetime in study is the datetime of the first prophylaxis dose (usually Visit 2)
- last datetime in study is the later of the date of Visit 6 (assume time of visit is noon) or last datetime in the EPD prior to the extension period.

Prophylaxis infusions per week will be defined using the following formula:

Number of prophylaxis infusions per week =
(number of prophylaxis infusions) / (last datetime in study – 1st datetime in study) / (60*24*7)

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

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

When sorting the infusion records for counting number of infusions associated with each bleed, 1st infusions for bleeds will use the bleed date (if missing then use the infusion date). Follow-up infusions will use the dose date.

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

4.6 Validity Review

Final decisions regarding validity will be made during the Validity Review Meeting and documented in the Validity Review Report. Any changes to the statistical analysis prompted by the results of this review meeting will be documented in an amendment and, if applicable, supplement to this SAP.

5. Analysis Sets

5.1 Assignment of analysis sets

The safety analysis set (SAF) will include all subjects who were entered into the study and received study drug. The intent-to-treat analysis set (ITT) will include all subjects in the SAF who have infusion/bleeding data from the EPD. The per-protocol analysis set (PPS) will include all ITT subjects who have no major protocol deviations and have EPD data. The ITT will be used for the primary efficacy analysis. The efficacy analysis of the PPS will be considered supportive. Data from Part B and the extensions will be summarized separately.

Specific rules for major protocol deviations will be documented in the "Protocol Deviations Document" (PDD) prior to validity review meeting. Final decisions regarding the assignment of subjects to analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report.

Subjects will be excluded from the PPS for non-compliance if they violate any of the following criteria (for PTPs only):

- at least 1 interval between all infusions > 30 days
- at least 2 intervals between all infusions > 21 days
- at least 3 intervals between all infusions > 14 days
- number of infusions < 80% number of expected infusions [use expected number of infusions = (prescribed number of infusions per week) * (last datetime in study – 1st datetime in study) / (60*24*7)]
- at least 20% of prophylaxis infusions at a dose level < 15 IU/kg (for PTPs)
- at least 20% of prophylaxis infusions at a dose level < 10 IU/kg (for PUPs) [Note: not applicable to this SAP)

All tables will summarize data with columns for PTP 0-<6 years, PTP 6-12 years, and Total.

Pharmacokinetic Analysis Set

All subjects with evaluable PK-data will be included in the analysis of pharmacokinetic data.

Subgroups:

Subgroup tables will be provided. Possible subgroups for number of bleeds within 48 hours after prophylaxis per year and number of bleeds per year to be presented are:

- Prophylaxis Treatment regimen (<=2x/week, >2x/week)
- Average prophylaxis dose high (>=30 IU/kg), low dose (<30 IU/kg)
- Average prophylaxis dose/week high (>=80 IU/kg), low (<80 IU/kg)
- prior treatment (on-demand, prophylaxis)
- Race Group (white, non-white)
- Region (North America, Europe, Israel)
- Number of Bleeds during previous 12 months (<median, >=median)
- Number of Joint Bleeds during previous 12 months (<median, >=median)
- Presence of Target Joint (no, yes)

6. Statistical Methodology

6.1 Population characteristics

6.1.1 Baseline

Demographic characteristics, including age, body weight, height, BMI and race will be presented for all infused subjects, in the form of summary statistics. Other baseline characteristics, including previous treatment characteristics, disease history, previous number of bleeds, laboratory findings and vital signs, will be handled similarly.

6.1.2 Extent of exposure

Extent of exposure to the study drug, including infusion characteristics, will be summarized for each subject receiving any amount of drug. In addition, extent of exposure for surgeries will be summarized separately.

6.2 Efficacy

All subjects receiving study drug who have infusion/bleeding data from the EPD will be included in the efficacy analysis. The primary efficacy variables will be the annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, and untreated bleeds) that occur within 48 hours after all prophylaxis infusions. Also summarized will be annualized number of joint bleeds, spontaneous bleeds, and trauma bleeds that occur within 48 hours after all prophylaxis infusions. Additional variables summarized will be annualized number of total bleeds, joint bleeds, spontaneous bleeds, and trauma bleeds. Other variables summarized will be the number of treatments required to control all bleeds and the subject's assessment of the response to treatment of all bleeds (poor, moderate, good, or excellent).

All efficacy variables will be summarized using the ITT analysis set. The primary efficacy variable will also be summarized using the PPS.

For subjects undergoing surgery (both major and minor), FVIII levels from the day prior to surgery through the post-operative period will be summarized by timepoint and listed. Study drug and blood product infusions will also be summarized and listed for these subjects, as well as blood loss at surgery and the assessment of hemostasis during the perioperative period by both the surgeon and the investigator.

Factor VIII concentration values and recovery values will be summarized by time point.

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

If a Factor VIII concentration value is below the LLOQ (lower limit of quantification), a data point will be substituted by one half of this limit.

