Study 984

A prospective, open-label, phase I/III study investigating pharmacokinetic properties of BT524 and efficacy and safety of BT524 in the treatment and prophylaxis of bleeding in patients with congenital fibrinogen deficiency

Biotest AG

Statistical Analysis Plan

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1 Introduction

1.1 Preface

This statistical analysis plan (SAP) is exclusively based on the following information and documents:

Study Protocol	08-MAY-2018 – Version 6.0

The objective of this document is to detail the statistical methodology to be used for the final statistical analysis of Biotest Study-№ 984 ("A prospective, open-label, phase I/III study investigating pharmacokinetic properties of BT524 and efficacy and safety of BT524 in the treatment and prophylaxis of bleeding in patients with congenital fibrinogen deficiency").

This SAP covers the part of the statistical analysis to be conducted PPD .

For the evaluation of pharmacokinetics (PK; fibrinogen antigen) and pharmacodynamics (PD; fibrinogen activity), PK/PD parameters will be derived from time-concentration profiles using adapted methodology, non-compartmental analysis, compartment analysis, or population modelling, as appropriate/ required. This part of the statistical analysis, including the analysis for the primary objective of PK-part, will be conducted by Pharmetheus and is described in a separate analysis plan.

1.2 Timing of statistical analyses

The statistical analysis, for which this SAP applies, is the final analysis after all data of this study is collected, cleaned and locked.

2 Modification History

2.1 Changes to the study protocol

The statistical analysis as specified in this SAP is consistent with the statistical analysis as specified in the study protocol (version 6.0).

In the study protocol age groups were defined to describe/define differences in time points of study assessments to be perfomed for different age groups (see flowchart of study in study protocol section 3). In the SAP age groups were defined differently for data analyses.

Shift tables specified in the study protocol for safety laboratory assessment will be not used.

No changes in the clinical study protocol were considered necessary by the Sponsor to handle clinical protocol deviations possibly related to the COVID-19 pandemic at the end of the study. It was therefore decided in the Blinded Data Review Meeting (BDRM) of June 25, 2020, that any non-conformancies in the study conduct caused by the COVID-19 pandemic will be described in a note to file, and any COVID-19 related protocol deviation per patient will be listed in BDRM minutes and presented in study listings where appropriate.

2.2 Changes to previous SAP versions

The first version of the SAP was based on study protocol version 4.0 and signed on 17-Sep-2015.

The amended SAP version 2.0 was intended to reflect the inclusion and treatment of children 0 to <6 years into the ongoing study 984. This extension of the ongoing study 984 was introduced within the study protocol version 5.0 after the positive opinion of the Paediatric Committee on the agreement of the Paediatric Investigation Plan (EMA-001931-PIP01-16) obtained in March 2017.

The amended SAP version 3.0 is intended to precisely describe the responsibilities of the different CROs to the analysis of the study. Definition of analysis sets was refined and PK population added for the descriptive analysis of PK within this SAP. For the age subgroups it was clarified how age of patients and bleeding events is calculated/defined for the respective analysis sets and study parts. Additional clarification for presentation of data was added where needed and the list of table shells in Appendix 15.1 was updated due to changes made.

3 Study Design

The present study is designed as a prospective, uncontrolled, open-label, multicentre, phase I/III study investigating the 14 day single-dose pharmacokinetic and pharmacodynamic properties, efficacy and safety of BT524 following intravenous administration in the treatment or prophylaxis of bleeding in patients with congenital afibrinogenemia or severe congenital hypofibrinogenemia.

The study is divided into two study parts (part I and part II), briefly described in the following:

Table 1: Overview of Study Design and Endpoints

PART I	PART II
	(Individual follow-up 49 ± 4 days after the last administration of BT524)
BT524 Single IV Infusion (70 mg/kg BW)	On-Demand Treatment (ODT) On-Demand Prophylaxis (ODP) BT524 Single or repetitive IV Infusion(s) as individually required
Pharmacokinetics (PK) Pharmacodynamics (PD)	Clinical Efficacy
n = 20 patients ≥ 6 to ≤ 75 years and at least 3 patients 0 to < 6 years In total: n = 23 patients (part I)	All patients who have completed part I (n = 23) and additional patients without PK/PD: at least 10 patients ≥ 6 to ≤ 75 years and at least 3 patients 0 to < 6 years In total (planned): n ≥ 36 patients (part II)
1-2 months	min. 12 months
Surrogate Efficacy	
Safety	

Part I

Part I is focused on the primary endpoint of the study, the 14 day single-dose pharmacokinetics, and on the 14 day single-dose pharmacodynamics and the evaluation of the maximum clot firmness (MCF) as a surrogate efficacy parameter. Moreover, safety will be investigated (by physical examination, vital signs, routine lab parameters, adverse events, development of fibrinogen antibodies and coagulation activation monitoring).

20 patients ≥ 6 to ≤ 75 years and at least 3 patients < 6 years are to be enrolled in part I. With respect to safety, study-specific enrolment procedures comprising consecutive

enrolment of the first five patients with a treatment-free safety interval of 7 days between each patient and restriction in age are implemented (see protocol).

Maximum duration of individual study participation in part I is up to 66±4 days for eligible screened patients (in case the patient does not experience a bleeding event within this safety interval).

Part II

Part I will subsequently be extended to a part II in which individual patients will be investigated for the efficacy and safety of single and/or repetitive administrations of BT524 in on-demand prophylaxis (ODP) and/or on-demand treatment (ODT) of different bleeding events [e.g., (elective) surgical procedure, spontaneous or posttraumatic severe bleeding], if required. Thus, part II is expected to comprise a variety of singular events of different types, severity, and BT524-dosing requirements. All patients who have taken part in the pharmacokinetic assessment (part I) without severe post-dosing complications ideally remain enrolled and will continue treatment for ODP and/or ODT with BT524 in part II.

At least 10 additional patients ≥ 6 to ≤ 75 years and at least 3 additional patients < 6 years will be treated in part II (ODP/ODT) without PK/PD assessments (part I).

Duration of individual study participation is variable and depends on the time point of the last bleeding episode necessitating application of study medication. For the last patient included the minimum duration is 12 months (12 months plus 49±4 days in case the patient experiences a bleeding event at the very end of his/her individual study participation on the last day of month 12).

Efficacy of BT524 will be assessed by clinical endpoints such as the overall hemostatic response to treatment (as assessed by the investigator according to a 4 point scale: "none", "moderate", "good" or "excellent"), total loss of blood (e.g., intra- and postoperatively, re-bleedings), need of other fibrinogen-containing products (fresh frozen plasma, cryoprecipitate), need of transfusion products (allogenic or autologous blood), and quality of wound healing, whenever applicable. Moreover, the consumption of BT524 required for effective treatment (pre-, intra-, post-operatively) will be calculated. Furthermore, MCF as a surrogate efficacy parameter will be evaluated.