A validity flag for recovery values and their corresponding pre- and post-infusion FVIII values will be created. These values will be considered valid except when any of the following conditions apply:

- If pre-infusion FVIII >= post-infusion FVIII [biologically impossible in the absence of inhibitors]
- If pre-infusion FVIII > 40 IU/dl (note 1 IU/dl=1%) [protocol violation]

In the tables displaying descriptive statistics of recovery values, if a recovery is flagged as not valid, then the corresponding pre-infusion FVIII, post-infusion FVIII, and recovery values will not be included.

Each subject's last FVIII trough value (pre-infusion value) will be summarized by time interval within 48 =/- 6 hours, 60 +/- 6 hours, 72 +/- 6 hours, 84 +/- 6, >=90 hours, and >36 hours after previous infusion will be summarized. Mean trough level >36 hours after last infusion will be calculated for correlations.

Spearman Correlations will be provided for the following:

- annualized bleeds and mean FVIII trough value (pre-infusion)

- annualized joint bleeds and mean FVIII trough value (pre-infusion)
- time to bleed treatment and bleed severity
- # of infusions to treat bleed and bleed severity
- first dose to treat bleed (IU/kg) and bleed severity
- time to bleed treatment and response to treatment of the bleed
- # of infusions to treat bleed and response to treatment of the bleed
- first dose to treat bleed (IU/kg) and response to treatment of the bleed

6.2.1 Required variables in efficacy data sets:

The following variables are needed in the efficacy data sets.

The sequence for derivation of these 3 data sets is: Infusion, bleed, and subject.

Subject level dataset:

One record per subject:
indicator variable: prophylaxis treatment regimen (<=2x/week or >2x/week) [see formula for number of prophylaxis infusions per week in Section 4.5]
prophylaxis dose (15-50 IU/kg)
indicator variable: weekly prophylaxis dose (<80 IU/kg, >=80 IU/kg)
indicator variable: prior treatment (prophylaxis, on-demand)
indicator variable: target joint (no/yes)
number of target joints
number of days in study [last day in study – 1st day in study + 1]
total bleeds (spontaneous/trauma/untreated/'other')
total bleeds (spontaneous/trauma/untreated/'other') within 48 hours after prophylaxis infusions
joint bleeds
joint bleeds within 48 hours after prophylaxis infusions
spontaneous bleeds
spontaneous bleeds within 48 hours after prophylaxis infusions
trauma bleeds
trauma bleeds within 48 hours after prophylaxis infusions
total bleeds per year
total bleeds within 48 hours after all prophylaxis infusions per year
joint bleeds per year
joint bleeds within 48 hours after all prophylaxis infusions per year
spontaneous bleeds per year
spontaneous bleeds within 48 hours after prophylaxis infusions per year
trauma bleeds per year
trauma bleeds within 48 hours after prophylaxis infusions per year

'other' bleeds
untreated bleeds
if subject has a target joint, % of joint bleeds in target joint
exposure days [number of different calendar days with at least one infusion]
number of infusions/subject
- total dose (IU)
- total dose per kg (IU/kg)
- total dose per kg per year (IU/kg/year)
- dose per infusion (IU/kg/infusion)
- total dose per infusion (IU/infusion)
- total dose per year (IU/year).

number of prophylaxis infusions/subject
- total dose for prophylaxis (IU)
- total dose for prophylaxis per kg (IU/kg)
- prophylaxis dose per year (IU/kg/year)
- dose per prophylaxis infusion (IU/kg/infusion)
- total prophylaxis dose per infusion (IU/infusion)
- total prophylaxis dose per year (IU/year)

number of infusions for bleeds
- Total dose for bleeds (IU)
- Total dose per bleed (IU/bleed)
- First dose per bleed (IU/kg/bleed)
- Total dose per kg for bleeds (IU/kg)
- Total dose per kg per bleed (IU/kg/bleed)
- Total dose per kg per spontaneous bleed (IU/kg/bleed)
- Total dose per kg per trauma bleed (IU/kg/bleed)
- Total dose per year for bleeds (IU/year)
- Total dose per infusion for bleeds (IU/inf)
- Dose per infusion for bleeds (IU/kg/inf)
- Dose per year for bleeds (IU/kg/year)

number of infusions for surgery
- Total surgery dose (IU)
- Total surgery dose per kg (IU/kg)
- Total surgery dose per infusion (IU/inf)
- Dose per surgery infusion (IU/kg/inf)

Bleed level dataset (ADCE):

One record per bleed per subject:
- indicator variable: bleed treated (no/yes)
- indicator 1st bleed since most recent prophylaxis infusion (no/yes)
- number of infusions
- number of infusions (0, 1, 2, 3, 4, >4)
- number of infusions (<=2, >2)

reason for 1st infusion (spontaneous, trauma, other, missing)
type of bleed (joint, muscle, skin/mucosa, internal, other)
if joint bleed and subject has a target joint,
indicator variable: bleed in target joint or bleed not in target joint
response to treatment (poor, moderate, good, excellent)
bleed severity (mild, moderate, severe)
time from this bleed to 1st infusion for this bleed (hours)
time from last prophylaxis infusion to this bleed (days)
time from last prophylaxis infusion to this bleed (<1, 1-2, 2-3, 3-4, 4+ days)
indicator variable: bleed within 48 hours after most recent prophylaxis infusion
time from last infusion to this bleed (days)

Infusion level dataset (ADEX):

One record per infusion per subject:
indicator variable: drug used was study drug (no/yes)
indicator variable: in reason for infusion was prophylaxis, was there a bleed within 48 hours (no/yes)
reason for infusion (prophylaxis (including additional prophylaxis), spontaneous-1st infusion, trauma-1st infusion, surgery, follow-up, other)
dose (IU)
most recent body weight
dose (IU/kg) [use most recent body weight]
time from last infusion to this infusion (days)
time of day [morning, (06:00 - 13:59), afternoon (14:00 - 21:59), night (22:00 - 5:59)]
time from last prophylaxis infusion to this infusion (days)

An example for infusion/bleed/subject data is shown below. The subject has 182 days in study with 52 exposure days and total bleeds equal 2:

Infusions data set (ADXB)	Bleeds data set (ADXC)	Subject data set (ADXA)
Infusion #/reason	# of infusions per bleed/type	# of bleeds/ # of joint bleeds/ # of spontaneous bleeds/ # bleeds per year
1/prophy		
2/bleed	1/joint	2/1/1/(2*365.25/182)
3/prophy		
4/ bleed	2/muscle	
5/follow-up		
Etc..		

52/prophy		

If subjects are treated with non-study FVIII drug, we may repeat the efficacy analysis combining non-study FVIII drug with study drug in bleeds/infusions. Alternatively, we may list these subjects, depending on the number of such cases we observe in the study. If we decide to repeat the efficacy analysis for combined study drug FVIII and non-study drug then corresponding variables will be derived.

6.3 Pharmacokinetics / pharmacodynamics

The concentration-times courses of FVIII will be tabulated for the planned sampling points at pre-infusion, 20-30 minutes, 4 hours (range approximately 3-5 hours for summary statistics), and 24 hours (range approximately 22-26 hours for summary statistics) after the end of infusion. The following statistics will be calculated for each of the sampling points (if appropriate): geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and coefficient of variation, arithmetic mean, standard deviation and coefficient of variation, minimum, median, maximum value, and the number of measurements.

Pharmacokinetic characteristics will be summarized by the statistics mentioned above.

Individual and mean (if appropriate) concentration vs time profiles (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted using both linear and semilogarithmic scale. Incremental recovery will be calculated taking the baseline value into account.

Pharmacokinetic parameters, as well as FVIII levels, will be displayed in subject listings.

6.4 Safety

All subjects receiving any amount of study drug will be included in the safety analysis. Laboratory findings, adverse events, concomitant medications, and medical history data will be provided in subject listings.

Laboratory values, incidence of high or low abnormal values, changes from baseline (Baseline value is the last value before the first study drug infusion.) will be summarized. 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). AEs with a start date prior to first infusion or more than 3 days after the last infusion are not treatment emergent. Treatment emergent determination will be derived after missing or incomplete AE start date is imputed. Imputation rules for missing and incomplete AE start are described in Section 4.3

Two laboratory analytes, Anti HSP70 and Anti BHK, will be summarized in a listing that will include all values for those subjects with any positive result. Incidence of HSP-70 antibody formation and hamster protein antibody formation will be assessed from these laboratory tests.

Inhibitor development, as measured by Bethesda assay, as well as the results from all ELISA assays, will be summarized by preparation and timepoint and presented in subject listings. The frequency of subjects who develop positive inhibitor titers (Bethesda ≥ 0.6 BU) will be presented.

Vital signs and change from baseline of vital signs will be summarized with descriptive statistics distinguishing pre-infusion and post-infusion readings. Baseline is the last measurement before the first study drug infusion. Post-infusion minus pre-infusion values will be summarized at Month 1, Month 2, and final visit in the main study.

6.5 Additional analyses planned to be reported outside the main report

Data from Part B and the extensions will be summarized separatly.

7. Document history and changes in the planned statistical analysis

Version 1.1 03 May 2012 This is the first version of the SAP to be signed off. Previous versions including V1.0 were circulated internally.

Version 2.1 19 Dec 2012 Many minor changes to be consistent with the TLF developed from 3 recent meetings and protocol version 3.0 , added ADMAP macro reference, and changed dataset names.

8. References

n/a

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

BSP study drug	BAY 81-8973		
Study purpose:	To demonstrate the safety and efficacy of treatment with BAY 81-8973 for prophylaxis and breakthrough bleeds in children with severe hemophilia A		
Clinical study phase:	Phase III	**Date:**	18Jul2013
Study No.:	13400	**Version:**	1.0

- Section 4.4, revised text:

The 6 month data for PTPs will be analyzed for regulatory purposes as a final analysis of the main study. This analysis is considered an interim analysis in the protocol because the trial is ongoing in the extension phase and an overall analysis of the whole study is planned after study completion.

- In Sections 4.1 and 6.2, the definition of total bleeds should read as follows:

The primary variable is the annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and infusions with reason = other) that occur within 48 hours after all prophylaxis infusions.

- Section 6.2:

All efficacy variables will be summarized using the ITT analysis set. The primary efficacy variable and the FVIII recovery results will also be summarized using the PPS, which will be supportive for the primary efficacy analysis, but will be considered the primary analysis for the FVIII recovery.