For details regarding the study flowcharts see section 3 of the study protocol.

3.1 Sample size estimation

The primary objectives of this study are key PK parameters. For the PK parameters no formal sample size calculation was carried out. As a general rule approximately 20 patients in this single cohort should suffice to calculate PK parameters with the corresponding range of distribution.

For the surrogate (secondary) efficacy variable MCF, a formal sample size calculation was performed. On the basis of a t-test assessing the difference between dependent means (post minus pre-treatment MCF difference; one sample) the sample size can be calculated. The mean MCF (measured by Fib-tem S of ROTEM) in the study population consisting of patients with congenital fibrinogen deficiency (i.e., a- or severe hypofibrinogenemia) will be determined prior to BT524 treatment and 1 hour after treatment.

With 15 patients, a pre-treatment mean of 4 mm (SD 7 mm) and a post-treatment mean of 10 mm (SD 8 mm) an effect size of 0.8 mm can be detected with a power of 80% at α = 5% (2-sided) significance level.

3.2 Randomisation, blinding and unblinding procedures

This is an uncontrolled, open-label study design and patients will not be randomized. No special procedures regarding blinding or unblinding are applied.

4 Analysis Sets

4.1 Study populations

4.1.1 Study populations (part I)

Please note, for all part I analysis populations the relevant framework in which to check the criteria (such as informed consent, exposure to BT524, protocol deviation, premature termination etc.) per patient is restricted to the period of its part I participation, i.e. from enrolment in part I up to PK safety visit (Day 49 +/- 4).

PK Set (PK)

The PK population consists of all patients of part I with PK data.

For the PK-specific study population of part I (PK/PD), please see also the PK-Analyses Plan (cf. section 1.1 above).

All Patients Enrolled Set (APE I)

The APE includes all patients who have given informed consent to part I of the study.

Intent to Treat Set (ITT I)

All patients, who received any portion of BT524 in part I of the study.

Full Analysis Set (FAS I)

All patients, who received any portion of BT524 in part I of the study, and have at least one part I efficacy assessment.

Per Protocol Set (PP I)

The PP is a subset of FAS and includes all patients in part I of the study who are compliant with the study protocol without any major protocol deviations in part I thought to have the potential to impact the results of the efficacy analysis (PK/PD).

In the BDRM, dated 25-Jun-2020, all minor and major protocol deviations on patient level were reviewed and agreed upon. Following from the decisions taken, assignments to per-protocol (PP I) analysis population were done. A complete list of all protocol deviations is attached to the meeting minutes of the BDRM, dated 25-Jun-2020, and included in the listings of the final analysis.

Safety Set (SAF I) / Treated Set

The safety population comprises of all patients who were exposed to BT524 in part I of the study.

4.1.2 Study populations (part II)

4.1.2.1 Study populations (part II –patient based)

Please note, for all part II analysis populations the relevant framework in which to check the criteria (such as informed consent, exposure to BT524, protocol deviation, premature termination etc.) per patient is restricted to the period of its part II participation, i.e. from enrolment into solely part II (or for patients who completed Part I from entry in part II defined as 1st day after part I PK safety visit) up to the safety visit (Day 49 +/- 4) of the last treated bleeding event.

All Patients Enrolled Set (APE II)

The APE includes all patients who have given informed consent to exclusive part II of the study and patients consented for Part I/II who completed Part I.

Intent to Treat Set (ITT II)

All patients, who received any portion of BT524 in part II of the study.

Full Analysis Set (FAS II)

All patients, who received any portion of BT524 in part II of the study, and have at least one part II efficacy assessment.

Per Protocol Set (PP II)

The PP is a subset of FAS and includes all patients in part II of the study who are compliant with the study protocol without any major protocol deviations in part II thought to have the potential to impact the results of the efficacy analysis.

In the BDRM, dated 25-Jun-2020, all minor and major protocol deviations on patient level were reviewed and agreed upon. Following from the decisions taken, assignments to per-protocol (PP II) analysis population were done. A complete list of all protocol deviations is attached to the meeting minutes of the BDRM, dated 25-Jun-2020, and included in the listings of the final analysis.

Safety Set (SAF II) / Treated Set

The safety population comprises of all patients who were exposed to BT524 in part II of the study.

4.1.2.2 Study populations (part II – event based)

For **part II (ODP/ODT)**, the following specifications as to analysis sets apply:

With respect to the evaluation of efficacy, surrogate efficacy and safety of the single or repetitive intravenous infusions of BT524, each bleeding event will be considered as an individual case in the primary analysis.

There are 2 event-based analysis sets:

Full Bleeding Event Set (FBE)

All events treated with any portion BT524, and with at least one efficacy assessment.

Per Protocol Bleeding Event Set (PPBE)

Subset of FBE of patients who are compliant with the study protocol (i.e. without any major protocol deviations in part II) and includes all bleeding events without any major protocol deviation with potential to impact the results of the efficacy analysis.

In the BDRM, dated 25-Jun-2020, all minor and major protocol deviations on bleeding event level were reviewed and agreed upon. Following from the decisions taken, assignments to PPBE analysis population were done. A complete list of all protocol deviations is attached to the BDRM minutes and included in the listings of the final analysis.

As agreed in the BDRM (25-Jun-2020), all bleeding events documented for a patient with at least one major protocol deviation (i.e. patients excluded from PP II set) will be excluded from the PPBE.

In addition, selected efficacy analyses for bleeding events and surgical interventions will be analyzed per patient in the FBE and PPBE populations as defined above.

With respect to the evaluation of adverse events, the patient is the relevant unit for analyzing these endpoints. Therefore, their evaluation across all parts is based on the safety population as defined in section 4.1 above.

5 General Statistical Methods and Definitions

5.1 General statistical methods

All data collected will be analyzed using appropriate statistical methods for the production of all tables, listings and figures and for the statistical analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations and measurements (cf. section 4). Tabulations will be presented for each parameter. Generally, age subgroups will be presented in columns and overall totals will be provided, too. Data will be presented for the overall population, and for ODP and ODT, each for minor events, major events and overall in rows, as specified in the section for the respective parameter.

For continuous variables descriptive statistics will be given including mean, SD, median, quartiles, minimum, and maximum. Additionally, for PK data, efficacy and safety parameters 95 % confidence intervals will be calculated where appropriate. Categorical data will be presented in frequency tables using counts and percentages. In addition, the number of patients with missing values will be displayed. Percentages relate to the number of patients (or events, for part II) with data. This includes data obtained by the respective missing data replacement strategy (see section 5.3 Missing data).