Title page

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

Leo Kids PUPs (Part B and extension) Interim Analysis

Bayer study drug	BAY 81-8973		
Clinical study phase:	III	**Date:**	22 Jan 2020
Study No.:	13400	**Version:**	2.0
Author:	PPD PPD		

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

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

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Abbreviations

AE	**Adverse event**
AESI	Adverse event of special interest
BMI	Body Mass Index
CRF	Case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ED	Exposure Day
EPD	Electronic Patient Diary
EU	European Union
FVIII	Factor VIII
HEOR	Health Economics, Outcomes & Reimbursement
ISR	Infusion site reaction
ITI	Immune tolerance induction
ITT	(modified) intent to treat set
IU	International Unit
IV	Intravenous
LOS	Listing only set
MedDRA	Medical dictionary for regulatory activities
MTP	Minimally Treated Patient
OD	On demand
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per protocol set
PUP(s)	Previously Untreated Patient(s)
SAE	Serious adverse event
SAF	Safety (set)
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
TLF	Tables, Listings, Figures
US	United States (of America)

1. Introduction

This statistical analysis plan (SAP) for study 13400 is based on the Integrated Protocol that integrates the original protocol and these following global amendments:

Original protocol, Version 1.4, 20 Sep 2010
Amendment 1 forming integrated protocol Version 2.0, 31 Mar 2011
Amendment 3 forming integrated protocol Version 3.0, 03 Sep 2012
Amendment 4 forming integrated protocol Version 4.0, 08 Apr 2014
Amendment 6 forming integrated protocol Version 5.0, 19 Feb 2016
Amendment 7 forming integrated protocol Version 6.0, 30 May 2017
Amendment 8 forming integrated protocol Version 7.0, 01 Feb 2019
(Amendment 2 and Amendment 5 are local amendments.)

Background

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

The standard treatment for hemophilia A is replacement therapy, with intravenous (IV) administration of plasma-derived or recombinant FVIII. Some subjects treat bleeding episodes as they occur (i.e., on-demand [OD] treatment), while others treat themselves prophylactically to prevent bleeding according to the recommendations from the World Health Organization. In recent years, prophylactic treatment has become the prevailing type of hemophilia treatment in most developed countries.

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

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

This SAP describes the objective, study design, analysis sets, all endpoints, and statistical analysis methods for the interim analysis of the part B of study 13400, where Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPS) where treated. Planned end was 50 exposure days (EDs), in case of inhibitor development the subjects should leave the study and get treatment in the extension part or outside of the study. Complete details of Tables, Listing and Figures (TLFs) specifications as well as dataset details and data handling

specifications will be provided in "TLF specifications" and "Analysis Datasets" documents which are an integral part of this SAP.

The analysis of the 6-month data for Previously Treated Patients (PTPs) in Part A is complete and reported in the clinical study report A51496. This SAP is applicable to completion of Part B. The extension study is ongoing.

The data upon completion of Part B will be analyzed later. The overall study will be closed after all subjects in Parts A and B have completed their respective extensions, in accordance with the protocol definition of 'end of study' (that is, last visit of the last subject [including subjects in the extension study]).

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

2. Study Objectives

General objectives of this study are:

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 children

As during part B of this study, where PUPs and MTPs were treated up to 50 EDs (or development of inhibitor) only few recovery and pharmacokinetic data were collected, the last two secondary objectives will be analyzed in the final analyses of the study where more data are available.

3. Study Design

From the 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.

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 [Cmax], 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)

4. General Statistical Considerations

4.1 General Principles

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

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

Data will be displayed for efficacy and main parts of demography by

- type of subjects: PUPs; MTPs; total
- inhibitor status: Subjects without inhibitor; Subjects with low titer inhibitor; Subjects without inhibitor or with low titer inhibitor; Subjects with high titer inhibitor
- inhibitor status of PUPs: The same as above restricted to PUPs

For safety data will be displayed for type of subject (PUPs; MTPs; total) only.

In general, data will be displayed as measured, individual values will be presented in listings.

4.2 Handling of Dropouts

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

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has received at least one dose of study drug. At the time of discontinuation, subjects should be requested to have a final visit to have performed the procedures and evaluations scheduled for the final study visit as described for last visit. Subjects who are withdrawn after the start of treatment will not be replaced.

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

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

The number of subjects who prematurely discontinue the study during the treatment phase or during the post-treatment observation phase for any reason, as well as the reasons for premature discontinuation of study, will be displayed.

Subjects who prematurely withdraw prophylaxis treatment due to inhibitor development will be considered premature discontinuations from Part B, even though they may continue with ITI treatment in the extension phase. For this reason a separate tabulation of the reason for premature termination will be given, where all reasons connected to ITI or inhibitors will be combined to "INHIBITOR MANAGEMENT". In addition subjects, who prematurely

discontinued part B without a clinical reason (inhibitor, AE) or withdrawal of informed consent or protocol violation, but just for logistical problems to match exactly the 50 EDs, will be counted as completers in this table.