Means and medians will be presented by 1 additional decimal place and standard deviation will be presented by 2 additional decimal places than the standard presentation level of the respective patient data. Minimum and maximum values will be presented using the same number of decimal places as the patient data. Percentages will be presented to 1 decimal place if not otherwise stated. Statistical tests will be performed descriptively, two-sided if not specified otherwise. Only the one test of a secondary efficacy endpoint of part I (1-hour post-end to pre-value of MCF) is considered confirmatory. A (two-sided) p-value less than 0.05 will then be considered statistically significant. The confidence level for calculation of confidence intervals will be chosen as (1-significance level) of the respective statistical test. All collected data will also be presented in listings (cf. separate tables shells document). Only additional special listings such as for protocol deviations (cf. section 6.3), bleeding history (cf. section 7.3), AEs leading to death (cf. section 11.2), AEs leading to discontinuation (cf. section 11.3), or normal ranges (cf. section 11.8) are explicitly referred to within the applicable section. In listings, data will be sorted by site, and patient, and when appropriate by visit or other identifiers for sequence or type of observation.

5.2 Subgroups

For analyses, patients are assigned to the following age subgroups: Adults (18 to 75 years), adolescents (12 to < 18 years), children (6 to < 12 years), and children < 6 years. The group < 6 years will in addition be subdivided into pre-school children (2 to < 6 years), infants and toddlers (28 days to < 2 years), and newborns (0 days to 27 days).

For patient-based analyses using the APE set, patients will be assigned to age subgroups according to their age (years) as derived from date of birth (year) as age at date of ICF signature for each of the study parts.

For patient-based analyses using the SAF, FAS, PP, or PK set in both study parts, patients will be assigned to age subgroups according to the age group assessment provided for their first BT524 treatment in the respective study part.

For the event-based analysis (FBE, PPBE) in part II, each bleeding event will be assigned to the age subgroup according to the age group assessment provided for the specific bleeding event.

Another subgroup for event based analysis is ODP/ODT with major/minor classification.

Results for the different subgroups will be presented descriptively by presenting the results for selected analyses (as defined in the respective section) separately for each subgroup and the overall population.

5.3 Missing data

5.3.1 Missing severity assessment for adverse events

If severity is missing for an AE starting prior to the administration of IMP, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after administration of IMP, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

5.3.2 Missing relationship to investigational product for adverse events

If the relationship to investigational product is missing for an AE starting on or after the administration of IMP, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

5.3.3 Missing seriousness assessment for adverse events

If no information about seriousness is available, the AE will be considered serious. The imputed values for seriousness assessment will be used for incidence summaries, while the actual values will be used in data listings.

5.4 Handling of partial dates and missing/incomplete times

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

For AEs, incomplete (i.e., partially missing) start dates and times and/or incomplete stop dates and times will be imputed.

Imputation rules for incomplete dates for prior or concomitant medications, incomplete dates and times for AEs are described in sections 5.4.1 and 5.4.2.

5.4.1 Incomplete start date and time

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

Missing/Incomplete Time

- If the time is missing and the date is complete and is the same as the date of the first dose of investigational product, or the date is imputed to be this date, then the time will be set to the time of the first dose of investigational product. Otherwise, missing times will be imputed as 00:00.
- If the minutes are given but the hour is not, then the time will be regarded as completely missing and handled as above. If the hour is given but the minutes are not, then if the hour is the same as the hour of the first dose of investigational product, then the minutes of that dose of investigational product will be assigned to the missing fields. Otherwise 00 will be assigned to the missing minutes.

5.4.2 Incomplete stop date and time

The following rules will be applied to impute the missing numerical fields. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- The stop day and month will be set to the maximum of the date of study discontinuation/completion, as appropriate, or the date of the Day 49 FU visit of the last dose of IMP.
- If the year of the incomplete stop date is before the year of the date of study discontinuation/ completion, as appropriate, or the date of the Day 49 FU visit of the last dose of IMP, the day and month will be set to 31 December;

- If the year of the incomplete stop date is after the year of the date of study discontinuation/ completion, as appropriate, or the date of the Day 49 FU visit of the last dose of IMP, the day and month will be set to 01 January.

Missing month only

- The stop day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- The stop day will be set to the last day of the month.

Totally missing stop date

- The concomitant medication will be considered ongoing.

Missing Time

- If the time is missing it will be imputed as 23:59.

5.5 Observation and analysis times

Study periods or stages

The study primarily differentiates between the two parts, part I (PK/PD) and part II (ODP/ODT). Within each part different periods are defined:

Part I:

- Screening period: Day -17 to Day -1
- PK/PD assessment/sampling period:
  - Hospitalization from Day 0 (IV infusion) through Day 2
  - Subsequent PK FU from Day 4 through Day 14
- PK safety FU period ending with the PK safety visit at Day 49 (+/- 4)

Accordingly, the participation time for part I is defined as time from screening visit (ICF date) until PK safety visit and defines the analysis time for part I.

Part II periods differ depending on conduct (with or without hospitalization) but are usually ending with the follow up safety visit at Day 49 (+/- 4). Please see the protocol (e.g. section 3) for more details.

Accordingly, the participation time of patients for part II starts

- ⇨ at screening visit (ICF date) for patients solely enrolled in part II or
- ⇨ at 1st day after part I PK safety visit for patients enrolled into part I/II

and lasts until the date of patients study completion/termination.

For the patient based analysis in part II the analysis time is defined by the participation start time until the safety visit (Day 49 +/- 4) of the patients last treated bleeding event.

For the bleeding event based analysis in part II the analysis time of a bleeding event starts with its Treatment Day 0 and ends with its safety visit. Accordingly, data from in-between

individual 49 day periods or after last Day 49 visit will only be listed and not included in the analysis.

For adverse events reporting related periods are defined:

- Patient Enrolment to the First Administration of Study Drug (NTEAE)
- After first Administration of Study Drug until respective Day 49 visit (part I and part II) (TEAE)
- In-between individual 49 day periods or after last Day 49 visit (only related SAEs will be listed and included in the analysis), all other AEs will be counted and listed.

For concomitant medication please refer to section 9.

Study days and bleeding event number

Primarily, study days are counted since first dose of study medication (i.e. in part I) up until the end of study participation.

Because the study is divided into parts with the possibility of multiple bleeding events in part II, study days are additionally considered for each part II bleeding event separately. More precisely, study day is also defined as the number of days since first dose of study medication of the applicable part II bleeding event and, for a particular date, is calculated as:

Study day = Assessment date – Date of first dose of study medication for this bleeding event

Due to consideration of several bleeding events as individual cases and the repeated observation periods in part II, related events will be numbered per patient, sorted by start date and time of the events associated with part II participation.

Definition of baseline values

Part I: The baseline value is defined to be the last value, which was assessed during screening before and up to PK dosing Day 0 (all pre-dose). In other words, if for example pre-dose value of fibrinogen antigen at Day 0 of PK is missing, baseline will use the value measured at the screening visit.

Part II: For event-based analysis in part II, baseline value is defined to be Day 0 (pre-dose) per event. In case this is not available, for fibrinogen antigen and fibrinogen activity the baseline values from last event will be used. For all other values Day 0 (pre-dose) will not be replaced, if missing.

Definition of analysis time points or time windows

The following definition of analysis time points, time windows and measurement assignments applies unless specified differently in the respective sections. In particular, for PK parameter specific decisions, the definitions in the PK analyses plans prevail.

Time points for the different endpoints to be measured are specified in the protocol, e.g. in the flowcharts. For each endpoint measurements are taken at an (individual) selection from

time points during Screening, on Day 0 (pre- as well as post-dose) and/or on Days 1, 2, 4, 7, 10, 14 or 49.

Time windows for measuring times are not provided except for the Day 49 measurements, where the window is +/- 4 days. Therefore, no exclusions due to window deviations will be applied. For the PK analysis, actual times will be used. Should time windows be set-up (at a later stage) and result in exclusions of data from analyses, this will be documented in an amendment to this SAP or - at the latest - by means of the applicable data review meeting minutes prior to data base lock.

5.6 Handling of MCF, Fibrinogen Activity and Fibrinogen Antigen values below detection limit

MCF (Maximum Clot Firmness) samples are analysed by central lab. Given that MCF values below the detection limit of "< 2mm" are indicated in the output of the testing as "not measurable", it was discussed and decided in the BDRM (dated 25-Jun-2020) that for the purpose of the planned descriptive statistical analyses these values will be set to half of the range below the detection limit (range is "0 to 2", i.e. value used is "1 mm"). In the listings of individual patient data, the MCF output "non measurable" will be presented as "< 2mm" (2 mm is the lower detection limit).

Fibrinogen Activity samples are analysed by local and central lab. Given that Fibrinogen Activity values below the detection limit are indicated by "<" sign before the lower detection limit in the output of the testing, it was discussed and decided that for the purpose of the planned descriptive statistical analyses these values will be set to half of the range below the detection limit.

Fibrinogen Antibody samples are analysed by central lab. Given that Fibrinogen Antibody values below the detection limit are indicated by "<" sign before the lower detection limit in the output of the testing, it was discussed and decided that for the purpose of the planned descriptive statistical analyses these values will be set to half of the range below the detection limit. For values indicated in the output of the testing as "<0.0" the value "0" will be used in the planned descriptive statistical analyses.

6 Patient Accounting and Disposition

6.1 Patient accounting

Based on all enrolled patients, the number and relative frequencies (i.e. percentages) of patients in each study population as defined in section 4 Analysis Sets will be presented by age subgroup and overall for part I. For part II the number and relative frequencies (i.e. percentages) of all enrolled patients will be presented by age subgroup and overall based on the APE set; number and relative frequencies of patients in the SAF, ITT, FAS, and PP sets will be presented based on the SAF set. A listing with patient accounting data will be also presented.

An analogue presentation, including age groups, will be generated showing frequencies and percentages of the event based analysis sets (FBE and PPBE) from part II (ODP or ODT, each for minor events, major events and overall). Note, however, that these reflect events rather than patients. A listing with bleeding event based data will also be presented.

6.2 Disposition and withdrawals

The number and relative frequency (i.e. percentages) based on all enrolled patients (APE) will be presented by study part and overall for

- Patients by site and country (worldwide)
- Patients by site and country (European Economic Area (EEA)
- Patients by age group according to EudraCT

  (in utero subjects, preterm newborn infants (gestational age <37 weeks), newborns (0-27 days), infants and toddlers (28 days-23 months), children (2-11 years), adolescents (12-17 years), adults (18-64 years), from 65 years on, from 65-84 years, 85 years and over)

The number and relative frequency (i.e. percentages) based on all enrolled patients (APE) will be presented by age group and overall for

Part I:

- Patients participating in part I (Patients enrolled)
- Patients not eligible (Screen failures)
- Patients eligible
- Patients who prematurely discontinued the study part I before treatment (with reasons for discontinuation)

Part II:

- Patients participating in part II (Patients enrolled)
- Patients not eligible (Screen failures)
- Patients eligible
- Patients who prematurely discontinued the study part II before treatment (with reasons for discontinuation)

- Patients who completed the study without bleeding event (study completion defined as regular study completion/no early termination)

The number and relative frequency (i.e. percentages) based on all treated patients (SAF) will be presented by age group and overall for

Part I:

- Patients treated in part I
- Patients who prematurely discontinued the study part I after treatment (with reasons for discontinuation)
- Patients who completed the study part I (Patient was treated in part I and completed/terminated the study after part I PK safety visit; in case PK safety visit was not done/has no date, date is calculated as 49 days after “PK Dosing Day 0”.)

Part II:

- Patients treated in part II
- Patients treated in part I and II
- Patients who prematurely discontinued the study part II after treatment (with reasons for discontinuation)
- Patients who completed the study part II (study completion defined as regular study completion/no early termination)

A listing with all the patient disposition data will be also presented.

For the event based analysis the frequencies of part II bleeding events by patient (total) and additional descriptive statistics for frequencies of events by age group and overall will be presented (mean, SD, min, max, median) for FBE and PPBE. A listing with bleeding event data will be also presented.

6.3 Protocol deviations

The number and relative frequency of patients (and/or events) with protocol deviations (major/minor) will be presented overall for SAF and FAS (part I and part II) and FBE in part II for total and categories. All patients/events with their protocol deviations will be listed.

In the BDRM, dated 25-Jun-2020, all minor and major protocol deviations on patient and on bleeding event level were reviewed and agreed upon. Following from the decisions taken, assignments to analysis populations were done. A complete list of all protocol deviations is attached to the BDRM minutes and included in the listings of the final analysis.

7 Demographics and Background Characteristics

All assessments will be done for part I and II separately.

Assessments made at screening visit and at PK Dosing Day 0 (pre-dose) will be summarized for patients treated with BT524 (SAF) using descriptive statistical methods only. These assessments will include demographic data and medical history as specified below as well as previous or concomitant medications (see section 9 below). Other relevant baseline characteristics from screening visit (such as physical examination, vital signs, etc.) will be presented as part of the applicable safety evaluations or only be listed (such as history of alcohol consumption or smoking).

Summary tables with summary statistics and frequency tables will be presented as appropriate. Graphical presentations will be used if they increase transparency and understanding of the data. Details on what outputs will be produced along with their layout and technical specifications will be provided in the separate tables shell document.

7.1 Demographics

The following demographic characteristics will be presented on patient level for both part I and part II

- Gender (male/female)
- Age (years) at date of first BT524 treatment in the respective study part.
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg) at baseline (if documented in lb it will be transformed into kg via: weight (kg) = weight(lb) x 0.4536, rounded to 2 digits)
- Height (cm) at baseline (if documented in inch it will be transformed into cm via: height (cm) = height (inch) x 2.54, rounded to 2 digits)
- BMI (kg/m^2) at baseline = weight in kg / (height in cm)$^2 \times$ 10000
- Disease characteristics (Afibrinogenemia, severe hypofibrinogenemia)

The following information will be presented on event level for the FBE set

- Age (years) as age at date of each event treatment (Day 0 of part II).