Subjects can be withdrawn at their parent's request, or at the investigator's discretion due to, for example, development of inhibitory antibody or lack of compliance. The reasons for withdrawal will be listed. The annualized number of total bleeds will be calculated for these withdrawn subjects, and the time of the last procedure in a visit or the last infusion in the EPD will serve as the end time point used for calculation.

4.3 Handling of Missing Data

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

General rules

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

- **Efficacy Variables**
  The EPD is designed to allow the collection of date and time for each infusion or bleed as well all other relevant data. Each subject's bleeding period start date will be needed to allocate the bleedings to the respective period. If dates for bleeds and infusions of rescue medication are both missing then these bleeds cannot be counted. If the bleed date is missing, but the infusion date is available, infusion date will be used.
  If the details of a bleed are missing (e.g., type of bleed spontaneous, non-spontaneous/non-traumatic or traumatic), the bleed will be counted for all categories of bleeds, but not for the corresponding subgroup of bleeds.
- **AE Variables**
  For the purpose of treatment-emergent flags, missing AE start day will be imputed as the 15th of the month. However, if the AE start day is missing, but the AE starts during the same month or on the same day as the first dose, but the AE start time is missing, the AE start day (and time in the second case) will be taken from first dose start day (and time). If both day and month of AE start date are missing, day and month will be imputed as the date of the first dose. Imputation date is to be set not to be before date of birth (if available).
  Drug-related AE tables will also include AEs with missing values of causality.
  Missing end date for an AE will not be imputed.
- **Missing or incomplete concomitant medication start and end date**
  When computing concomitant medication start dates, if day is missing, use 15. If month and day are missing, use 1 JUL. If necessary, adjust imputed dates so they are not before the birth date. A totally missing start date will not be imputed.
  Missing end date for a concomitant medication will not be imputed.
- **Additional descriptive analyses in the presence of missing data**
  The number of subjects who prematurely discontinue the study (subjects who stop updating the EPD and stop coming back for scheduled visits) and study treatment (subjects who stop using the medication but still come back for the last visit) for any

reason, as well as the time point and reasons for discontinuation of study and study treatment, will be reported. All dropouts will be evaluated with respect to the reasons for discontinuation of study and/or study treatment and potential dropout patterns When computing age at diagnosis, age at start of therapy, age at start of prophylaxis, and time since start of therapy; if day is missing, use 15. If month and day are missing, use 1 JUL. If necessary, adjust imputed dates so they are not before the birth date. A totally missing date will not be imputed.

4.4 Interim Analyses and Data Monitoring

The trial data is reviewed periodically by an independent Data Monitoring Committee (DMC). The DMC reviews certain safety and efficacy data sets as defined in the charter and provides written reports to the sponsor.

The 6 month data for PTPs was analyzed for regulatory purposes as a final analysis for Part A of the study. That analysis for PTPs is an interim analysis as defined in the protocol because the trial is ongoing for Part B and the extension phase. Safety was assessed in 20 PTPs before enrollment of PUPs began.

This SAP describes the interim analysis of part B of the study, originally planned for 25 PUPs. Amendment 3,6 and 7 of the protocol added up to 25 additional subjects to part B and the study was opened for MTPs. It will summarize data from Part B without extension phase. Extension study data will be described in the final CSR.

4.5 Data Rules

All bleed and infusion data will be entered into the EPD (hospital infusions will be entered into the eCRF) and imported into SAS. If an infusion is given for a bleed and the bleed information is not provided, the infusion date and time will be used as the bleed date. Vice versa will a bleed date be used for surrogate of a missing infusion.

All bleeds include spontaneous bleeds, trauma, untreated bleeds and ‘other’ bleeds. ‘Other’ bleeds are infusions with reason given as ‘other’, an untreated bleed is a bleed with no corresponding infusion for the bleed.

During the period of ITI treatment all prophylactic infusions will also be counted as ITI treatment, as during ITI no other prophylaxis will be given.

4.5.1 Baseline values

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

4.5.2 Annualized bleed rate

The definition of annualized bleed rate is generally defined as

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

The different periods used for analysis are described in section 6.2.1.

4.5.3 24 hours rule

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

4.5.4 72 hours rule

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

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

4.6 Blind Review

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

4.7 Recovery

Recovery or incremental recovery

The terms recovery and incremental recovery are synonymous and are used interchangeably in this context. Recovery is calculated using the formula below:

Recovery=(post-infusion FVIII value – pre-infusion FVIII value) * body weight / dose (in IU)

Recovery will be determined by collecting a sample for the FVIII level pre-infusion of FVIII and a second sample collected 20 to 30 minutes post-infusion of FVIII. The exact sampling times before and after infusion and the dose administered will be documented in the CRF.

If a FVIII concentration value is below the LLOQ (lower limit of quantification), a data point will be substituted by one half of this limit.

A validity flag for recovery values and their corresponding pre- and post-infusion FVIII values will be created. These FVIII values and their corresponding recoveries will be considered valid except when any of the following conditions apply:

- If pre-infusion FVIII ≥ post-infusion FVIII [biologically impossible in the absence of inhibitors]
- If pre-infusion FVIII > 40 IU/dl (note 1 IU/dl=1%) [protocol violation]

- If post-infusion FVIII < 10 IU/dl (note 1 IU/dl=1%) [biologically impossible in the absence of inhibitors]

Furthermore, if there are multiple FVIII values for a subject and timepoint, only the record with the highest FVIII will be used. The others values will be excluded from the analysis dataset.