  Presentations for event level will be done overall as well as by ODP or ODT.

Presentations will be done overall as well as by age group (0 to 27 days, 28 days to < 2 years, 2 to < 6 years, < 6 years, 6 to < 12 years, 12 to < 18 years, >=18 years).

An additional table will be generated presenting the age classification according to EudraCT (in utero subjects, preterm newborn infants (gestational age < 37 weeks), newborns (0-27 days), infants and toddlers (28 days-23 months), children (2-11 years), adolescents (12-17 years), adults (18-64 years), from 65 years on, from 65-84 years, 85 years and over), but the classification is only presented in the patient disposition part of the analysis.

All patients/events with their demographics data will be listed.

7.2 Medical history/ concomitant diseases

The diseases and conditions are coded on a regular base during study conduct and at time of database lock the 2012Q3 version of the WHO Drug Dictionary will be used for the final coding. The medical conditions will be classified as follows:

- Previous medical conditions, i.e. medical conditions that stopped prior to start of first treatment
- Concomitant medical conditions, i.e. medical conditions still present or occurring after start of first treatment

The frequency of diseases recorded from medical history will be presented (SAF) after classification into previous and concomitant conditions by system organ class (SOCs) as well as the frequencies of preferred terms within each SOC. If patients have more than one disease within an SOC or Preferred Term they will be counted only once for the respective SOC or Preferred Term. A listing with all patient medical history/concomitant medical condition data will be also presented.

7.3 Bleeding history

On patient level the following analyses will be done:

- Frequencies of bleeding events for Epistaxis, Oral cavity bleeding, Gastrointestinal bleeding, Post-partum bleeding, Umbilical cord bleeding, Menorrhagia, Muscle Haematoma, Haemarthrosis, Intraperitoneal bleeding, Intracranial bleeding, Others, and total.
- Annual bleeding rate = Number of bleedings within the last 12 months before ICF signature (spontaneous, total). Not applicable for patients < 1 year.
- Frequencies of bleedings due to surgical procedure

Descriptive statistics for total number of bleedings and Number of bleedings due to surgical procedure, as well as for annual bleeding rate (based on patients ≥ 1 year at ICF signature) will be presented for each age group and overall.

For patients below 1 year of age total number of bleeds will be given and described in a footnote.

A listing with all patient bleeding history data will be also presented.

8 Exposure and Compliance

All assessments will be done for part I and II separately.

8.1 Treatment groups

Not applicable.

8.2 Dosage

For part I descriptive statistics for the following dose data will be presented for SAF, FAS, PP, PK sets for the overall population and each age group.

- Calculated dose (of fibrinogen) (mg)
- Calculated dose (of fibrinogen) per kg (mg/kg) = Calculated dose (of fibrinogen) (mg)/ body weight (kg)
- Calculated volume (mL)
- Volume administered (mL),
- Total dose administered (mg),
- Nominal dose (of fibrinogen) administered (mg) = calculated dose x (volume administered / calculated volume)
- Nominal dose (of fibrinogen) per kg administered (mg/kg) = calculated dose per kg x (volume administered / calculated volume)

For part II (ODP or ODT) descriptive statistics for the following dose data will be presented for FBE and PPBE on event level (ODP or ODT, each for minor events, major events and overall) for the overall population and each age group:

- Target Fibrinogen level (g/L)
- Baseline Fibrinogen level (g/L)
- Total volume administered (mL)
- Total dose administered (mg)
- Total dose administered per kg BW (mg/kg) (will be calculated)
- Number of infusions per bleeding event

In case of repetitive infusions for treatment of one bleeding event (only applicable for part II), all parameters per single infusion will be listed. In addition the mean values of the repeated infusions will be listed for Target Fibrinogen level and Baseline Fibrinogen level and the sum of the repeated infusions will be listed for Total volume administered, Total dose administered, and Total dose administered per kg BW. For the descriptive statistics, the mean of the Target Fibrinogen level and the Baseline Fibrinogen level will be calculated for each patient per bleeding event. These mean values will then be used for the descriptive analysis. For all other parameters in the list above, the sum of single infusions for treatment of one bleeding event will be used for the descriptive statistics.

Descriptive statistics (frequencies and percentages) for treated surgery events will be provided for the FBE set, separated into pre-operative administration, intra-operative administration and post-operative administration.

Descriptive statistics for the FBE set (frequencies and percentages) of number of infusions per bleeding event will also be produced according to no repeated infusion (only one infusion), at least one repeated infusion (at least 2 infusions), and numbers of infusions per bleeding event: 1, 2, 3, >3.

A listing with all patient study medication dosage data will also be presented.

8.3 Treatment/infusion duration

Descriptive statistics for the following treatment duration data will be presented for part I (SAF, FAS, PP, PK) and on event level from part II (for FBE and PPBE) for the overall population and each age group.

- Treatment duration will be calculated in minutes as end of administration (time/date) – start of administration (time/date)
- Infusion rate (mL/min.)

Also descriptive statistics (frequencies and percentages) of changes in infusion rates will be produced according to no change in infusion rates, at least one change in infusion rate, and numbers of changes in infusion rates (per treatment/event): 1, 2, 3, >3. Same evaluation will be done for infusion interruption.

A listing with all patient treatment/infusion duration data will also be presented.

8.4 Compliance

For part I compliance can be assessed by the statistics on calculated dose of fibrinogen per kg (mg/kg) presented within the dosage evaluation (cf. section 8.2 above). For part I, analyses will use actual time, actual dose and infusion rate to derive the different characteristics.

Due to the individually tailored dose for treatment of part II bleeding events no compliance rules based on calculated dose as for part I treatments apply. As the IMP will be administered intravenously to each patient under the supervision of the study investigator or designated qualified study personnel, the compliance is expected to be 100%. In addition, compliance can be assessed based on infusion interruptions (cf. section 8.3 above).

9 Previous and Concomitant Medication or Treatment

All assessments will be done for part I and part II separately for the SAF set.

Previous and concomitant medications are coded according to WHO drug dictionary. version 2012Q3 which will be used at time of database lock and stored with A(natomical) T(herapeutical) C(hemical) codes and generic names.

Treatment will be classified as previous if stopped prior first infusion and as concomitant if overlapping with study participation after first infusion.

The numbers and frequencies of previous and concomitant medications will be given per ATC level 2. If a patient has received more than 1 drug within an ATC class he/she will be counted only once for this ATC class. A listing with all patient previous and concomitant medication or treatment will be also presented.

10 Pharmacokinetics, Pharmacodynamics and Efficacy

All assessments will be done for part I and part II separately.

Unless explicitly specified otherwise efficacy analyses will consist of descriptive methods and not test hypotheses but rather aim at parameter estimation and determination of confidence intervals. Should tests be conducted and/or p-values be given (beyond the one in section 10.2), note that these are not adjusted for multiplicity (which would be needed for fully confirmatory conclusions across all tests given the number of endpoints to investigate).

Also, only descriptive analyses will be performed to compare the efficacy results of study 984 with the results from published clinical trials (cf. protocol section 15.2).

10.1 Primary endpoint analysis of part I

The primary objective being the description of the PK characteristics of BT524 is not covered in great detail by this SAP. In the scope of this SAP, descriptive summary statistics, including changes from baseline for the fibrinogen antigen (from part I), will be provided for each age group (based on SAF, FAS, PP, and PK population). Values from each age group will be evaluated by a one-sample t-test (pre-/post-comparison) and presented in a tabular format.

A listing with all patient fibrinogen antigen (from part I) data will be also presented.

PK parameters defined for the primary objective will be derived from concentration-time profiles using adapted methodology, non-compartmental analysis, compartment analysis, or population modelling, as required. Details related to the analysis of these PK parameters will be specified in separate PK analyses plans.

10.2 Secondary endpoint analyses of part I

PD parameters defined for the secondary objective will be derived from concentration-time profiles using adapted methodology, non-compartmental analysis, compartment analysis, or population modelling, as required. Details related to the analysis of these PD parameters will be specified in separate PK analyses plans.

In the scope of this SAP, descriptive summary statistics, including changes from baseline for the fibrinogen activity (from part I), will be provided for each age group (based on SAF, FAS, PP, and PK population). Values from each age group will be evaluated by a one-sample t-test (pre-/post-comparison) and presented in a tabular format. Surrogate efficacy parameter MCF, assessed by fib-tem S, will be measured in part I pre-dose and at 1 and 8 hours post-end of each IV infusion in patients ≥ 6 years. MCF will be measured pre-dose and at 1 hour post-end of infusion in children between 2 and < 6 years and pre-dose and at the end of each infusion in children < 2 years.

Descriptive statistics including change from baseline will be presented for each age group, i.e. < 2 years, 2 to < 6 years, ≥ 6 to < 12 years, 12 to < 18 years, ≥ 18 years (based on FAS, PP, and SAF population).

Values for the patients ≥ 18 years will be evaluated by a one-sample t-test (pre-/post-comparison) and presented in a tabular format.

This analysis, done for both post-dosing time points, will be considered confirmatory for the 1 hour post-end of infusion assessment in patients ≥ 18 years. Additionally, 95%-confidence levels will be calculated.

More precisely, the t-test will assess the mean difference $\mu_{1,0}$ between dependent measurements (1h post minus pre-treatment MCF difference; one sample) and test the null hypothesis H_0: $\mu_{1,0} < 0$ versus the alternative H_1: $\mu_{1,0} > 0$ at a two-tailed α-level of 0.05.

Correlation between MCF and fibrinogen activity pre-dose and at 1 and 8 hours post-end of each IV infusion will also be assessed in patients ≥ 6 years.

Note that (according to protocol section 14.4.5.2.5) consumption of BT524 (dose per kilogram body weight and total dose) during part I, calculated and presented in the framework of exposure and compliance (cf. section above), can also be assessed and interpreted as efficacy endpoint in respect to MCF.

Also the efficacy parameter MCF will be presented as a whisker box plot for FAS.

10.3 Secondary endpoint analyses of part II

Each of the below secondary efficacy parameters will be evaluated and descriptive statistics presented on event level from part II (ODP or ODT, each for minor events, major events and overall) for the overall population and each age group. More precisely, the following efficacy parameters after each event will be assessed:

Overall haemostatic response to treatment with BT524 for each surgical procedure and each treated bleed as assessed by the investigator according to a 4 point scale ("none", "moderate", "good" or "excellent") will be evaluated presenting response rates with 95 % confidence intervals for each scale and for the sum of excellent and good, classified as success. These event-based evaluations will be conducted according to two concepts:

1) descriptively (showing frequencies and percentages based on the event level FBE and PPBE analysis set) considering each event as an individual case and
2) by modelling considering events as repeated measurements within the same patient (based on FBE and PPBE), if applicable (e.g. by general estimation equations with intra-patient correlation structure). Provided sufficient numbers of ODT and ODP, minor /major events should be considered (e.g. analysis by type according to concept 1 above).

Overall haemostatic response will also be presented in pie chart and listed.

For each surgical procedure loss of blood (intra- and postoperatively, re-bleedings) will be listed considering each event as an individual case (based on the event level FBE and PPBE analyses sets).

In addition, loss of blood is to be rated by the investigator according to classifications (loss of blood is below/within/above the expected range for the procedure performed) for surgical bleeding events. These ratings will be evaluated presenting numbers and percentages of events considering each bleeding event as an individual case (cf. concept 1 above).

Descriptive analysis on event level (based on event based FBE and PPBE analyses sets) will be conducted for and also listed

- Units of other fibrinogen-containing products infused besides BT524 (e.g., fresh frozen plasma or cryoprecipitate) given to counteract hemodynamic instability at the day of BT524 administration or 1 day after.
- Units of transfusion products infused, e.g., allogenic or autologous blood (packed red blood cells, fresh whole blood), platelets, given to counteract hemodynamic instability at the day of BT524 administration or 1 day after.

- Consumption of BT524 (dose per kilogram body weight, dose per infusion and total dose) required pre-, intra- or post-operatively for effective treatment of surgical bleeding events.
- Quality of wound healing assessed after wound healing is expected to be completed.

Furthermore, MCF as a surrogate efficacy parameter will be evaluated pre-dose and at 1 hour post-end of each IV infusion (including repetitive infusion for one bleeding event) by means of non-confirmatory t-test(s) pre/post comparison plus correlation between MCF and fibrinogen activity. Also MCF will be presented as a whisker box plot and also listed. Descriptive summary statistics including changes from baseline for the fibrinogen activity will be provided for each age group. MCF and fibrinogen activity values from additional samplings (beside pre-dose and 1 hour post-dose) taken as required per investigator will be listed and not used in the analyses described above. These analyses will be conducted on event level, i.e. based on the event based FBE and PPBE analysis set. Otherwise, details correspond to those of part I analysis, except that the testing is considered as non-confirmatory.

With respect to the two evaluation concepts of efficacy, the concept when multiple events per patient are to be handled as individual cases is considered primary analysis within the framework of secondary analyses of part II.

Descriptive summary statistics and a listing for the fibrinogen antigen at screening will be provided for each age group on patient level (SAF, FAS, and PP analysis sets).

11 Safety

All assessments will be done for part I and part II separately.

APE-Set will be used to present overall numbers of AEs incl. NTEAEs. All safety analyses will be based on the SAF.

11.1 Adverse events

All assessments will be done for all patients, part I and part II separately.