Measurements of pediatric patients' weights are performed at each visit. When calculating recovery, the available body weight measurement from the same or most recent visit will be used. If this value is missing, then the body weight from the next visit will be used.

As measurements of recovery values are expected not to be often taken in this very young population, they will only be listed.

5. Analysis Sets

5.1 Assignment of analysis sets

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

The statistical analysis sets are defined as follows:

SAFety analysis set (SAF)

All subjects with at least one intake of study drug.

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

(modified) Intent To Treat Set (ITT)

All subjects of the SAF, who have infusion/bleeding data.

Per Protocol Set (PPS)

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

Major protocol violations would be for example:

- Severe hemophilia A not confirmed
- Evidence of inhibitor antibody present at the time of screening.
- MTP has previously received more than 3 exposure days with any FVIII product, PUP has received any amount of FVIII
- In the prophylactic period here was/were at least
    - one instance of >30 days between infusions
    - two instances of >21 days between infusions
    - three instances of >14 days between infusions

PharmacoKinetic Analysis Set (PK)

Not applicable to this interim analysis, as it is not expected to get enough subjects for a reasonable analysis from part B. There will be an analysis of the pharmacokinetic data for the final CSR.

Listing Only Set (LOS)

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

6. Statistical Methodology

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

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

6.1 Population characteristics

6.1.1 Demography and baseline characteristics

Demographic and baseline data will be evaluated descriptively for the SAF resp. for the ITT. Data will be described by pre-treatment (PUPs/MTPs) and where meaningful with the inhibitor status as given in 4.1. No statistical tests will be performed to compare these characteristics across different groups.

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

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

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

- sex,
- race/ethnicity.

Reasons for exclusion from analysis populations will be summarized.

6.1.2 Medical history

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

6.1.3 Disease history

The following baseline characteristics of the disease history will be evaluated descriptively for the ITT, by pre-treatment (PUPs/MTPs) and overall:

- Age of hemophilia diagnosis
- Start of therapy (MTPs)
- Family history of hemophilia
- FVIII level and type of assay
- Family and personal history of past inhibitor formation
- Number and type of bleeds in the past 12 months
- Presence and location of target joints

6.1.4 Medication history

Medication history data including include prior FVIII products (MTPs) as well as a history of other prior and current medications will be evaluated descriptively for the SAF, both overall and by pre-treatment (PUPs/MTPs).

6.2 Efficacy

All subjects receiving study drug who have infusion/bleeding data from the EPD will be included in the efficacy analysis.

Primary Efficacy Analysis

The primary efficacy variable according to protocol will be the annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and 'other' bleeds) that occur within 48 hours after all prophylaxis infusions. 'Other' bleeds are infusions with reason given as 'other'.

For this primary efficacy variable, the number of data available and missing data, mean, standard deviation (SD), minimum (Min), quartiles, median, and maximum (Max) will be summarized and presented.

Additional Efficacy Analysis

Also summarized will be annualized number of joint bleeds, spontaneous bleeds, and trauma bleeds that occur within 48 hours after all prophylaxis infusions. Additional variables summarized will be annualized number of total bleeds, joint bleeds, spontaneous bleeds, and trauma bleeds as well as the annualized numbers.

Other variables summarized will be the number of treatments required to control all bleeds and the subject's assessment of the response to treatment of all bleeds (excellent, good, moderate, or poor), further on description of joint bleeds according to site as well as proportion of subjects with no bleed

FVIII usage/consumption will be described expressed as number of infusions, number of prophylaxis infusions, and number of infusions to treat breakthrough bleeds. Infusions will be summarized in IU, IU/kg, IU/kg/year, IU/kg/infusion, IU/year, and IU/infusion.

All efficacy variables will be summarized using the ITT analysis set. The summary of bleeds, the exposure to study drug and the treatment administration for bleeds will also be given in the ITT.

The number of infusions used to treat a bleed will be summarized. The number of infusions used to treat a bleed is defined as the first infusion to treat the bleed plus all follow-up infusions to treat the same bleed, if any. The proportion of bleeds controlled by <= 2 and >2 infusions will be presented.

6.2.1 Additional analyses

For subjects undergoing surgery (both major and minor), the following information will be listed:

- Blood loss
- Need for additional hemostatic medication, including blood products
- Units of blood transfused
- Hemostatic-related surgical complications
- Assessment of hemostasis as excellent, good, moderate or poor
- Study drug usage

Factor VIII concentration values and recovery values will be listed where available. As only few values are expected, no tabulation will be done.

Health care resource utilization will be tabulated. This includes additional visits to hematologists, family physician, nurse or other health care provider, additional tests, like blood tests but also radiological tests, hospital visits and nights in hospital.

6.2.2 Subgroup analysis

Subgroups of analysis are already described in 4.1:

- type of subjects: PUPs; MTPs; total
- inhibitor status: Subjects without inhibitor; Subjects with low titer inhibitor; Subjects without inhibitor or with low titer inhibitor; Subjects with high titer inhibitor
- inhibitor status of PUPs: The same as above restricted to PUPs

These different periods for analysis are planned:

Period	Definition	To be used
Total part B period	MAINSDTM to MAINEDTM	always
On-demand period	if OD_STDTM >. : OD_STDTM (is equal to MAINSDTM) to OD_EDTM	for response to treatment of bleeds

Period	Definition	To be used
Prophy period (without once per week treatment)	if an infusion with EXSCATN = 8 exists and last infusion with EXSCATN = 8 < MAINEDTM: last infusion with EXSCATN = 8 to MAINEDTM. If last infusion with EXSCATN = 8 is at MAINEDTM no such period exists. If no infusion with EXSCATN = 8 exists: PX_SDTM to PX_ENDTM.	later for publications
Prophy period (including once per week treatment)	if SDTM > .: PX_SDTM to PX_ENDTM	always
Total treatment period (starting after 1st treatment)	TRTSDT to MAINEDTM	always
Period of once per week treatment only	if an infusion with EXSCATN = 8 exists: if OD_STDTM ne . then PX_SDTM to last infusion with EXSCATN = 8 else TRTSDT to last infusion with EXSCATN = 8	later for publications
Period of high inhibitor of high titer inhibitor subjects	if HINHSDTM < HINHEDTM: HINHSDTM to HINHEDTM	For extension only
Period of total inhibitor of high titer inhibitor subjects	if HINHSDTM > .: INHSDTM to INHEDTM	For extension only
Period of total inhibitor of low titer inhibitor subjects	if HINHSDTM = . and INHSDTM < INHEDTM: INHSDTM to INHEDTM	ABR & response to treatment

Further specification of the different periods are as following:

- The **total part B period** starts with the baseline visit and ends with the final visit. In case the study drug were already administered between the screening visit and the baseline visit, the period starts with the date of injection.
- The **on-demand period** starts with the first injection in an on-demand schedule and ends with the start of the prophylaxis period or final visit, whatever comes first.
- The **prophylaxis** period starts with the first and ends with the last injection of prophya ctic study drug.
- The **total treatment period** starts with the first injection of study drug and end with th e final visit.
- **The period of low titer inhibitor** starts with the day when low titer inhibitor was detected and ends with either the final visit or the day when no inhibitor was detected, whatever comes first.

6.3 Pharmacokinetics/pharmacodynamics

As already mentioned these analyses will be postponed to the final analysis.

6.4 Safety

All subjects receiving any amount of study drug will be included in the safety analysis. Laboratory findings, AEs, concomitant medications, and medical history data will be provided in subject listings.

6.4.1 Adverse events

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

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

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

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

AEs will be considered treatment-emergent if they begin after the first administration of study drug and they do not start after more than 7 days after the last administration. Determination of whether or not an event is treatment-emergent will be derived after the missing or incomplete AE start date is imputed. In case an adverse event starts on the day of first administration of study drug and the time of onset is not known, the event is considered to be not treatment emergent, if it is reported to occur before the first dose of study drug. In all other cases the event is considered to be treatment emergent. Inhibitors will be defined as treatment-emergent if they develop after first study drug application. Imputation rules for missing and incomplete AE start are described in section 4.3.

6.4.2 Vital signs

Vital signs (systolic blood pressure (BP), diastolic BP, heart rate, respiratory rate, body temperature, body weight, and height) and change from baseline of vital signs will be summarized with descriptive statistics distinguishing pre-infusion and post-infusion readings. Post-infusion minus pre-infusion values will be summarized at Month 1, Month 2, Month 3, Month 4, and final visit in Part B.

6.4.3 Laboratory parameter

Laboratory values, incidence of high or low abnormal values, and changes from baseline will be summarized. In general only central laboratory values will be used for analysis. Where also local values are taken into consideration will be explicitly mentioned.

Two laboratory analytes, Anti HSP-70 and inhibitors, will be summarized in a listing that will include all values for those subjects with any positive result. Incidence of HSP-70 antibody formation and inhibitors will be assessed.

Inhibitor development, as measured by Bethesda assay will be summarized timepoint and presented in subject listings. The frequency of subjects who develop positive inhibitor titers (Bethesda ≥ 0.6 BU) as well as high titer (> 5.0 BU) will be presented. For the inhibitors as well as for the high titer inhibitors Kaplan Meier graphics for the occurrence will be provided.

A positive inhibitor testing is defined with a threshold of ≥ 0.6 BU in the central laboratory and a confirmation by

- a second plasma sample and a positive central testing

or

- two consecutive local measurements (2nd and 3rd sample) with doubled threshold (Bethesda ≥ 1.2 BU).

In case a central value of the same samples used for local confirmation shows no inhibitor, the local confirmation is not valid.

High titer inhibitor needs not to be confirmed by a second high (> 5.0 BU) value, but the inhibitor itself needs a confirmation.

6.4.4 Subgroup analysis

Tables will be summarized by pre-treatment (PUPs/MTPs) and total.

6.4.5 Pregnancies

Not applicable for this population.