Adverse events (AE) will be coded using the MedDRA® dictionary. The current version will be used at time of database lock and presented by primary System Organ Class (SOC) and Preferred Term.

The analysis will focus on the treatment-emergent AEs (TEAEs). When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. An AE that occurs (or worsened) on or after the time the patient receives his/her first dose of study drug (until his/her last study visit) will be considered a treatment emergent AE (TEAE). See also CSP section 14.6.2 for definition of non-treatment adverse events.

Please note the definition of study periods and adverse event reporting periods in section 5.5 above. Please also note that analyses for TEAE will be based on the safety population (SAF). Overview tables including non-TEAEs will be based on the APE to also include patients not treated in the study.

For the analysis of TEAEs only those TEAEs are taken into consideration which are reported from first treatment to the safety visit after treatment (independent of the planned duration between treatment start and Day 49 safety visit). For part I this is the duration between PK treatment and the Day 49 PK safety visit or ealier (if a bleeding event happened before Day 49 PK safety visit), and for part II this is for each bleeding event the duration between treatment of the bleeding event and Day 49 safety visit or ealier (if another bleeding event happened before Day 49 safety visit).

All other TEAEs reported out of these time frames will be counted and listed. Exception is the analysis of related serios adverse events (related SAEs) which are inlcuded in the analysis irrespective of the onset time after first administration of IMP:

If Day 49 safety visit' is not done, the period for inclusion of TEAEs in the analysis is from baseline (treatment start) to 49 days post-baseline .

The total number and percentage of patients reporting at least one AE and the absolute count of AEs will be tabulated for each age group and overall. This initial summary will be based on the APE set and provide a breakdown of the following:

- Any AE
- Any non-severe AE
- Any TEAE
- Any non-serious TEAE
- Any non-severe TEAE
- Any treatment-related TEAE
- Any severe AE

- Any severe TEAE
- Any severe treatment-related TEAE
- Any SAE
- Any serious TEAE
- Any serious treatment-related TEAE
- Any AE leading to discontinuation from study
- Any TEAE leading to discontinuation from study
- Any treatment-related TEAE leading to discontinuation from study
- Any AE with outcome of death
- Any death
- Any pregnancy

In the SAF number and frequencies (i.e. percentages) of patients with TEAEs will be given by System Organ Class (SOC) and by Preferred term within each SOC (total, for each age group) together with the number of events for the following:

1. All TEAEs
2. Serious TEAEs
3. All TEAEs considered related (see details below)
4. Serious TEAEs considered related (see details below)
5. All TEAEs by maximum severity (‘mild’, ‘moderate’, ‘severe’)
6. TEAEs leading to death
7. TEAEs leading to study discontinuation
8. The TEAEs occurring under infusion and within 24 hours after the start of IMP infusion (Infusion related reaction (IRR))
9. Related TEAEs occurring within 24 hours after start of infusion
10. Adverse events of special interest (AESI):
    - Hypersensitivity/ Anaphylactic reactions/anaphylactic shock: Hypersensitivity (SMQ, restricted to narrow search), Anaphylactic reaction (SMQ, restricted to narrow search), "Anaphylactic shock conditions" (SMQ, restricted to narrow search)
    - Thrombogenicity: SMQ Embolic and thrombotic events (restricted to narrow search)
    - Transmission of infective agents: Preferred Term "Transmission of infectious agent via product" and "Suspected transmission of an infectious agent via product (Preferred Term)
    - Fibrinogen inhibitory antibodies: SOC"Investigations"
11. Related AESI:

- Hypersensitivity/ Anaphylactic reactions/anaphylactic shock: Hypersensitivity (SMQ, restricted to narrow search), Anaphylactic reaction (SMQ, restricted to narrow search), "Anaphylactic shock conditions" (SMQ, restricted to narrow search)
- Thrombogenicity: SMQ Embolic and thrombotic events (restricted to narrow search)
- Transmission of infective agents: Preferred Term "Transmission of infectious agent via product" and "Suspected transmission of an infectious agent via product (Preferred Term)
- Fibrinogen inhibitory antibodies: SOC"Investigations"

Additionally, number and frequencies of patients with TEAEs will be presented by decreasing frequency for all TEAEs, serious TEAEs and TEAEs considered related.

11.2 Deaths

Patient listings will be provided for patients with AEs leading to death.

11.3 Adverse events leading to discontinuation from study

Patient listings will be provided for patients with AEs leading to discontinuation.

11.4 Pregnancies

Pregnancy test results will be listed for all enrolled female patients (APE).

11.5 Vital signs

Vital signs are measured with the following method/unit:

- Blood pressure [mmHg]
- Heart rate in beats/min measured by pulse rate
- Body temperature in grade Celsius [°C] (tympanic measurements)

Measured values of vital signs will be summarized descriptively across the measurement time points (per observation period, cf. study protocol flowchart section 3) for part I (SAF) and on event level from part II (separated by ODP/ODT, hospitalization, age group) for FBE. Note that ‘baseline’ refers to the pre-dose measurement within each observation period of the indication/event. A listing with all patients vital signs data will be presented.

11.6 Fibrinogen inhibitory antibodies

Fibrinogen inhibitory antibodies are locally measured from sampling at screening, pre-dose (if applicable) and at the safety visit and will be categorized as positive, negative, or missing/not done.

Number of patients and percentages in each category will be summarized for part I (PK) and part II for SAF and on event level from part II for FBE. A listing with all patients fibrinogen inhibitory antibodies data will also be presented.

11.7 Viral safety

For part I viral safety is assessed based on pre-dose sample.

The following statistical analyses will be presented for part I pre-dose samples:

1. Qualitative data based on laboratory specific normal ranges will be categorized according to the categories “negative/positive”.
2. Quantitative results will be categorized qualitatively based on specific normal ranges and presented as qualitative result ”normal”/”above normal”. The quantitative data for these parameters will be listed.
3. Number and percentages of patients with values considered as clinically significant by the investigator will be tabulated.

Retention samples from safety visit of part I and II and pre-dose samples from part II are only listed. No summaries will be produced.

11.8 Clinical safety laboratory

All safety lab values will be re-calculated to SI units before further processing.

The following statistical analyses will be presented for part I (SAF) and on event level from part II for FBE (separated by ODP/ODT, hospitalization, age group as appropriate) per lab test (as listed subsequently). Note that ‘baseline’ refers to the pre-dose measurement within each observation period of the indication/event:

1. Quantitative data will be examined for trends using descriptive statistics (number of patients/events with data, number of patients/events with missing values, mean, SD, median, minimum, and maximum) of measured values at baseline and each planned post-baseline visit over time.
2. Qualitative data based on laboratory specific normal ranges will be categorized according to the categories (e.g. below normal/normal/above normal) and presented as number and relative frequency of patients (and/or events).
3. Number and percentages of patients/events with on treatment values considered as clinically significant (CS) by the investigator will be tabulated (across planned visits). Out of range values not assessed for clinical significance are not included in the analysis and are provided in Listing.

Note that in the listings, laboratory values that are outside the normal range will additionally be flagged. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in an extra data listing. Additionally, a separate listing showing the normal ranges will be generated.

Hematology and clinical chemistry

Hematology tests include RBC, WBC, platelet count, hemoglobin, and hematocrit (all quantitatively).

Biochemistry tests measure aspartate aminotransferase, alanine aminotransferase, γ-glutamintransferase, alkaline phosphatase, total bilirubin, creatinine, urea, potassium, sodium, calcium, chloride (all quantitatively).

Urinalysis

Blood, leukocytes, protein, glucose, ketones, nitrite, bilirubin, urobilinogen were measured only qualitative, pH was measured quantitatve. For the analysis only qualitative results will be used (for pH the normal ranges are used for classification of results into “normal”, “abnormal”). Frequencies and percentages of normal and abnormal values will be presented. The quantitative results will only included in the listings.

Markers of coagulation activation

Coagulation activation parameters include PT, PT(INR), aPTT, TAT, F1+2, D-dimer.

Measurements of coagulation activation parameters from additional samplings (beside pre-defined timepoints) taken as required per investigator will be listed and not used in the analyses.

11.9 ECG

Overall ECG evaluations for part I will be analyzed for SAF. ECG measurements - according to the qualitative data categories “normal”, “abnormal – not clinically significant”, and “abnormal – clinically significant” - will be described by means of “shift-tables” between baseline and each of the planned post-baseline visits. ‘Baseline’ visit is the time point of pre-dose measurement at screening within the PK period. ECG at screening for part II and unscheduled measurements will only be provided in the listings.

11.10 Physical examination

Physical examination will include the inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, musculoskeletal and nervous system.

Number and percentages of patients for each category (“normal”, “abnormal – not clinically significant”, and “abnormal – clinically significant”) for part I and on event level from part II, will be generated per inspected organ (plus ‘other’) for pre-dose and overall.

The overall assessment per inspected organ number and percentage of patients/events will be presented for the categories

- NORMAL, defined as patients/events without any abnormal post baseline evaluation,
- ABNORMAL NOT CS, defined as patients/events with at least one abnormal not clinically significant post baseline evaluation, and
- ABNORMAL CS, defined as patients/events with at least one abnormal clinically significant post baseline evaluation.

‘Baseline’ visit is the time point of pre-dose measurement within each observation period of the indication/event.

Shift tables comparing baseline visit and Day 49 visit will also be produced for part I and on event level from part II. Values that are identified by the investigator as being clinically significant will also be shown in an additional data listing.

12 Software

If not stated otherwise, the data will be analyzed using SAS Version 9.4 or higher.

13 Abbreviations

AE	Adverse Event
APE	All Patients Enrolled Set
aPTT	Activated partial Thromboplastin Time
ATC	Anatomical Therapeutical Chemical
BW	Body Weight
°C	Degrees Centigrade
cf.	confer
CHMP	Committee for Medicinal Products for Human Use
cm	Centimetre
COA	Certificate Of Analysis
CRO	Contract Research Organization
CS	Clinically Significant
BDRM	Blind Data Review Meeting
ECG	Electrocardiogram
e.g.	For example
EMA	European Medicines Agency
FAS	Full analysis set
F1+2	Prothrombin Fragment 1 and 2
FiAc	Fibrinogen activity
FiAg	Fibrinogen antigen
FU	Follow-up
g	Gram
h	Hour
ICF	Informed Consent Form
ICH	International Council for Harmonization
i.e.	That is
IMP	International Medicinal Product
INR	International Normalized Ratio
IRR	Infusion Related Reaction
IV	Intravenous
kg	Kilogram
L	Liter
lb	Pound
max	Maximum
MCF	Maximum Clot Firmness
MedDRA	Medical Dictionary for Regulatory Activities
mg	Miligram
min	Minimum
min.	Minute
mL	Mililiter
mm	Millimetre

mmHg	millimeters of mercury
NTEAE	Not Treatment Emergent Adverse Event
ODP	On-Demand Prophylaxis
ODT	On-Demand Treatment
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PT	Prothrombin Time
RBC	Red Blood Cell
ROTEM	Rotational Thromboelastometry
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety analysis set
SAS	Statistical Analysis Software
SD	Standard Deviation
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TAT	Thrombin Antithrombin III Complex
TEAE	Treatment Emergent Adverse Event
WBC	White Blood Cell

14 References

1. ICH Harmonised Tripartite Guideline E9, Statistical Principles for Clinical Trials, 1998
2. ICH Harmonised Tripartite Guideline E3, Structure and Content of Clinical Study Reports. 1995
3. ICH Harmonised Tripartite Guideline E6(R1), Guideline for Good Clinical Practice, 1996
4. ICH guideline E2F, Note for guidance on development safety update reports, EMA/CHMP/ICH/309348/2008, September 2010
5. SAS / STAT® 9.22 User's Guide (2010). The Power Procedure, Cary, NC: SAS Institute Inc.

15 Appendices

15.1 Table of Content of TLF numbers, titles, and analysis populations

Table	Number	Table Name
		Patient Accounting and Disposition
		Patient Accounting
Table	14.1.1.1.1	Analysis Set: Frequencies and Percentages of Patients – APE I
Table	14.1.1.1.2	Analysis Set: Frequencies and Percentages of Children < 6 years – APE I
Table	14.1.1.1.3	Analysis Set: Frequencies and Percentages of All Patients Enrolled – APE II
Table	14.1.1.1.4	Analysis Set: Frequencies and Percentages of All Children < 6 years Enrolled – APE II
Table	14.1.1.1.5	Analysis Set: Frequencies and Percentages of Patients – SAF II
Table	14.1.1.1.6	Analysis Set: Frequencies and Percentages of Children < 6 years – SAF II
Table	14.1.1.1.7	Analysis Set: Frequencies and Percentages of Bleeding Events – FBE
Table	14.1.1.1.8	Analysis Set: Frequencies and Percentages of Bleeding Events of Children < 6 years – FBE
Table	14.1.1.1.9	Analysis Set: Frequencies and Percentages of Bleeding Events – PPBE
Table	14.1.1.1.10	Analysis Set: Frequencies and Percentages of Bleeding Events of Children < 6 years – PPBE
		Disposition
Table	14.1.1.2.1	Disposition: Frequencies and Percentages of Patients by Country (Worldwide) – APE I and II
Table	14.1.1.2.2	Disposition: Frequencies and Percentages of Patients by Country (EEA) – APE I and II
Table	14.1.1.2.3	Disposition: Frequencies and Percentages of Patients by Age Clasification according to EudraCT – APE I and II
Table	14.1.1.2.4	Disposition: Frequencies and Percentages of Patients by Age Group and Overall – APE I
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