7. Document history and changes in the planned statistical analysis

Changes occurred on 10 October 2020:

- Deleted the following paragraph in section 4.2: “Subjects who have completed the final visit of Part B, but do not complete the follow-up telephone assessment or enter the extension will not be considered to have prematurely discontinued the study.”
- Added the following paragraph in section 4.2: “For this reason a separate tabulation of the reason for premature termination will be given, where all reasons connected to ITI or inhibitors will be combined to “INHIBITOR MANAGEMENT”. In addition subjects, who prematurely discontinued part B without a clinical reason (inhibitor, AE) or withdrawal of informed consent or protocol violation, but just for logistical problems to match exactly the 50 EDs, will be counted as completers in this table.”

- Added the following paragraph to section 4.5: “During the period of ITI treatment all prophylactic infusions will also be counted as ITI treatment, as during ITI no other prophylaxis will be given.”
- Deleted the wording “in addition” from the first sentence in section 6.1.3 (previous sentence: “The following baseline characteristics of the disease history will be evaluated descriptively for the ITT, by pre-treatment (PUPs/MTPs) and overall in addition”
- Changed the sub-title in section 6.2 from “Efficacy Analysis” to “Additional Efficacy Analysis”
- Changed “Besides this different periods for analysis are planned:” to “These different periods for analysis are planned:” in section 6.2.2
- Added the following sentence to section 6.4.3: “Where also local values are taken into consideration will be explicitly mentioned.”
- Changed “Incidence of HSP-70 antibody formation and inhibitors will be assessed from the central laboratory.” to “Incidence of HSP-70 antibody formation and inhibitors will be assessed.” in section 6.4.3.
- Added definition of positive inhibitor in section 6.4.3 which ready as follows: “A positive inhibitor testing is defined with a threshold of ≥ 0.6 BU in the central laboratory and a confirmation by a second plasma sample and a positive central testing or two consecutive local measurements (2nd and 3rd sample) with doubled threshold (Bethesda ≥ 1.2 BU). In case a central value of the same samples used for local confirmation shows no inhibitor, the local confirmation is not valid. High titer inhibitor needs not to be confirmed by a second high (> 5.0 BU) value, but the inhibitor itself needs a confirmation.”

Changes occurred by 16 January 2020:

- Added further specification of the analysis periods to the end of section 6.2.2 starting with “Further specification of the different periods are as following: […]”
- Added further specification regarding the definition of a treatment-emergent AE to section 6.4.1 dealing with a missing time of onset of such an event. The addition reads as following “In case an adverse event starts on the day of first administration of study drug and the time of onset is not known, the event is considered to be not treatment emergent, if it is reported to occur before the first dose of study drug. In all other cases the event is considered to be treatment emergent.”.

8. References

This SAP is based on the Integrated Protocol that integrates all global amendments up to amendment 8, dated February 1st, 2019.

9. Appendix

9.1 Determination of sample size

Due to the fact that the analysis of the efficacy endpoints is exploratory only, no formal determination of sample size was done. The planned number of subjects followed guidelines as well as common practice for this kind of studies.

Title page

Study Protocol Title (incl. version no. and date): A multi-center Phase III uncontrolled open-label trial to evaluate safety and efficacy of BAY 81-8973 in children with severe hemophilia A under prophylaxis therapy (Integrated protocol Version 7.0, 01 Feb 2019)

Leo Kids PUPs (Part B and extension) Interim Analysis

SAP (incl. Version no. and date): Statistical Analysis Plan version 2.0, dated 22 Jan 2020

[Analysis purpose:]	Supplement		
Clinical study phase:	III	**Date:**	28 JAN 2020
Study No.:	13400	**Version:**	1.0
Author:	PPD		

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

Table of Contents

1. Introduction

This SAP Supplement 1.0 is based on the SAP version 2.0. The purpose of this SAP Supplement 1.0 is to align the labeling of the endpoints specified in the SAP 2.0 to the specification described in the SAP for Part A and in the protocol . None of the alignments detailed in this document are considered to change the primary efficacy analysis and other analyses as described in the study protocol and its amendments and in the SAP version 2.0.

2. Clarifications

2.1 Secondary Endpoints

The secondary parameters are the following:

- Annualized number of total bleeds (sum of spontaneous bleeds, trauma bleeds, untreated bleeds, and 'other' bleeds) during prophylaxis treatment
- Hemostatic outcome of surgeries (both major and minor) including blood loss, transfusion, and/or hemostatic-related surgical complications
- Inhibitor development, as measured by Nijmegen modified Bethesda assay
- FVIII recovery values
- Pharmacokinetics (in a subset of children)

The annualized number of total bleeds will be calculated as described in section 4.5.2 of the SAP 2.0 and summarized accordingly.

The hemostatic outcome of surgeries will presented in a subject listings.

The incidence of inhibitor development during the total part B period will be presented in a summary table, additionally a subject listing will be provided relating the number of total exposure days to the corresponding FVIII Inhibitor value.

The FVIII recovery values will be calculated as described in section 4.7 of the SAP 2.0 and summarized accordingly. In addition, a subject listing will be provided.

The summary of pharmacokinetic values in Part B of the study will only be presented in the final report for the extension study due to the limited number of collected samples.